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Aims and Scope

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

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Blood pressure management in stroke patients

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REVIEW ARTICLE

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Hypertension is a major, yet manageable, risk factor for stroke, and the benefits of well-controlled blood pressure are well established. However, the strategy for managing blood pressure can differ based on the pathomechanism (subtype), stage, and treatment of stroke patients. In the present review, we focused on the management of blood pressure during the acute stage of intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction. In patients with cerebral infarction, the target blood pressure was discussed both before and after thrombolysis or other endovascular treatment, which may be an important issue. When and how to start antihypertensive medications during the acute ischemic stroke period were also discussed. In regards to the secondary prevention of ischemic stroke, the target blood pressure may differ based on the mechanism of ischemic stroke. We have reviewed previous studies and guidelines to summarize blood pressure management in various situations involving stroke patients.

Keywords: Stroke; Hypertension; Cerebral infarction; Intracranial hemorrhage

INTRODUCTION

Stroke is a disease with a heterogeneous pathomechanism, and is primarily considered to be hemorrhagic or ischemic. Hemorrhagic stroke is the result of ruptured blood vessels in the brain, resulting in intracerebral hemorrhage (ICH). This includes ruptured perforator vessels in the deep structures of the brain, including the basal ganglia, thalamus, pons, and cerebellum [1]. In cases of lobar hemorrhage, two potential causes are underlying cerebral amyloid antipathy or cancer metastases. The rupture of an intracranial aneurysm may lead to subarachnoid hemorrhage (SAH), which has a high mortality rate during the acute phase [2]. The mechanism of ischemic stroke is more heterogeneous, compared to hemorrhagic stroke. Embolisms caused by large artery atherosclerosis in the proximal vessels can cause infarction. The heart chambers may be one such source of embolism (cardioembolism). Another example of this is lacunar infarction, which results from the occlusion of small perforators due to lipohyalinosis, which subsequently causes small infarctions [3].

Hypertension is one of the most important risk factors for stroke, and is the risk factor with the highest population-attributable risk [4]. High blood pressure (BP) may lead to endothelial

dysfunction, resulting in the development of atherosclerosis [5]. Hypertension also affects the heart directly and increases the risk of cardioembolic stroke [6].

Additionally, small perforators originating from the intracranial artery are affected by hypertension. In contrast to capillary vessels, the perforator branches are perpendicular to their source vessels, and are characterized by a sudden decrease in diameter, which makes them vulnerable to increased BP. High BP may cause these small perforators to rupture, leading to ICH, or may cause occlusion, resulting in lacunar infarction. Therefore, lowering BP is highly effective for the prevention of secondary stroke and acute complications of ICH [7]. However, the target BP may differ slightly per patient, based on the stroke mechanism.

Furthermore, the goal of BP control may differ based on the stage (acute vs. chronic) and treatment (thrombolysis or thrombectomy) of stroke. In this comprehensive review, we aimed to discuss BP control in a variety of situations involving stroke.

BP MANAGEMENT IN HEMORRHAGIC STROKE

Hemorrhagic strokes are categorized as either ICH or SAH, with ICH accounting for 10% to 20% of all strokes, and SAH accounting for approximately 5% [8]. Hemorrhagic stroke occurs less frequently than ischemic stroke, but the morbidity and mortality are still considerable. Since patients often deteriorate rapidly within a few hours after onset, appropriate management in the acute stage is important. The primary medical treatment for acute spontaneous ICH is BP management, in which the goals are to reduce hematoma expansion and perihematomal edema, improving the functional outcome and reducing mortality. In patients with SAH, BP should be controlled to balance the risk of rebleeding while maintaining cerebral perfusion pressure (CPP).

BP target in acute ICH

Increased BP is very common in ICH, which may stem from premorbid hypertension or secondary increase due to increased intracranial pressure (ICP), stress, or pain [9]. Elevated BP during the acute phase of ICH has been found to be associated with hematoma expansion, perihematomal edema, rebleeding, neurological deterioration, and death [10,11]. However, there are concerns about decreasing BP too far, which may cause cerebral ischemia around the hematoma. To evaluate this concern, a randomized clinical trial (RCT) was conducted to measure cerebral blood flow (CBF) following a decrease in BP [12]. Participants included patients within 24 hours of onset of acute ICH, with a systolic BP (systolic blood pressure [SBP]) > 150 mmHg. The patients were divided into two groups, with targeted SBPs of < 150 mmHg and < 180 mmHg. Perfusion computed tomography (CT) imaging was used to compare the CBF around the hematomas. It was found that the degree of BP reduction did not affect the CBF around the hematoma, and thus, it the reduction was safe.

Two large clinical trials have evaluated the efficacy of the intensive lowering of BP in patients with acute ICH [13,14]. First, the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage-2 (INTERACT-2) trial evaluated 2,839 patients with SBPs between 150 and 220 mmHg within 6 hours of ICH onset, who were randomized into groups with target SBPs of < 140 or < 180 mmHg [13]. The primary outcome was death or major disability, defined as a modified Rankin scale (mRS) score ≥ 3, which did not differ significantly between the two groups. This was evidenced by an odds ratio (OR) of 0.87 in the intensive treatment group, a 95% confidence interval (CI) of 0.75–1.01, and a P = 0.06. However, the intensive treatment group had better functional recovery and an improved physical and mental health-related quality of life compared to the standard treatment group. Additionally, the drastic reduction in BP did not cause serious adverse events. In concurrence with these results, the American Heart Association (AHA) and American Stroke Association (ASA) have provided evidence-based consensus guidelines which state that for patients with an SBP between 150 and 220 mmHg and without contraindications, the acute lowering of SBP to 140 mmHg is considered safe and may improve functional outcomes in patients with ICH [15].

Another trial, the Antihypertensive Treatment of Acute Cerebral Hemorrhage-2 (ATACH-2) trial, was published after the publication of these AHA/ASA guidelines [14]. This randomized trial evaluated patients with acute ICH and hypertension, assigning them to groups with targeted SBPs of 110–139 and 140–179 mmHg, however, antihypertensive treatment had to be initiated within 4.5 hours of the onset of ICH. The trial was terminated early due to futility, after an interim analysis demonstrated that the rates of death or severe disability (mRS ≥ 4) at three months were similar in both groups (relative risk, 1.04 in intensive treatment group; 95% CI, 0.85–1.27; $P = 0.72$). Unlike the INTERACT-2 trial, ATACH-2 showed no difference in the ordinal distribution of mRS scores, but did show a higher rate of adverse renal events within 1 week in the intensive treatment group than was found in the standard treatment group (9.0% vs. 4.0%, $P = 0.002$). This discrepancy was due to the excessive lowering of BP on the first day. The results of that study suggested that rapid and aggressive BP reduction could result in end-organ damage [16].

The difference between the results of these two trials can be attributed to the difference in both the degree and rate of BP reduc-

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tion. Although the target SBPs were the same in both trials, the actual BP reduction was faster and more pronounced in ATACH-2 (mean minimum SBP during the first 2 hours, 128.9 mmHg in ATACH-2 vs. 141.1 mmHg in INTERACT-2). This means that the SBP for the standard treatment group in the ATACH-2 trial was similar to those for the intensive treatment group in INTERACT-2 (Table 1). Additionally, SBP < 130 mmHg were also associated with worse prognoses in the post-hoc analysis of INTERACT-2 [17]. Therefore, it was suggested that a SBP of approximately 140 mmHg, rather than rapidly lowering the SBP to below 130 mmHg, may be the optimal SBP target.

A recent retrospective study suggested a potentially lower SBP limit for BP management in acute ICH [16]. When comparing the target SBP < 160 mmHg group and the SBP < 140 mmHg group, acute cerebral ischemia and acute neurological deterioration were more common in the SBP < 140 mmHg group. More specifically, cerebral ischemia increased when the minimum SBP < 120 mmHg was observed for more than 72 hours. In the case of a minimum SBP > 130 mmHg, no patients showed additional cerebral ischemia. Thus, that study suggested the possibility that an SBP of 130 to 140 mmHg would be an appropriate target SBP.

Few studies have been done regarding the safety and effectiveness of BP-lowering therapy in patients with extremely elevated BP (sustained SBP > 220 mmHg) as related to symptom presentation. The AHA/ASA guidelines recommend that the aggressive reduction of BP with continuous intravenous infusion and frequent BP monitoring may be reasonable for such patients. Additionally, the optimal time at which to start lowering BP to prevent recurrent stroke is not well known; however, starting BP management with a target BP of < 130/80 mmHg is recommended when the patient is medically and neurologically stable [15].

Based on the currently available information, the optimal management of hypertension in acute ICH remains unclear. Large RCTs did not provide consistent evidence that a specific target BP is beneficial, and provided information that rapid and aggressive BP reduction can be harmful. Ultimately, individualization of the BP target, taking into account the risk and benefit in each patient, may be needed.

BP variability in acute ICH

In addition to absolute SBP levels, BP variability may predict poor clinical outcomes in ICH, although the exact mechanism by which BP variability affects poor outcomes in patients with ICH is not fully understood [18]. Recurrent excessive BP fluctuations may increase oncotic and hydrostatic pressure gradients in the perihematomal region, and subsequently enhance perihematomal edema. Furthermore, these fluctuations may be associated with autonomic dysfunction that promotes proinflammatory cytokine production, hyperglycemia, disruption of the blood-brain barrier, and vasogenic edema, all of which may contribute to worse outcomes in patients with ICH [19].

Subarachnoid hemorrhage

Rebleeding in patients with SAH leads to an extremely poor prognosis. Although proper BP control is necessary to prevent rebleeding, the magnitude of BP control necessary to reduce the risk of rebleeding has not been established. For most patients with acute SAH, the AHA/ASA recommends maintaining a SBP < 160 mmHg to balance the risks of ischemia and rebleeding [20]. The Neurocritical Care Society states that extreme hypertension in SAH should be avoided, and suggests maintaining a mean arterial pressure (MAP) < 110 mmHg [21]. When increased ICP is suspected, given the risk of impaired cerebral perfusion, increasing MAP may be the only way to maintain CPP. Therefore, antihypertensive therapy is often withheld unless there is an extreme elevation in BP. European guidelines recommend a MAP above 90

Table 1. Comparison of INTERACT-2 and ATACH-2 trials

Variable	INTERACT-2	ATACH-2
Initial SBP criteria	SBP ≥150 mmHg	SBP ≥180 mmHg
Randomization	Within 6 hours from symptom onset	Within 4.5 hours from symptom onset
Treatment goal	Intensive: <140 mmHg	Intensive: 110–139 mmHg
	Standard: <180 mmHg	Standard: 140–179 mmHg
Antihypertensive treatment	Multiple	Single agent (intravenous nicardipine)
Mean SBP achieved	Intensive: 150 mmHg	Intensive: 128.9 mmHg
	Standard: 164 mmHg	Standard: 141.1 mmHg
Treatment failure rate in the intensive treatment group	67%	12.20%
Death or severe disability at 3 months	Intensive: 52.9%	Intensive: 38.7%
	Standard: 55.6% (P=0.06)	Standard: 37.7% (P=0.72)

INTERACT-2, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage-2; ATACH-2, Antihypertensive Treatment of Acute Cerebral Hemorrhage-2; SBP, systolic blood pressure.

mmHg to maintain proper CPP [22]. Recent studies have reported that BP variability is also associated with rebleeding or other negative outcomes in patients with acute SAH [23,24].

In the case of symptomatic cerebral vasospasm and delayed cerebral ischemia after SAH, induced hypertension is recommended by some guidelines [20,21]. A previous recommendation for triple-H therapy (consisting of hypertension, hemodilution, and hypervolemia) is no longer supported by current guidelines due to the adverse events no known to be associated with hemodilution. Instead, induced hypertension and euvolemia are now recommended [20,21,25]. While an optimal or maximum goal BP has not been established, physicians should consider concomitant cardiac and pulmonary diseases as well as the brain for each patient. Table 2 summarizes BP management in patients with hemorrhagic stroke.

BP MANAGEMENT IN ACUTE ISCHEMIC STROKE

Before and after intravenous thrombolysis treatment

BP management in acute ischemic stroke (AIS) is complex, and is associated with multiple factors. The AHA/ASA guidelines recommend that if AIS patients have a BP >185/110 mmHg and they are eligible for treatment with intravenous alteplase, their BP should be lowered carefully before intravenous alteplase treatment is initiated (class I, level of evidence [LOE] B) [26]. Moreover, current guidelines recommend maintaining BP <180/105 mmHg during and after intravenous alteplase treatment for the first 24 hours after treatment (class I, LOE B) [26]. However, it was not proven by an RCT and was based on the protocol of RCTs. Studies regarding target BP are difficult because it is impossible to blind either the physicians or the patients, and the occurrence of contamination due to lack of true blinding must be considered.

The intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED) trial showed that intensive BP control (SBP target 130–140 mmHg) failed to improve the functional outcome (OR, 1.01; 95% CI, 0.87–1.17), but lowered bleeding risk (OR, 0.75; 95% CI, 0.60–0.94) after intravenous thrombolysis treatment compared with guideline-recommended treatment (SBP target <180 mmHg) [27]. However, the ENCHANTED trial did not consider revascularization status, and only 1.9% of the study cohort underwent endovascular treatment. Therefore, the results of that study cannot be applied to patients who have undergone endovascular treatment. Moreover, some observational studies suggest that the risk of hemorrhage after the administration of alteplase is greater in patients with higher BP and BP variability [28]. The exact BP at which the risk of hemorrhage after thrombolysis increases is unknown. It is thus reasonable to target the BPs used in the RCTs involving intravenous thrombolysis, although it may be prudent to consider intensive BP lowering in patients with a high risk of bleeding.

Table 2. Blood pressure management in hemorrhagic stroke

ICH
For patients with ICH with SBP between 150 and 220 mmHg without contraindication
- Acute lowering of SBP to 140 mmHg is generally safe.
- Reducing SBP below 140 mmHg in the first hours after onset may increase the risk of renal adverse events.
For patients with ICH with SBP >220 mmHg
- It may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring.
Control of BP variability may be useful.
For prevention of recurrent stroke
- BP management for target BP of <130/80 mmHg is recommended when the patient is medically and neurologically stable.
SAH
Between the time of SAH onset and aneurysm obliteration, BP should be controlled with a titratable agent to balance the risk of stroke, HTN-related rebleeding, and maintenance of CPP.
SBP <160 mmHg is recommended until surgical clipping or coiling.
For the prevention of rebleeding
- Maintenance of mean arterial pressure above 90 mmHg is considerable to maintain CPP.
In the case of symptomatic cerebral vasospasm and delayed cerebral ischemia after SAH
- Induced HTN is recommended.

ICH, intracerebral hemorrhage; SBP, systolic blood pressure; BP, blood pressure; SAH, subarachnoid hemorrhage; HTN, hypertension; CPP, cerebral perfusion pressure.

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Before and after intra-arterial endovascular treatment

Current AHA/ASA guidelines recommend that for patients who undergo endovascular treatment, BP during and for 24 hours after treatment should be maintained at < 180/105 mmHg (class IIa, LOE B). In particular, if successful reperfusion is achieved, guidelines recommend that BP be maintained at < 180/105 mmHg (class IIb, LOE B) [26]. This recommendation was based on an endovascular treatment protocol from certain RCTs, although RCT data on optimal BP management are not available yet.

The protocol from the endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times (ESCAPE) trial stated that if reperfusion failed, an SBP ≥ 150 mmHg may be useful in promoting and maintaining adequate collateral flow, and if successful reperfusion was achieved, normal BP was then targeted [29]. Similarly, in the diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention (DAWN) trial protocol, a goal SBP < 140 mmHg was recommended for patients who achieved successful reperfusion [30]. A recent international multicenter cohort study demonstrated that higher BP within the first 24 hours after successful endovascular treatment was associated with a higher risk of secondary ICH, mortality, and hemicraniectomy [31]. Moreover, when the patients were divided into three groups based on the SBP goal for the first 24 hours after endovascular treatment (< 140 mmHg, < 160 mmHg, and < 180 mmHg), SBP goals of < 140 mmHg following successful reperfusion with endovascular treatment appeared to be associated with better clinical outcomes than SBPs < 160 and < 180 mmHg [32]. Moreover, after reperfusion, lower BP goals have been proposed due to concerns about hemorrhagic complications and reperfusion injury.

However, another recent analysis of individual patient data from three separate RCTs showed that critical MAP thresholds and durations for poor outcome after endovascular treatment were found to be those < 70 mmHg for more than 10 minutes and those > 90 mmHg for more than 45 minutes [33].

Typically, higher baseline BPs in AIS patients with large vessel occlusions or severe stenosis is associated with better collateral flow. However, a previous study has showed that greater infarct growth was observed in patients without reperfusion, leading to an unfavorable clinical outcome, even in those with a higher baseline BP. Contrarily, a higher baseline BP was associated with decreased infarct growth in patients with successful reperfusion. Therefore, the relationship between baseline BP and outcomes is highly dependent on reperfusion status, and active BP-lowering treatments may be inappropriate in AIS patients prior to reperfusion treatments [34].

In this regard, setting a target BP before and after intravenous thrombolysis treatment and intra-arterial endovascular treatment was difficult. As cerebral autoregulation is impaired in patients with AIS, BP control may be important for improving clinical outcomes. Based on the present knowledge, multiple factors related to clinical outcomes must be considered in order to determine the BP target, including the reperfusion status (successful or not), baseline BP prior to treatment, MAP during treatment, and hemorrhagic transformation after reperfusion treatment (yes or no), and the BP target may be continuously adjusted based on the situation.

Acute phase of ischemic stroke

An acute hypertensive response can also be observed in patients with AIS. It is usually self-limiting, and the BP spontaneously falls over the week after the onset of stroke [10,35]. However, since the acute hypertensive response to stroke is known to be an independent predictor of poor outcome, it is necessary to maintain optimal BP during the acute stroke period. Many previous trials and studies have investigated the optimal BP level and the effect of early, rapid lowering of elevated BP, however, no ideal BP has been established. A higher BP may be beneficial for the penumbra, which is viable but under-perfused, by increasing collateral flow. On the other hand, a higher BP may increase the risk of hemorrhagic transformation and cerebral edema [36]. In contrast, lowering BP may potentially increase the risk of infarction growth.

BP control recommendations vary depending on the comorbid conditions. According to the AHA/ASA guidelines, early treatment is indicated in patients with severe acute comorbidities such as acute coronary event, acute heart failure, aortic dissection, post-fibrinolysis spontaneous intracranial hemorrhage, hypertensive emergency, or pre-eclampsia/eclampsia (class I, LOE C-EO). An excessive decrease in BP can exacerbate cerebral infarction and should be noted [37], and BP management in these situations should be individualized. Although there is no standard, it is generally considered safe and reasonable to lower BP by 15% from baseline.

For patients who did not receive intravenous alteplase or endovascular treatment and those without comorbid conditions, the recommendations differ based on the BP level. In patients with a BP ≥ 220/120 mmHg, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain (class IIb, LOE C-EO). Patients with severe hypertension were excluded from clinical trials, and the effects of rapid BP reduction have not been formally studied. However, it is generally considered reasonable to lower BP by 15% during the first 24

hours after stroke onset.

In patients with a BP < 220/120 mmHg, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after AIS is safe, but not effective in preventing death or dependency (class III: no benefit, LOE A). Except for a few previous studies, the Intravenous Nimodipine West European Stroke Trial (INWEST) [38] and Very Early Nimodipine Use in Stroke (VENUS) [39] trial, which reported that early BP control was associated with worse of outcomes, most RCTs, the Prevention Regimen To Effectively Avoid Second Strokes (PRoFESS) [40], scandinavian candesartan acute stroke trial (SCAST) [41], Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) [42], Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) [43], ENCHANTED [27], and efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS) [44] trials and two meta-analyses [45,46] have consistently shown that initiating or reinitiating antihypertensive therapy within the first 48 to 72 hours after AIS is safe, although this strategy is not associated with improved mortality or functional outcomes. The International Stroke Trial (IST) [35] showed a U-shaped response between BP level and mortality. An SBP level around 150 mmHg was associated with the lowest risk of mortality and poor outcomes of death or dependency.

Persistent hypotension is uncommon in AIS. If a patient does have persistent hypotension, potential caused should be investigated, to look for issues such as aortic dissection, hypovolemia, and decreased cardiac output due to myocardial infarction or arrhythmia. Management of hypotension in patients with AIS has not been well studies. Some observational studies have shown an association between worse outcomes and lower BP, whereas others have not [35,47-49]. The 2019 AHA/ASA guidelines recommend that hypotension and hypovolemia should be corrected to maintain systemic perfusion levels sufficient to support organ function (class I, LOE C-EO).

In patients with a BP > 140/90 mmHg who are neurologically stable, starting or restarting antihypertensive therapy during hospitalization is safe (class IIa, LOE B-R) and has been shown to be associated with improved control of BP after discharge in both the COSSACS [43] and china antihypertensive trial in acute ischemic stroke (CATIS) [50] trials. These studies included only patients with a previous diagnosis of hypertension, or enrolled primarily

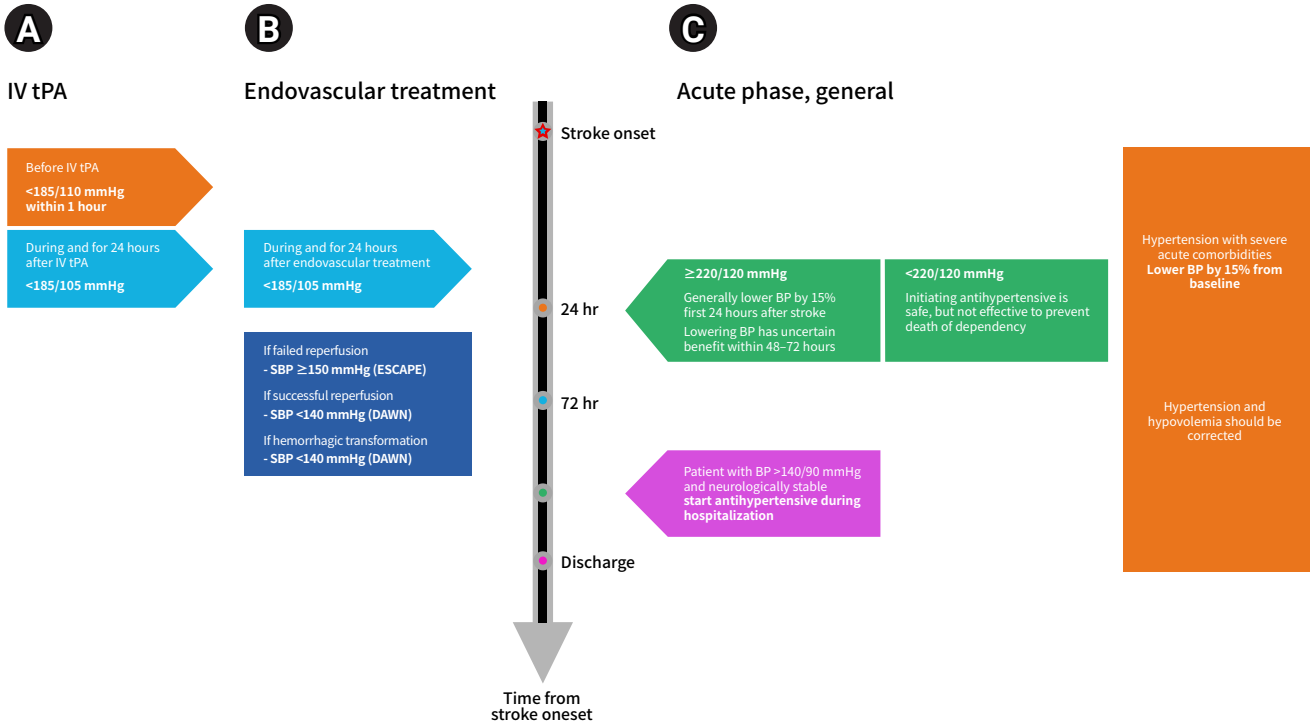

Fig. 1. Blood pressure (BP) management according to treatment of ischemic stroke; (A) intravenous thrombolysis (IV tPA), (B) endovascular treatment, and (C) not indicated for reperfusion therapy and secondary stroke prevention. SBP, systolic blood pressure; ESCAPE, endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing computed tomography (CT) to recanalization times; DAWN, diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention.

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patients with previous hypertension. However, it is also reasonable to apply this recommendation to patients without preexisting hypertension. BP management based on treatment of ischemic stroke is summarized in Fig. 1.

BP control for secondary ischemic stroke prevention

The majority of patients with ischemic stroke have hypertension, and lowering BP may be critical in preventing recurrent stroke. Several RCTs have focused on this issue. The Post-Stroke Antihypertensive Treatment Study (PATS) randomized 5,665 patients with stroke or TIA into two groups, indapamide 2.5 mg or placebo. After 2 years, indapamide 2.5 mg was found to significantly reduce recurrent stroke, with a hazard ratio (HR) = 0.70 and 95% CI, 0.57–0.86 [51]. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) randomized 6,105 patients with stroke or transient ischemic attack (TIA) into two groups, perindopril or placebo. After 4 years, it was found that perindopril reduced recurrent stroke significantly, HR = 0.78 and 95% CI, 0.62–0.83 [52]. However, the PRoFESS study randomized 20,322 patients into two groups, telmisartan or placebo, and failed to show a benefit in reducing recurrent stroke or composite vascular events after 2.5 years of follow-up [53]. In a meta-analysis including 10 RCTs with a total of 38,421 patients, lowering BP with medication significantly reduced stroke, OR = 0.78 and 95% CI, 0.68–0.90 [54]. Typically, a J-curve was observed from trials on the secondary prevention of coronary artery disease using diastolic BP (DBP). Post-hoc analysis of the PRoFESS study, however, did not reveal a J-curve between BP and recurrent stroke [55]. Furthermore, stroke mortality continuously decreases as SBP decreases under 120 mmHg [56]. However, the effects of and target for BP lowering in ischemic stroke may differ based on the mechanism of stroke.

In patients with symptomatic carotid occlusions, the results of the COSSACS study showed that the effect of lowering BP < 130/85 mmHg was a lower risk of ipsilesional ischemic stroke compared to those with BP > 130/85 mmHg (HR = 0.27; 95% CI, 0.08–0.94) [57]. In another study that included patients with symptomatic carotid stenosis, lowering SBP to 140 mmHg continuously decreased the risk of stroke. BP may be safely lowered to 140 mmHg in those with carotid stenosis. However, it was found that if the stenosis was > 70%, the risk of stroke increased as BP decreased. This may be explained by poor collateral flow of the contralateral carotid artery in severe bilateral carotid stenosis [58].

Symptomatic intracranial atherosclerosis is more common than symptomatic extracranial stenosis in patients in Asia. In the post-hoc analysis of Warfarin Aspirin Symptomatic Intracranial Disease (WASID) study, various risk factors were associated with vascular events. Among them, SBP > 140 mmHg showed a higher risk of major cardiovascular events (HR = 1.79; 95% CI, 1.27–2.52) [59]. In regards to the progression of atherosclerotic burden

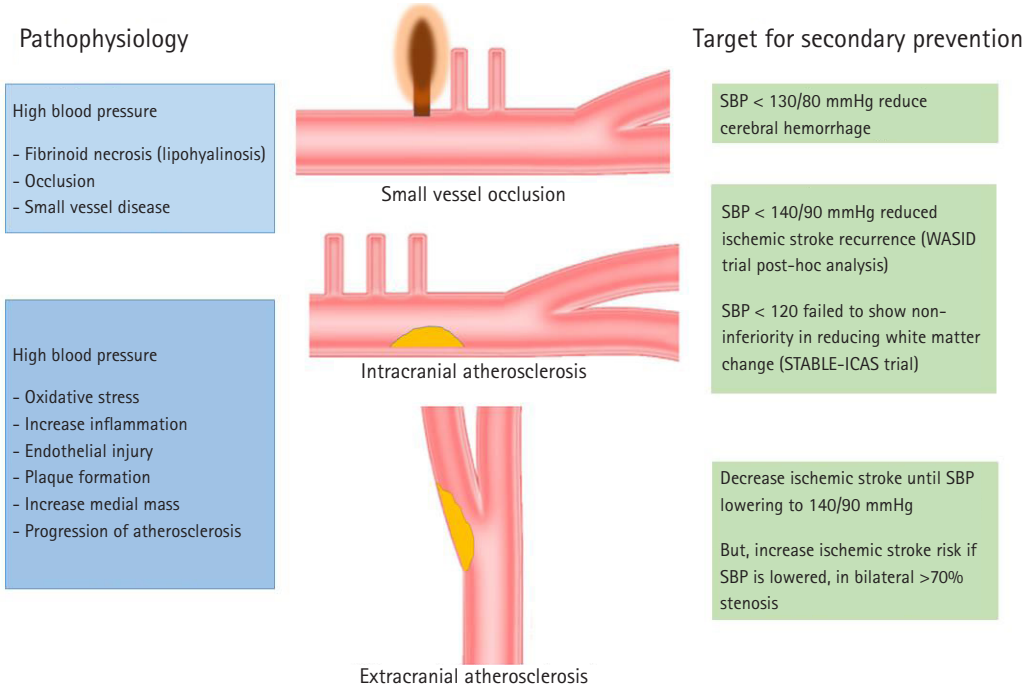

Fig. 2. Pathophysiology and blood pressure target according to ischemic stroke mechanisms. SBP, systolic blood pressure; WASID, Warfarin Aspirin Symptomatic Intracranial Disease; STABLE-ICAS, strategy for adequate blood pressure lowering in the patients with intracranial atherosclerosis.

in intracranial atherosclerosis, the post-hoc analysis of the Trial of Cilostazol in Symptomatic Intracranial Stenosis (TOSS)-2 study showed the lowest rate of progression between 120 and 160 mmHg [60]. The strategy for adequate blood pressure lowering in the patients with intracranial atherosclerosis (STABLE-ICAS) compared two strategies of BP lowering—intense (target SBP 110–120 mmHg) and standard (target SBP 130–140 mmHg)—on the expansion of white matter hyperintensity lesions. That study was designed as a non-inferiority trial, and failed to show the non-inferiority of intense BP lowering compared to standard BP lowering [61]. There is no evidence based on which to lower BP intensively in patients with intracranial atherosclerosis, and they should be treated with a target SBP between 120 and 140 mmHg.

Small vessel disease is significantly associated with hypertension. The Secondary Prevention of Small Subcortical Strokes (SPS-3) trial was a well-designed RCT focusing on the target BP for lacunar infarction. Using a 2×2 factorial design, the BP arm was an open label trial, comparing the effects of target SBPs of 130–139 and < 130 mmHg. The primary endpoint was reduction in stroke, which failed to show a statistical significance between the two groups (HR = 0.81; 95% CI, 0.64–1.03). However, the lower target group significantly reduced the risk of ICH (HR = 0.37; 95% CI, 0.15–0.95) [7]. Therefore, lowering BP under 130 mmHg may be beneficial in patients with small vessel disease.

Based on these trial results, the ASA/AHA guidelines on the secondary prevention of stroke suggest controlling BP in patients with an established SBP higher than 140 mmHg or DBP higher than 90 mmHg. A reasonable target for lowering BP is < 140/90 mmHg. In particular, for patients with small vessel disease or lacunar infarction, a reasonable target BP was suggested as SBP < 130 mmHg [62]. Pathophysiology and target BP based on ischemic stroke mechanisms are summarized in Fig. 2.

CONCLUSION

The management of BP in stroke is complex and challenging due to the variety of stroke subtypes, heterogeneous etiologies, hemodynamic statuses, and comorbidities. Recent data have suggested that lowering BP in acute ICH is probably safe; however, if BP is lowered rapidly in the acute phase, adverse renal events may occur. BP management in AIS remains problematic, and questions such as when to start antihypertensive medications and how significantly to reduce BP have yet to be answered. Large RCTs have not demonstrated the benefit of lowering BP earlier, but the comorbidities, baseline BP, and stroke mechanism should be considered, and the time and target of lowering BP must be individualized based on this information. When reperfusion is achieved through thrombolysis or thrombectomy, lowering BP reduces the risk of hemorrhagic complications. For secondary stroke prevention, BP targets may differ based on the stroke mechanism; intensive lowering of BP may be beneficial in patients with small vessel disease.

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Minimal-risk traumatic brain injury management without neurosurgical consultation

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ORIGINAL ARTICLE

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Background: Traumatic brain injury (TBI) with intracranial hemorrhage management results in clinical practice variability, complexity, and/or limitations in acute care surgical and radiological workflow, which can prompt neurosurgical consultation, even when unnecessary. To facilitate an interdisciplinary practice for minimal-risk TBI, our objective was to create and sustain a neurotrauma protocol change that we hypothesized would not result in outcome differences.

Methods: A retrospective pre-post cohort study was conducted over an 8-month period to evaluate the protocol change toward trauma team management of TBI with isolated pneumocephalus and/or subarachnoid hemorrhage (SAH) given a normal neurologic exam (i.e., minimal-risk TBI) without neurosurgery consultation. Demographics of age and Glasgow coma scale (GCS) were collected and expressed in means. Target outcomes consisted of protocol compliance, management compliance (e.g., nursing neurologic checks, thromboembolism prophylaxis, seizure prophylaxis, speech-cognitive testing, follow-up), neurological worsening, increasing therapeutic intensity levels, and TBI-related 30-day readmission.

Results: Of the 49 patients included, 21 were in the pre-group (age, 54.19 years; GCS, 15) and 28 were in the post-group (age, 52.25 years; GCS, 15). There was 5% and 36% non-compliance with pre- and post-protocol practices in terms of neurosurgery consultation rates. In both pre- and post-periods, management compliance was similar, and none of the TBI patients experienced a worsening neurologic exam, increased therapeutic intensity level, or re-admission.

Conclusion: Minimal TBI-risk protocol compliance was weaker after the practice change although management compliance and outcomes remained unchanged. This work supports that minimal-risk TBI patients with SAH and normal neurologic exams can be safely managed by trauma teams without neurosurgery consultation.

Keywords: Trauma; Nervous system; Brain Injuries; Traumatic; Brain Injuries

INTRODUCTION

Management of severe brain injuries can require invasive neurosurgical intervention, such as intracranial monitoring, surgical removal of skull fragments for relief of cerebral edema, or surgical evacuation of intracranial hemorrhage. Minimal-risk traumatic brain injuries (TBIs), on the contrary, can be managed almost exclusively without surgical or invasive interventions [1] and such consults may be medically unnecessary [1,2]. Minimal-risk TBI can be defined as an injury of blunt mechanism with Glasgow coma scale (GCS) 15, no baseline use of anticoagulants/antiplatelets, no witnessed seizures, and admission head computed tomography (CT) radiographic pattern including either isolated pneumocephalus without displaced skull fracture and/or subarachnoid hemorrhage without displaced skull fracture. Further, it has been noted that neurosurgical consultation for management of these minimal-risk TBIs can overburden neurosurgery providers [1,2].

In one practice environment, brain injury guidelines were created and categorized TBI into three tiers based on a variety of injury-related radiographic and clinical factors. These three tiers of TBI were then associated with treatment plans [3]. This work supported that minimal-risk TBIs can be safely and effectively managed without the consultation of a neurosurgery service [3], and has the potential to reduce cost [4]. Variability in complexity and/or limitations in acute care surgical and radiological workflow can lead to neurosurgical consultation, even when clinically unnecessary based on existing evidence.

To facilitate a first step toward modifying interdisciplinary neurotrauma practice, our objective was to create and sustain a quality improvement protocol change for minimal-risk TBI management. We hypothesized the protocol change in practice towards exclusive trauma team leadership of minimal-risk TBI (i.e., no neurosurgery consultation) would not result in outcome differences with respect to protocol compliance, management compliance (e.g., nursing neurologic checks, thromboembolism prophylaxis, seizure prophylaxis, speech-cognitive testing, follow-up), neurological worsening, increasing therapeutic intensity levels, and TBI-related 30-day readmission.

METHODS

A retrospective pre-post cohort study was conducted over an 8-month period to evaluate the protocol change toward trauma team leadership (without neurosurgery consultation) of adult blunt mechanism TBI patients fitting the criteria of minimal-risk TBI. The quality improvement protocol applied to individuals meeting the aforementioned inclusion criteria for minimal-risk TBI. For these patients, neurosurgery consultation was not indicated. These patients received neurological checks every 4 hours, a speech therapy consult was placed for in-depth cognitive evaluation, deep-venous thrombosis (DVT) prophylaxis was held according to established institutional practice [5], and levetiracetam was ordered for post-TBI seizure prophylaxis per existing institutional protocol [6]. The admission head CT radiographic pattern was either isolated pneumocephalus without displaced skull fracture and/or subarachnoid hemorrhage without displaced skull fracture. Data sources included the electronic medical record, the trauma registry, daily trauma census, and radiology images.

All other neurotrauma injury patterns on admission head CT were excluded (e.g., subdural hemorrhage, epidural hemorrhage, intraparenchymal hemorrhage or contusion, intraventricular hemorrhage, depressed skull fracture). Our quality improvement change also excluded patients with observed injury-related seizures or those on anticoagulants and/or antiplatelet agents (see Fig. 1 for eligibility criteria). This conservative focus on minimal-risk TBI patients served as an acceptable institutional strategy across the disciplines of emergency medicine, radiology, trauma surgery, nursing, and neurosurgery.

Our aforementioned eligibility criteria and protocol change (i.e., no neurosurgery consultation for those eligible) were incorporated into a management guideline (Fig. 1). The document was then disseminated electronically to all emergency department faculty and residents; trauma faculty, fellows, and residents; trauma advanced practice providers; multidisciplinary trauma performance improvement team members (including radiology); and neurosurgery faculty and residents.

Demographics of age, sex, and GCS were collected and expressed in medians. The mechanism of injury and initial head CT findings (brain injury type) were noted for each patient as well as the status of neurosurgical consultation (i.e., presence or absence). Our outcomes consisted of protocol compliance, management compliance (e.g., nursing neurologic checks, thromboembolism prophylaxis, seizure prophylaxis, speech-cognitive testing, follow-up), neurological worsening (as defined by decline in GCS of 1 or more points that is unexplained by alternative cause), increasing therapeutic intensity levels, and TBI-related 30-day readmission.

TBI management compliance was defined using five elements that were captured and identically relevant in the pre- and post-implementation periods. Orders were assessed for pharmacologic DVT prophylaxis being held for 72 hours following the time of admission for TBI [5]. Similarly, orders were reviewed for institutional seizure prophylaxis protocol compliance [6]. Formal cognitive evaluation by speech therapy and frequency of neurologic exams were also captured. Neurological exam orders placed outside

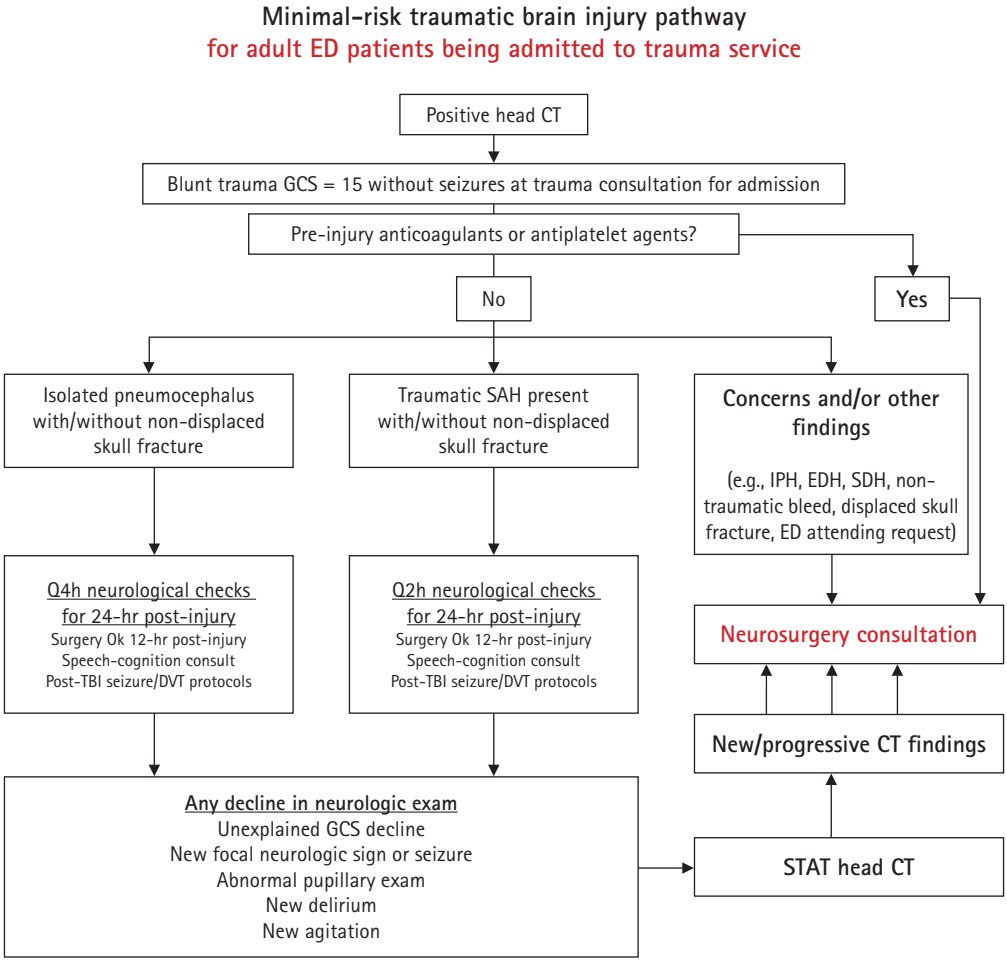

Fig. 1. Minimal-risk traumatic brain injury without neurosurgery. ED, emergency department; CT, computed tomography; GCS, Glasgow coma scale; SAH, subarachnoid hemorrhage; IPH, intraparenchymal hemorrhage; EDH, epidural hemorrhage; SDH, subdural hemorrhage; Q4h, every 4 hours; Surgery OK 12 hr post-injury, surgery authorized on/after 12 hours post-injury; Q2h, every 2 hours; TBI, traumatic brain injury; DVT, deep-venous thrombosis.

of 2 hours from admission orders were considered compliance failure. Lastly, trauma clinic follow-up orders were assessed for compliance. Table 1 highlights the timing thresholds for each management compliance metric. Results are presented using descriptive statistics (n, %) for pre- and post-periods. Comparisons between groups were conducted using independent samples *t*-tests, chi-square, or Fisher's exact tests. IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) was used to conduct statistical analyses with alpha set to 0.05.

RESULTS

Of the 49 patients included in this retrospective study, 21 were in the pre-intervention group and 28 were in the post-intervention group. Demographic information including age, biologic sex, admission GCS, mechanism of injury, and TBI type for each group is shown in Table 2. Subarachnoid hemorrhage without presence of skull fracture on admission head CT was the most common minimal-risk TBI type in both groups; pre-protocol (n = 16, 76.2%) and post-protocol (n = 25, 89.3%).

Of the patients in the pre-protocol group, 20 (95.2%) had neurosurgery consults placed for TBI management. One patient (5%) in the pre-protocol group had a neurosurgery consult placed for spinal injuries. For this patient, separate recommendations for TBI management were not included in the neurosurgery notes (i.e., protocol non-compliance). Ten patients (35.7%) in the post-protocol group inappropriately received a neurosurgery consult for TBI management (i.e., protocol non-compliance). In both pre- and post-implementation periods, management compliance was similar (Table 3), and none of the TBI patients experienced a worsening neurologic exam, increased therapeutic intensity level, or re-admission for complaint related to TBI within thirty days of

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Table 1. Minimal-risk TBI management domains

Order	Order entry timing
Neurologic evaluation checks at appropriate time intervals	Within 2 hours of admission
TBI seizure prophylactic guidelines	Within 1 hour of admission
Withholding DVT prophylaxis	Held for 72 hours following time of injury
Cognitive evaluation	During hospitalization
Follow-up request for trauma clinic	By time of discharge

A retrospective pre-post cohort study was conducted over an 8-month period to evaluate the protocol change toward trauma team management of TBI with isolated pneumocephalus and/or subarachnoid hemorrhage given a normal neurologic exam (i.e., minimal-risk TBI) without neurosurgery consultation.
TBI, traumatic brain injury; DVT, deep-venous thrombosis.

Table 2. Patient demographics of minimal-risk TBI

Variable	Pre-protocol implementation (n=21)	Post-protocol implementation (n=28)
Age (yr)	54.19±20.28	52.25±20.54
Male (%)	52.38	57.14
GCS 15 (%)	100	100
Mechanism of injury		
MVC[a]	4 (19.0)	14 (50.0)
Assault	2 (9.5)	0
Fall (ground level)	7 (33.3)	5 (17.9)
Fall (from height)	2 (9.5)	4 (14.3)
Other blunt mechanism	6 (28.6)	5 (17.9)
AC/AP	0	0
TBI type		
SAH with non-displaced skull fracture	1 (4.8)	1 (3.6)
SAH without skull fracture	16 (76.2)	25 (89.3)
Pneumocephalus with non-displaced skull fracture	2 (9.5)	0
Pneumocephalus without skull fracture	2 (9.5)	2 (7.1)

Values are presented as mean±standard deviation or number (%). A retrospective pre-post cohort study was conducted over an 8-month period to evaluate the protocol change toward trauma team management of TBI with isolated pneumocephalus and/or SAH given a normal neurologic exam (i.e., minimal-risk TBI) without neurosurgery consultation.
TBI, traumatic brain injury; GCS, Glasgow coma scale; MVC, motor vehicle collision; AC/AP, anti-coagulant/anti-platelet use; SAH, subarachnoid hemorrhage.
[a]Significant difference at α=0.05.

discharge.

DISCUSSION

Although our minimal-risk TBI protocol compliance was weaker after the practice change (i.e., at times, older practices continued), our management compliance and outcomes remained unchanged, thus supporting existing literature that minimal-risk TBI patients with subarachnoid hemorrhage and normal neurologic exams can be safely managed by trauma team leadership without neurosurgery consultation. When evaluating patient outcomes, none of the patients in either group meeting mild TBI criteria experienced a worsening neurologic exam that required repeat imaging, invasive measures, or escalation of care during hospitalization. There was no change in 30-day readmissions related to TBI. These results also support that a minimal-risk TBI patient can be safely and effectively managed without a neurosurgery consultation based on existing practice management guidelines [1,3].

One limitation of this minimum-risk TBI study is the sample size. Ideally, one future direction for this protocol change is to grow the target population to encompass more patients meeting the generalized mild TBI definition, as outlined in existing studies [1,7-9]. Another noted limitation is its retrospective nature. This could be potentially limiting due to reliance on the unstructured text documentation, and potential inability to note pertinent or confounding variables due to lack of documentation. In addition, the minimal-risk TBI population was a smaller, more conservative target population that may have limited our observations of ad-

Table 3. Minimal-risk compliance with TBI management

Outcome	Pre-protocol (compliant, consult of neurosurgery)	Pre-protocol (non-compliant)	Post-protocol (non-compliant)	Post-protocol (compliant, no consult of neurosurgery)	*P*-value[a]
SAH	16	1	10	16	0.307
Neurocheck complete	7 (43.8)	0	6 (60.0)	11 (68.8)	
Neurocheck incomplete	0	0	1 (10.0)	0	
Not ordered	9 (56.2)	1 (100.0)	3 (30.0)	5 (31.2)	
Pneumocephalus	4	0	0	2	0.472
Neurocheck complete	1 (25)	-	-	1 (50)	
Neurocheck incomplete	2 (50)	-	-	0	
Not ordered	1 (25)	-	-	1 (50)	
Cognitive evaluation	17 (85)	0	10 (100)	16 (88.9)	0.033
DVT prophylaxis held for 72 hours post-TBI	13 (65.0)	0	7 (70.0)	14 (77.8)	0.385
Seizure prophylaxis	16 (100.0)	1 (100.0)	9 (90.0)	15 (83.3)	0.876
Follow-up clinic order	16 (100.0)	1 (100.0)	8 (80.0)	17 (94.4)	0.555

Values are presented as number (%). A retrospective pre-post cohort study was conducted over an 8-month period to evaluate the protocol change toward trauma team management of TBI with isolated pneumocephalus and/or SAH given a normal neurologic exam (i.e., minimal-risk TBI) without neurosurgery consultation.
TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; Neurocheck complete, assesses the accuracy with which neurologic checks were ordered, such that neurological exam orders placed outside of 2 hours from admission orders were considered compliance completions; Neurocheck incomplete, assesses the accuracy with which neurologic checks were ordered, such that neurological exam orders placed outside of 2 hours from admission orders were considered compliance failures; DVT, deep-venous thrombosis.
[a]Significant difference at α=0.05.

verse events. However, given priorities of patient safety, optimal implementation, and quality improvement, this approach of assessing minimal TBI patients was a strategically safe and appropriate first step. We noted an additional limitation where 35.7% of patients in the post-protocol group had inappropriate Neurosurgery consultations, and we believe this can be explained by the general challenge with implementing quality improvement change guidelines as providers tend to revert to historical practice. Another limitation is the reliance on different radiologists' interpretations of head CT findings. Additionally, results may not necessarily be generalizable as this study was executed at a single academic medical institution, but we crafted our minimal-risk TBI protocol to be broadly applicable without a neuroradiologist, for example, clinical safety was prioritized over rigorous subarachnoid hemorrhage classification to facilitate execution in other institutions where this expertise is not available.

Strengths of this study include the analysis of objective measures such as order entry which can easily be evaluated in chart review. Standardized chart review processes also strengthened the data collection process of this study. However, there is general opportunity for improvement in each of the TBI-related management orders based on existing protocols and practices at our institution. A potential method for improvement could include an electronic order set within the medical record that would trigger providers to enter the target TBI-management orders. By developing a minimal-risk TBI order set, the template could then be copied into the consult notes of TBI patients, and therefore would prompt providers to order elements of the minimal TBI management pathway more consistently.

This study supports existing evidence that patients who present neurologically intact with low-risk, blunt mechanism TBIs with intracranial hemorrhage can be safely managed by a mature trauma team without the need for neurosurgical consultation. Although this was a retrospective cohort study on a subgroup of a mild TBI population, the results are encouraging for this protocol to be further expanded in a more generalizable mild TBI population. In summary, the implementation of a new protocol to manage minimal TBI patients without neurosurgical consultation yielded no significant negative patient outcomes and supports the claim that minimal-risk TBI patients managed with the application of this protocol are done so in a way comparable to a prior era with neurosurgical consultation.

ARTICLE INFORMATION

Ethics statement

This quality improvement project was submitted to Institutional Review Board of Institutional Review Board of Vanderbilt University Medical Center, Health Sciences Committee I (No. IRB00000475) and approved on May 2, 2019. Owing to the ret-

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rospective design, the requirement for informed consent was waived.

Conflict of interest

No potential conflict of interest relevant to this article.

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The etiologies of altered level of consciousness in the emergency department

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ORIGINAL ARTICLE

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Background: New-onset altered level of consciousness (ALC) is a common condition in patients visiting the emergency department (ED). We evaluated the clinical characteristics, causes, and prognosis of adult patients presenting with ALC at an ED of a university hospital to determine the etiologies, outcomes, and destinations of these patients.
Methods: The medical records of patients with ALC who visited the ED of a university hospital from February 2019 to January 2020 were reviewed. The cause of ALC and its classification were carefully decided by agreement through a discussion among board-certified clinicians in emergency medicine, neurology, and internal medicine.
Results: Of the 731 patients with ALC in the ED, whose mean age was 68.81±16.40 years, most were in their 80s (198, 27.09%). The most common etiology of ALC was systemic infection (30.78%), followed by metabolic causes (21.07%) and stroke (18.19%). Extracerebral and intracerebral etiologies of ALC in the ED accounted for 51.85% and 26.68% of the cases, respectively. The overall mortality of ALC in the ED was 17.67%. The largest number of ALC cases of 443 patients, i.e., 60.6% of all ALC patients in the ED, visited within the time zone of 07:00–19:00.
Conclusion: This study identified the extra-cerebral etiologies as the major causes of ALC in the ED.

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

INTRODUCTION

New-onset altered level of consciousness (ALC) is a common condition in patients visiting the emergency department (ED). ALC is a state of altered attention or arousal, not caused by physiological drowsiness. It refers to any change in the patient's consciousness level from the baseline and is related to neurological manifestations of not only neurological diseases but also general medical illnesses [1].

Several studies have evaluated the cause of ALC in the ED. ALC can be caused by various diseases of a wide range of urgency and severity and has been reported from 5% to 40% of the patients visiting the ED, depending on how the population was defined in those previous studies [2-5]. Kanich et al. [1] reported that the most common causes of ALC in the ED were neurological causes (28%), followed by intoxications (21%), traumas (21%), psychi-

atric causes (14%), and infections (10%). Völk et al. [4] reported that approximately a quarter of all ALC cases in the ED were attributable to cerebrovascular diseases (24%), followed by systemic infections (12%), epileptic seizures (12%), psychiatric disorders (8%), metabolic causes (7%), and intoxications (7%). A recent German study of coma patients in the ED showed that intracranial hemorrhages (22%), epileptic seizures (22%), intoxications (19%), cerebral infarctions (11%), and metabolic causes (6%) were the common causes of coma [5]. In a Turkish study involving 790 patients with ALC in the ED [6], the etiologies were neurological problems (71.6%), trauma (10.4%), metabolic causes (6.1%), cardio-pulmonary disorders (6.2%), systemic infections (3.8%), gynecologic and obstetric causes (0. 4%), and intoxications (1.5%).

Since ALC is a classic life-threatening condition, the patients are given priority and medical resources are intensively infused into the patients with ALC used in these cases. Nonetheless, ALC in the ED is an intricate challenge for clinicians because the presentation of ALC itself is not always typical, does not indicate a diagnosis, and can change rapidly. We evaluated the clinical characteristics, causes, and prognosis of adult patients presenting with ALC to an ED of a university hospital to determine the etiologies, outcomes, and the destinations of these patients. This is the first study to analyze the etiology of ALC in the EDs in the context of South Korea.

METHODS

This is a retrospective study in which we reviewed the medical records of patients with ALC who visited the ED of a university hospital from February 2019 to January 2020 to find patients whose initial Glasgow Coma Scale (GCS) score was not 15 (15 being the perfect score, indicating fully awake). The GCS grader was the first doctor to examine the patient, and was either the chief resident in charge or a faculty member in emergency medicine. We reviewed the patients' medical records from the time of entry to the ED to discharge from the hospital. Patients under the age of 18 years were excluded, as the causes of altered mental status in children are different from those in adults. Cases of ALC after cardiac arrest and ALC after visiting the ED were excluded from the analysis. In addition, all patients transferred from other hospitals were excluded in order to exclude patients with existing ALC, such as those with severe dementia, stoke, or psychiatric disorders. Revisit at more than 24 hours after discharge was considered a new visit.

Based on the medical records, the patients' age, sex, history, tentative diagnosis in the ED, treatment, destination from the ED and discharge were reviewed. The following evaluation reports were reviewed: vital sign records, physical examination, neurological examination, electrocardiogram, chest radiography, laboratory results, brain computed tomography, brain magnetic resonance imaging, cerebrospinal fluid (CSF) analysis, and electroencephalography. The cause of ALC and its classification were determined after discussion with the authors, who are board-certified clinicians in emergency medicine, neurology, and internal medicine. The reference point for determining the cause of ALC in this study was the time of discharge from the ED. Thus, the tentative cause of ALC in the ED could differ from the definitive diagnosis at discharge. In addition, during the review of the medical records, the authors assessed which work-up was decisive in reaching the diagnosis of the ALC in the ED.

Student *t*-test was used to compare the prognosis and destination from the ED. The statistical test was two-tailed, and $P < 0.05$ was considered statistically significant. IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA) was used for analysis.

RESULTS

Patient characteristics

From February 2019 to January 2020, a total of 42,376 patients visited the ED. Pediatric patients (age < 18 years) and cases of cardiac arrest, death on arrival, and revisit within 24 hours were excluded. A total of 32,149 patients were reviewed, resulting in 731 eligible patients with ALC in the ED, whose mean age was 68.81 ± 16.40 years (427 females, 54.5%) (Table 1, Fig. 1). Most patients were in their 80s, accounting for 27.09% (n = 198) of the patients with ALC in the ED. The combined number of patients in their 70s and 80s was 391, accounting for 53.49% of the study population (Table 1).

Destination of patients from ED

Thirty patients died in the ED without being admitted to the general ward or intensive care unit (ICU) or transferred to another

Table 1. Demographic data of the patients with ALC in the ED

Variable	No. (%) (n=731)
Female sex	427 (54.5)
Age (yr)	
≤ 29	20 (2.74)
30–39	37 (5.06)
40–49	35 (4.79)
50–59	92 (12.59)
60–69	127 (17.37)
70–79	193 (26.40)
80–89	198 (27.09)
≥ 90	29 (23.97)

ALC, altered level of consciousness; ED, emergency department.

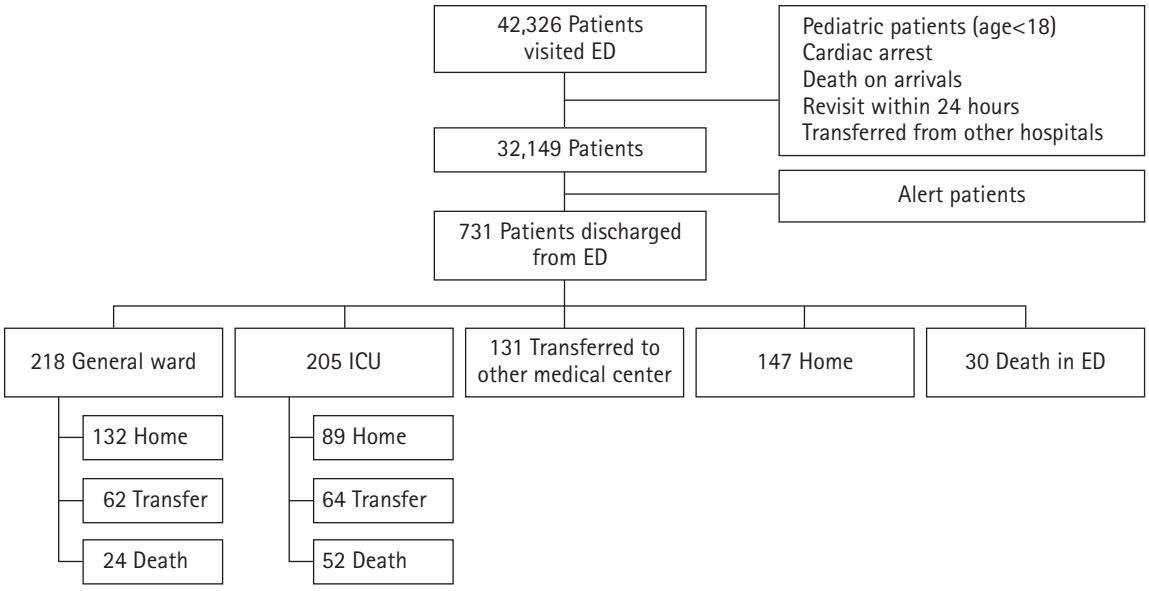

Fig. 1. Enrollment, destinations from emergency department (ED), and results of patients with altered level of consciousness (ALC). ICU, intensive care unit.

hospital. The most common causes of the decease-in-ED were complications related to ALC, such as systemic infection followed by shock, metabolic causes resulting in cardiac arrest, and cardiac arrest due to arrhythmia. Additionally, in three cases, there were two or more causes of death aside from ALC, but this could not be specified. Only one stroke patient died and no patients with seizure or central nervous system (CNS) infection died in the ED.

All the 147 ALC patients sent home eventually recovered consciousness after arriving in the ED; 131 were transferred to another hospital for emergency surgery, lack of hospital rooms, or the guardian's demand. Of the 423 hospitalized patients, 218 were hospitalized in the general wards, and 205 in the ICU. Of the 205 in the ICU, 112 were admitted after emergency surgery (Fig. 1). Of the 218 patients hospitalized in the general ward, 132 were sent home; 62 transferred to other hospitals after acute management; and 24 (11.01%) died eventually. Of the 205 patients admitted to the ICU, 89 were sent home; 64 transferred to another hospital after acute management; and 52 (25.37%) died. Although there were no statistical differences in mortality between the etiologies of ALC in the ED, the mortality was higher in the ICU than in the general ward (25.37% vs. 11.01%, $P=0.000$).

Etiologies of ALC in the ED

The causes of ALC vary. The identified etiologies of ALC in the ED are listed in Table 2 and illustrated in Fig. 2. The authors classified the etiologies as follows: systemic infection, metabolic causes, stroke, cardiogenic causes, seizure, toxicity, psychiatric disorders, traumatic brain injury (TBI), CNS infection, and undetermined. The leading cause of ALC in the ED was systemic infection, which accounted for approximately 30% of the cases, namely sepsis, septic shock, and acute confusion caused by fever, where CNS infection was excluded through CSF analysis. The second main cause was metabolic cause (154, 21.07%), which can be diagnosed on the basis of a significant abnormality in blood test findings, such as hyponatremia, hypoglycemia, diabetic ketoacidosis, hepatic encephalopathy, uremic encephalopathy, posterior reversible encephalopathy syndrome, and hyperammonemia. The third main cause was stroke (133, 18.19%), diagnosed when the acute CNS symptoms were compatible with the brain lesions found on neuroimaging. There were 51 patients (6.98%) developed ALC because of heart problems, such as sick sinus syndrome, ventricular tachycardia, paroxysmal supraventricular tachycardia, and myocardial infarction. Regardless of the presence of epilepsy, 51 patients (6.98%) developed ALC because of seizures. This group included patients with epileptic seizure as well as psychogenic non-epileptic seizure. Further, 44 (6.02%) and 16 (2.19%) patients developed ALC from toxic agents and psychiatric disorders, respectively. The "toxic agents" were sedatives, pesticides, chemical agents, anaphylaxis, and adverse effect of medications. In six patients (0.82%), ALC was caused by TBI, including two cases of concussion. There were five cases of CNS infection, three of which were viral, one bacterial, and one fungal. Despite 1 or 2 days of intensive evaluation in the ED, the cause of ALC remained undetermined in 46 patients.

Etiologies of ALC in the ED by time zone

The patient configuration by time zone is shown in Table 3 and il-

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Table 2. The causes of ALC in the ED

Etiology	No. (%) (n=731)
Systemic infection	225 (30.78)
Metabolic cause	154 (21.07)
Stroke	133 (18.19)
Cardiogenic	51 (6.98)
Seizure	51 (6.98)
Toxicity	44 (6.02)
Psychiatric	16 (2.19)
Traumatic brain injury	6 (0.82)
CNS infection	5 (0.68)
Undetermined	46 (6.29)

ALC, altered level of consciousness; ED, emergency department; CNS, central nervous system.

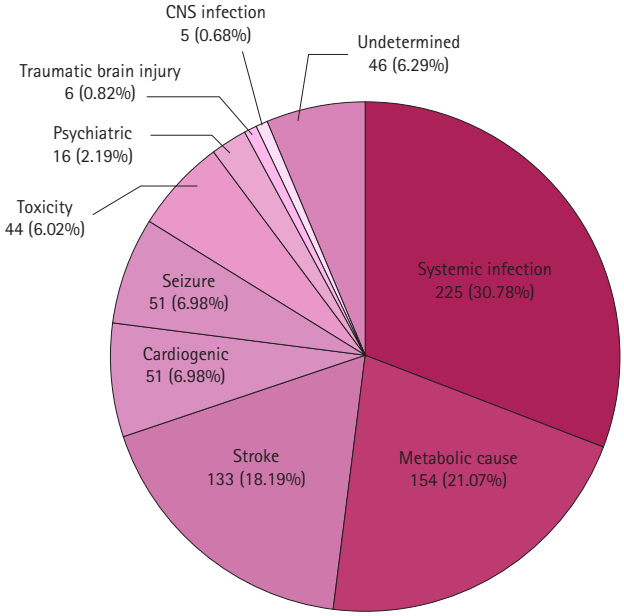

Fig. 2. Causes of altered level of consciousness in the emergency department. CNS, central nervous system.

lustrated in Fig. 3. In the time zones, the largest number of patients with ALC visited the ED between 11:00 and 12:00. Three hundred thirty-two (45.42%) patients with ALC visited the ED during the 8-hour period between 09:00 and 17:00, the working time of the outpatient clinic. Throughout this period, systemic infection was the most common etiology. The time zone with the highest number of patients with ALC due to systemic infection was from 09:00 to 10:00, and due to metabolic cause was between 19:00 and 20:00. During the daytime (07:00–19:00), 443 patients with ALC visited the ED, accounting for 60.6% of all patients with ALC in the ED.

DISCUSSION

This is the first study to analyze the etiology of ALC in ED in South Korea. ALC is a manifestation of extensive medical problems, and it is not easy to accurately define ALC. In the real world, various symptoms, such as confusion, disorientation, hallucination, psychosis, lethargy, and infrequent behavior are called ALC. Accordingly, extensive history taking, readymade pathways, and rapid and appropriate actions are needed to assess ALC in the ED. This study is significant as patients who visit the ED for ALC were analyzed in detail by etiology and time zone, and the findings can be used as fundamental data in the EDs. All the patients who were not alert when entering the ED were included in the analysis. Not only neurological, but also systemic critical illnesses should be considered in the management of patients with ALC in the ED.

The classifications of the etiologies of ALC in the ED in previous studies varied [1-8]. For example, a previous study included all patients with GCS < 15, Mini-Mental State Examination < 24, disorientation, hallucinations, confusion, or abnormal behavior [1], whereas another study evaluated all patients in the ED with "sudden onset unconsciousness" as the chief complaint [4]. There was a cross-sectional study that evaluated patients with delirium [2], and another study included only comatose patients [5]. Nonetheless, there is a general trend in classification: systemic infections, metabolic causes, and brain disorders per se. Although the cause (whether infection, metabolic, or other causes) may vary depending on the researcher's opinion, it does not mean that the classification of cause is confusing. In this study, we organized a research team of board-certified clinicians in ED-related fields, including emergency medicine, internal medicine, and neurology. For example, there was a case in which acute renal failure was caused by drugs used to treat pneumonia, and we regarded it as a case of ALC due to metabolic cause. The classification of etiologies and causes was made by agreement through sufficient discussions to ensure the validity of this study.

In previous studies, neurological problems (such as seizure and CNS infection) or stroke was reported as the leading cause of ALC in the ED [1,3,4,6,8], accounting for at least 28% [1] to 38% of the cases [4]. In our study, however, the two most common etiologies, systemic infection and metabolic cause, were extracerebral and accounted for more than half (51.85%). Nonetheless, significant acute cerebral pathologies cannot be excluded. There were 195 patients with acute intracerebral etiologies (i.e., stroke, seizure, CNS infection, and TBI)—26.68% of all ALC cases in the ED. The characteristics of patients with ALC visiting the ED may vary depending on various factors, such as regional or demographic background, location of the hospital, and national health

Table 3. Cause analysis of ALC in the ED by time zone

Time zone	Total (n=731)	Systemic infection	Metabolic cause	Stroke	Cardiogenic	Seizure	Toxic	Psychiatric	CNS infection	TBI	Undetermined
00:00–00:59	22 (3.01)	5 (22.73)	7 (31.82)	3 (13.64)	1 (4.55)	2 (8.3)	2 (9.09)	1 (4.55)	0	0	1 (4.55)
1:00–1:59	14 (1.92)	3 (21.43)	2 (14.29)	1 (7.14)	4 (28.57)	1 (7.14)	2 (14.29)	0	0	0	1 (7.14)
2:00–2:59	17 (2.33)	4 (23.53)	4 (23.53)	1 (5.88)	3 (17.65)	0	2 (11.76)	0	0	0	3 (17.65)
3:00–3:59	14 (1.92)	3 (21.43)	1 (7.14)	3 (21.43)	4 (28.57)	0	2 (14.29)	1 (7.14)	0	0	0
4:00–4:59	17 (2.33)	2 (11.76)	4 (23.53)	4 (23.53)	1 (5.88)	2 (11.76)	3 (17.65)	1 (5.88)	0	0	0
5:00–5:59	18 (2.46)	4 (22.22)	4 (22.22)	5 (27.78)	1 (5.56)	1 (5.56)	1 (5.56)	1 (5.56)	0	0	1 (5.56)
6:00–6:59	19 (2.60)	4 (21.05)	4 (21.05)	3 (15.79)	1 (5.26)	2 (10.53)	2 (10.53)	0	0	1 (5.26)	2 (10.53)
7:00–7:59	25 (3.42)	6 (24.00)	7 (28.00)	3 (12.00)	4 (16.00)	3 (12.00)	1 (4.00)	0	0	1 (4.00)	0
8:00–8:59	25 (3.42)	3 (12.00)	4 (16.00)	6 (24.00)	2 (8.00)	4 (16.00)	3 (12.00)	1 (4.00)	0	0	2 (8.00)
9:00–9:59	46 (6.29)	18 (39.13)	10 (21.74)	9 (19.57)	4 (8.70)	1 (2.17)	2 (4.35)	0	0	0	2 (4.35)
10:00–10:59	39 (5.34)	17 (43.59)	8 (20.51)	4 (10.26)	1 (2.56)	2 (5.13)	2 (5.13)	1 (2.56)	0	1 (2.56)	3 (7.69)
11:00–11:59	54 (7.39)	16 (29.63)	12 (22.22)	9 (16.67)	7 (12.96)	4 (7.41)	1 (1.85)	1 (1.85)	1 (1.85)	0	3 (5.56)
12:00–12:59	38 (5.20)	14 (36.84)	3 (7.89)	10 (26.32)	3 (7.89)	2 (5.26)	1 (2.63)	1 (2.63)	1 (2.63)	0	3 (7.89)
13:00–13:59	40 (5.47)	12 (30.00)	10 (25.00)	4 (10.00)	1 (2.50)	3 (7.50)	5 (12.50)	0	0	0	5 (12.50)
14:00–14:59	37 (5.06)	13 (35.14)	9 (24.32)	6 (16.22)	2 (5.41)	2 (5.41)	0	1 (2.70)	1 (2.70)	1 (2.70)	2 (5.41)
15:00–15:59	34 (4.65)	15 (44.12)	5 (14.71)	6 (17.65)	3 (8.82)	2 (5.88)	0	1 (2.94)	1 (2.94)	0	1 (2.94)
16:00–16:59	44 (6.02)	15 (34.09)	11 (25.00)	8 (18.18)	2 (4.55)	3 (6.82)	2 (4.55)	0	0	0	3 (6.82)
17:00–17:59	36 (4.92)	10 (27.78)	11 (30.56)	7 (19.44)	1 (2.78)	2 (5.56)	3 (8.33)	1 (2.78)	1 (2.78)	0	0
18:00–18:59	25 (3.42)	11 (44.00)	3 (12.00)	4 (16.00)	0	1 (4.00)	3 (12.00)	0	0	0	3 (12.00)
19:00–19:59	45 (6.16)	12 (26.67)	13 (28.89)	8 (17.78)	2 (4.44)	4 (8.89)	1 (2.22)	1 (2.22)	0	1 (2.22)	3 (6.67)
20:00–20:59	39 (5.34)	16 (41.03)	7 (17.95)	7 (17.95)	2 (5.13)	3 (7.67)	1 (2.56)	1 (2.56)	0	1 (2.56)	1 (2.56)
21:00–21:59	35 (4.79)	9 (25.71)	7 (20.00)	7 (20.00)	2 (5.71)	3 (8.57)	2 (5.71)	1 (2.86)	0	0	4 (11.43)
22:00–22:59	28 (3.83)	8 (28.57)	5 (17.86)	7 (25.00)	0	0	3 (10.71)	2 (7.14)	0	1 (3.57)	2 (7.14)
23:00–23:59	21 (2.87)	5 (23.81)	3 (14.29)	8 (38.10)	0	4 (19.05)	0	0	0	0	1 (4.76)

Values are presented as number (%).
ALC, altered level of consciousness; ED, emergency department; CNS, central nervous system; TBI, traumatic brain injury.

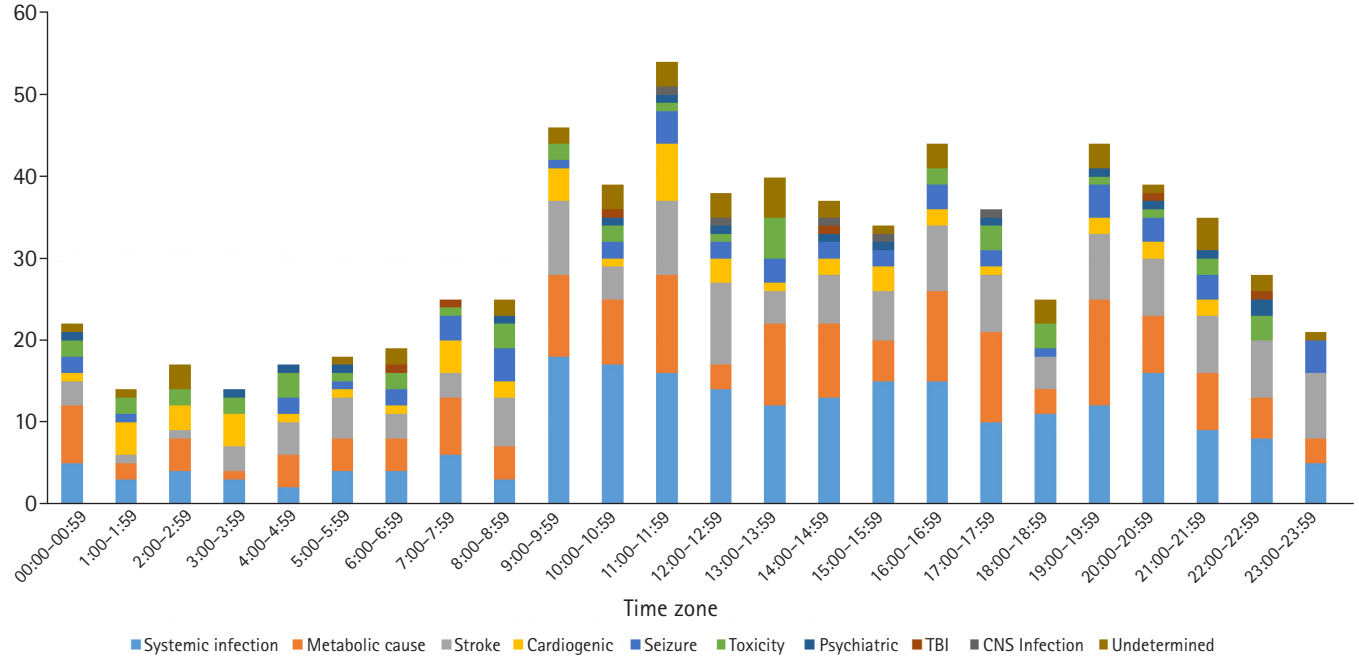

Fig. 3. Cause analysis by time zone. TBI, traumatic brain injury; CNS, central nervous system.

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care system. It should be noted, nonetheless, that this study demonstrated the importance of extra-cerebral etiologies in treating patients with ALC in the ED.

The composition of the patients or causes may change depending on the season or period. The majority of the patients tended to visit the ED mainly during the day. This study alone could not find the cause of the changes in patient composition over time. We only conjecture that patients with ALC tend to be referred from primary healthcare clinics, especially in cases of infection in which the doctor is the first to identify the signs, such as fever. We found that the combination of etiologies varied with the time zone, however, what we need to note is that patients categorized under "undetermined" was steady across all the time zones. There were 46 patients with undetermined etiology, accounting for 6.29% of all ALC cases in the ED. In a recent study of patients with seizures in the ED [7], in 65.95%, the cause could not be determined until discharge. In practice, the cause of ALC diagnosed in the ED is not the definitive diagnosis. In addition, even if the patient is unconscious, a single seizure cannot be diagnosed as epilepsy when the evaluation does not yield any abnormal results. In this study, we found such an example wherein a patient diagnosed with stroke in the ED was actually found to have multiple sclerosis after sufficient examination. Indeed, the definitive diagnosis of a patient with ALC could differ from the tentative diagnosis in the ED. What we should do in ED is not to make a definitive diagnosis, but to take an appropriate and immediate action.

The overall mortality of ALC in the ED managed in our hospital was 17.67%. Although the 30 deceased-in-ED may have been unavoidable, it suggests that patient flow and shortage of hospital beds should be addressed. This study reported a higher mortality in patients with ALC in the ICU than in the general ward. The reason for being hospitalized in the ICU could not be analyzed for all patients; in addition, there was no difference in the causes of ALC between the general ward and ICU. We suppose that the severity of disease rather than the classification of the causes of ALC would affect the mortality rate of ALC in the ED.

There are several limitations. First, as this was a single-center retrospective study, selection bias could not be avoided. Second, since the scope of this study was limited to clinical practice in the ED, whether the diagnosis was changed after hospitalization or at the outpatient clinic thereafter was not determined. The issue in this study was the tentative diagnosis of ALC in the ED; subsequent studies could analyze the definitive diagnoses.

ALC has a wide variety of causes; it can take a long time to achieve a definitive diagnosis, some diagnostic approaches require additional evaluation that is not available in the ED, and two or more causes can occasionally be present concomitantly. These obstacles make it challenging to study ALC in the ED; however, this is why further study and analysis are needed.

ARTICLE INFORMATION

Ethics statement

The study was approved by the ethics committee of the Keimyung University Dongsan Medical Center (No. 2019-07-002-001). The need for written informed consent was waived due to the study's retrospective design.

Conflict of interest

No potential conflict of interest relevant to this article.

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The good genotype for clopidogrel metabolism is associated with decreased blood viscosity in clopidogrel-treated ischemic stroke patients

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ORIGINAL ARTICLE

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Background: Blood viscosity (BV) is a measurement of the intrinsic resistance of blood to flow, and high BV increases thromboembolic risk. Although laboratory documentation of clopidogrel resistance has been shown to predict an increased risk of cardiovascular events in patients with ischemic stroke, there is no evidence that cytochrome P450 2C19 (CYP2C19) polymorphisms in clopidogrel-treated patients influence BV after ischemic stroke.
Methods: Patients with ischemic stroke or transient ischemic attack within 7 days of symptom onset from April 2018 to October 2019 were included. Patients were classified into the good genotype group for clopidogrel metabolism (ultrarapid or extensive metabolizer) and poor genotype group (intermediate/unknown or poor metabolizer) based on their CYP2C19 genotype status. A scanning capillary-tube viscometer was used to assess whole BV, and patients were divided into decreased BV and increased BV groups.
Results: The final analyses included 174 patients (109 men and 65 women) with a mean age of 66.4±11.2 years. The good genotype was found in 44% of patients with decreased systolic BV (SBV) and 27% of those with increased SBV (P=0.029), suggesting that BV changes were related to the CYP2C19 genotype for clopidogrel metabolism. Binary logistic regression analysis showed that CYP2C19 genotype status (P=0.024) and baseline SBV (P<0.001) were significantly associated with decreased BV. The good genotype for clopidogrel metabolism was associated with decreased BV in patients with ischemic stroke treated with clopidogrel.
Conclusion: The present results indicate that the effect of clopidogrel treatment on ischemic stroke prevention could be modulated not only by inhibition of platelet function but also by changes in the hemorheological profile.

Keywords: Blood viscosity; Hematocrit; Stroke

INTRODUCTION

Blood viscosity (BV) is a measurement of the intrinsic resistance of blood to flow and is characterized by blood thickness and stickiness [1-3]. High BV increases thromboembolic risk and plays an important role in cardiovascular disease [2-6]. We previously reported that prior antithrombotic use is significantly associated with decreased BV in patients with acute ischemia [7]. Our findings demonstrate that prior antithrombotic medication may change the hemorheological profile in the acute phase of ischemic

stroke. Enhancement of erythrocyte deformability and inhibition of platelet aggregation may be related to decreased BV when antithrombotics are used. Evidence has begun to develop regarding the relationship between cytochrome P450 2C19 (CYP2C19) polymorphisms in clopidogrel-treated patients and stroke recurrence following ischemic stroke [8,9]. Our previous study revealed that in patients with acute ischemic stroke treated with clopidogrel, a good CYP2C19 genotype for clopidogrel metabolism was associated with a 31% decrease in the relative risk of recurrent stroke [10]. Informative studies on pharmacological therapies for reducing BV are limited [11,12]. One study showed that in patients with subclinical carotid or femoral atherosclerosis, clopidogrel reduces the mean low-shear BV by 18% after 3 weeks of treatment [12]. Aspirin with dipyridamole is also more effective than aspirin alone in reducing low-shear BV [13]. However, there is no evidence that CYP2C19 polymorphisms in clopidogrel-treated patients influence BV after ischemic stroke.

We hypothesized that CYP2C19 polymorphisms in clopidogrel treatment may inhibit platelet aggregation, which is related to BV. We presumed that a good genotype for clopidogrel metabolism may decrease BV, and this effect could be demonstrated by serial BV measurements. In this context, this study was designed to evaluate the difference between the propensities of a good genotype group for clopidogrel metabolism and a poor genotype group to reduce BV in patients with ischemic stroke on clopidogrel treatment.

METHODS

Patients

For this study, patients (aged ≥ 40 years) who developed ischemic stroke or transient ischemic attack (TIA) within 7 days of symptom onset from April 2018 to October 2019 were enrolled. Weakness, speech disturbance, dysarthria, or dysphasia for > 5 minutes, had to be part of the symptom complex of TIA for patients to be eligible [14]. Patient demographics and clinical information were assessed at admission. An expert pharmacist checked all medications that each patient took regularly during the week that preceded their admission. Systemic investigations were performed for all patients. Each patient underwent brain magnetic resonance imaging or computed tomography (CT) and at least one vascular imaging study, such as magnetic resonance angiography or CT angiography. Echocardiography and 24-hour Holter monitoring were performed in selected patients to detect the potential cardiac sources of embolism. Stroke subtype classification was performed according to the Trial of ORG 10172 in the Acute Stroke Treatment classification system [15]. Patients with high-risk cardiac sources of emboli or stroke of other determined etiology as a stroke subtype were excluded from this study. All patients received appropriate treatment, including antihypertensive or antidiabetic drugs or statins, during the study.

BV measurement

The methods of BV measurement used in this study have been published previously [7]. A scanning capillary-tube viscometer (SCTV; Hemovister; Pharmode Inc., Seoul, Korea) was used to assess whole BV. The SCTV assesses systolic BV (SBV) and diastolic BV (DBV). SBV and DBV characterize viscosities at high and low shear rates, respectively. In this study, whole BV measured at a shear rate of 300 s^{-1} was selected as the SBV and at 1 s^{-1} as the DBV [7]. Laboratory tests, including BV, hemoglobin (Hb), hematocrit (Hct), and platelets, were conducted at admission and 180 ± 30 days after the onset of stroke. All BV samples were obtained before hydration therapy, and measurements were taken within 24 hours after collection. For the study, patients were divided into decreased BV and increased BV groups. Decreased BV suggested that the BV value in the baseline study minus the value in the 180-day study was positive, and vice versa. If the calculated BV values were zero or discordant between SBV and DBV, they were excluded from the study (nine patients).

CYP2C19 genotyping assay

The methods used for the CYP2C19 genotyping assay have been published previously [10]. In brief, the CYP2C19 genotype of the study population was measured using the Real-Q CYP2C19 genotyping kit (Biosewoom, Seoul, Korea) and the Seeplex CYP2C19 ACE Genotyping system (Seegene, Seoul, Korea). Patients were classified as an ultrarapid metabolizer (UM; *1/*17, *17/*17), extensive metabolizer (EM; *1/*1), intermediate (IM)/unknown metabolizer (*1/*2, *1/*3 and *2/*17, *3/*17), or poor metabolizer (PM; *2/*2, *2/*3, *3/*3) based on CYP2C19 genotype status. For this study, UM or EM status patients were allocated to the good genotype group for clopidogrel metabolism, while IM/unknown metabolizer or PM status patients were allocated to the poor genotype group.

Statistical analysis

Variables were verified for normality using the Kolmogorov-Smirnov test. Descriptive data are expressed as number (percentage) or mean ± standard deviation. Categorical data were examined using the chi-square or Fisher's exact test. Univariate analyses of patient characteristics were performed using an independent-samples *t*-test or the Mann-Whitney *U*-test for continuous variables and the chi-square or Fisher's exact test for categorical

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variables. Binary logistic regression analysis was performed to examine the association of univariate variables. Two-sided null hypotheses of no difference were rejected if *P*-values were less than 0.05. Statistical analyses were performed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Fig. 1 shows the study flow and the identified reasons for exclusion from the study. A total of 539 patients who had experienced ischemic stroke or TIA within 7 days of symptom onset were screened, of which 294 (55% of the screened population) were excluded from the study. One hundred and sixty-two patients (30%) refused to participate in the study, and 132 (25%) were excluded based on the exclusion criteria. During the study, 71 patients (13%) did not follow the study protocol, and as a result, 174 (32%) were included in the final analysis. The most frequent stroke subtype was lacunar stroke (n=82, 47%), followed by stroke of undetermined etiology, negative work-up (n=50, 29%), large artery atherosclerosis (n=28, 16%), and TIA (n=14, 8%).

The baseline characteristics of the study population according to CYP2C19 genotype status are shown in Table 1. The mean age was 66.4±11.2 years, and 37% of the patients were women. Of these, 67% had a history of hypertension, 28% had a history of diabetes, 43% had a history of dyslipidemia, 11% had a history of stroke, and 2% had a history of coronary artery disease (CAD). In addition, 37% of the patients had a good genotype for clopidogrel metabolism, and 34% were current smokers. There were no significant differences in the baseline characteristics between the two groups. Regarding prior antiplatelet therapy, 36 patients (21%) were regularly taking antiplatelet drugs (aspirin alone, 36%; clopidogrel plus aspirin, 25%; clopidogrel alone, 20%; others, 19%) at admission. Although there were no differences in baseline BV values among the different antiplatelet therapy groups ($P=0.446$), a trend toward a decreased baseline BV value was observed in the prior treatment group ($P=0.137$ for SBV and $P=0.125$ for DBV).

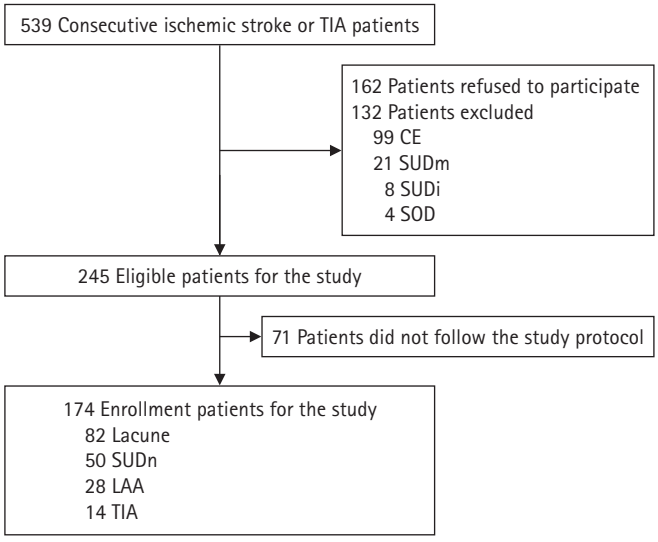

Fig. 1. Study profile. TIA, transient ischemic attack; CE, cardioembolism; SUDm, stroke of undetermined etiology (SUD), more than two causes identified; SUDi, SUD, incomplete evaluation; SOD, stroke of other determined etiology; SUDn, SUD, negative work-up; LAA, large artery atherosclerosis.

Table 1. Baseline characteristics of the study population according to CYP2C19 genotype status

Variable	Total (n=174)	Good genotype group (n=64)	Poor genotype group (n=110)	*P*-value
Age (yr)	66.4±11.2	65.1±10.8	67.2±11.4	0.227
Female	65 (37.4)	21 (32.8)	44 (40)	0.345
Hypertension	116 (66.7)	42 (65.6)	74 (67.3)	0.824
Diabetes mellitus	48 (27.6)	14 (21.9)	34 (30.9)	0.199
Dyslipidemia	74 (42.5)	26 (40.6)	48 (43.6)	0.698
Stroke	19 (10.9)	7 (10.9)	12 (10.9)	0.995
Coronary artery disease	4 (2.3)	2 (3.1)	2 (1.8)	0.627
Current smoking	59 (33.9)	23 (35.9)	36 (32.7)	0.666
Prior antiplatelets use	36 (20.7)	14 (21.9)	22 (20)	0.768
TOAST classification				0.305
LAA	28 (16.1)	8 (12.5)	20 (18.2)	
Lacune	82 (47.1)	34 (53.1)	48 (43.6)	
SUDn	50 (28.8)	15 (23.4)	35 (31.8)	
TIA	14 (8)	7 (10.9)	7 (6.4)	

Values are presented as mean±standard deviation or number (%).
CYP2C19, cytochrome P450 2C19; TOAST, Trial of ORG 10172 in the Acute Stroke Treatment classification; LAA, large artery atherosclerosis; SUDn, stroke of undetermined etiology, negative work-up; TIA, transient ischemic attack.

Table 2 shows the laboratory findings according to CYP2C19 genotype status. There were no differences in the baseline findings between the two groups. In the 180-day study, Hct and changes in DBV were significantly higher in the good genotype group. No differences were observed in other laboratory findings between the groups.

The decreased-SBV group had a better genotype for clopidogrel metabolism than the increased-SBV group on clopidogrel treatment (Table 3). The good genotype was found in 44% of the decreased-SBV patients and 27% of the increased-SBV patients ($P=0.029$), suggesting that BV changes were related to the CYP2C19 genotype for clopidogrel metabolism. The analysis using DBV demonstrated the same results ($P=0.013$). Baseline Hb, Hct, SBV, and DBV values were significantly higher in the decreased-SBV group. A trend toward older age was observed in the increased-SBV prior treatment group ($P=0.053$). Binary logistic regression analysis using age, baseline Hb, Hct, SBV value, and CYP2C19 genotype status revealed that CYP2C19 genotype status (odds ratio [OR], 2.45; 95% confidence interval [CI], 1.13–5.32; $P=0.024$) and baseline SBV (OR, 0.15; 95% CI, 0.06–0.37; $P<0.001$) were significantly associated with decreased SBV (Table 4). Regarding DBV, the analysis using age, baseline Hb, Hct, DBV value, and CYP2C19 genotype status revealed that CYP2C19 genotype status (OR, 2.69; 95% CI, 1.15–6.27; $P=0.022$) and baseline DBV (OR, 0.91; 95% CI, 0.84–0.98; $P=0.019$) were strongly correlated with decreased DBV.

During the study, clopidogrel plus aspirin was administered to 144 patients (83%), and clopidogrel alone was administered to the remaining 17%. The baseline characteristics and laboratory indices according to SBV changes and type of antiplatelet therapy are shown in Table 5. In the decreased-SBV group, the proportion of patients with prior stroke and those who had prior antiplatelet ther-

Table 2. Laboratory findings of the study population according to CYP2C19 genotype status

Variable	Total (n=174)	Good genotype group (n=64)	Poor genotype group (n=110)	*P*-value
Baseline study				
Hb (g/dL)	14±1.75	14.2±1.72	14±1.78	0.421
Hct (%)	41.4±4.9	42±5.1	41±4.8	0.218
White blood cell (10^3/μL)	7.6±2.38	7.73±2.54	7.53±12.28	0.613
Platelets (10^3/μL)	244±81.52	250±106.68	240±61.64	0.417
BUN (mg/dL)	16.3±5.44	16.9±5.32	15.9±5.51	0.279
Creatine (mg/dL)	0.84±0.25	0.8±0.2	0.86±0.28	0.151
Random plasma glucose (mg/dL)	147±63.78	141±56.11	150±67.78	0.406
Total cholesterol (mg/dL)	163±40.62	159±45.92	165±37.29	0.310
LDL cholesterol (mg/dL)	100±29.13	97±32.46	102±27.04	0.288
HDL cholesterol (mg/dL)	41±10.08	42±10.27	41±9.99	0.523
Triglyceride (mg/dL)	132±73.04	129±75.94	134±71.66	0.701
INR	1±0.07	0.99±0.08	1±0.06	0.557
SBV (cP)	4.56±0.87	4.66±0.96	4.5±0.81	0.260
DBV (cP)	37.77±8.91	38.72±9.9	37.22±8.28	0.299
At 180-day study				
Hb (g/dL)	13.8±1.73	14±1.64	13.6±1.77	0.106
Hct (%)	40.9±4.9	41.9±4.71	40±4.94	0.042[b]
Platelets (10^3/μL)	243±79.72	245±103.29	241±62.17	0.801
SBV (cP)	4.39±0.7	4.41±0.63	4.38±0.73	0.806
DBV (cP)	32.86±8.63	33.09±7.94	32.73±9.04	0.792
Change in laboratory findings[a]				
Hb (g/dL)		0.2±1.2	0.4±1.2	0.299
Hct (%)		0.1±3.31	0.7±3.44	0.303
Platelets (10^3/μL)		7±36.79	0.9±39.07	0.315
SBV (cP)		0.29±0.77	0.16±0.77	0.305
DBV (cP)		6.6±7.3	3.44±7.89	0.016[b]

Values are presented as mean±standard deviation.
CYP2C19, cytochrome P450 2C19; Hb, hemoglobin; Hct, hematocrit; BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; INR, international normalized ratio; SBV, systolic blood viscosity; cP, centipoise; DBV, diastolic blood viscosity.
[a]The changes in Hb, Hct, platelets, SBV, and DBV were calculated by subtracting the 180-day value from the baseline value; [b]Significant *P*-value.

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Table 3. Patient characteristics and laboratory findings according to SBV changes

Variable	Decreased-SBV group (n=101)	Increased-SBV group (n=73)	*P*-value
Baseline study			
Age (yr)	65±11.25	68.4±11.02	0.053
Female	41 (40.6)	24 (32.9)	0.299
Hypertension	68 (67.3)	48 (65.8)	0.828
Diabetes mellitus	27 (26.7)	21 (28.8)	0.767
Dyslipidemia	40 (39.6)	34 (46.6)	0.359
Stroke	13 (12.9)	6 (8.2)	0.332
Coronary artery disease	1 (1)	3 (4.1)	0.312
Current smoking	36 (35.6)	23 (31.5)	0.324
Prior antiplatelets use	19 (18.8)	17 (23.3)	0.472
Good genotype for clopidogrel metabolism	44 (43.6)	20 (27.4)	0.029[b]
Hb (g/dL)	14.4±1.59	13.5±1.85	0.001[b]
Hct (%)	42.4±4.75	40±4.78	0.001[b]
White blood cell (10^3/μL)	7.79±2.62	7.35±1.98	0.241
Platelets (10^3/μL)	251±92.67	234±62.4	0.200
BUN (mg/dL)	16±4.59	16.7±6.48	0.399
Creatine (mg/dL)	0.83±0.23	0.85±0.29	0.654
SBV (cP)	4.85±0.89	4.14±0.63	<0.001[b]
DBV (cP)	40.64±8.93	33.53±7.03	<0.001[b]
At 180-day study			
Hb (g/dL)	13.7±1.66	13.9±1.84	0.407
Hct (%)	40.7±4.91	41.3±4.91	0.479
Platelets (10^3/μL)	247±94.24	236±51.11	0.398
SBV (cP)	4.23±0.59	4.61±0.78	0.001[b]
DBV (cP)	31.75±7.49	34.39±9.84	<0.001[b]
Change in laboratory findings[a]			
Hb (g/dL)	0.7±1.1	−0.3±1.08	<0.001[b]
Hct (%)	1.6±3.18	−1.2±2.85	<0.001[b]
Platelets (10^3/μL)	3.8±34.45	2.45±43.47	0.826
SBV (cP)	0.67±0.61	−0.46±0.41	<0.001[b]
DBV (cP)	8.1±6.28	−0.92±0.64	<0.001[b]

Values are presented as mean±standard deviation or number (%). Decreased-SBV means the SBV value in the baseline study minus the SBV value in the 180-day study was positive, and vice versa.
SBV, systolic blood viscosity; Hb, hemoglobin; Hct, hematocrit; BUN, blood urea nitrogen; cP, centipoise; DBV, diastolic blood viscosity.
[a]The changes in Hb, Hct, platelets, SBV, and DBV were calculated by subtracting the 180-day value from the baseline value; [b]Significant *P*-value.

Table 4. Multivariate association between decrease in blood viscosity and clinical indices

Variable	SBV		DBV	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1 (0.962–1.03)	0.815	0.98 (0.95–1.02)	0.295
Baseline Hb	1.1 (0.48–2.55)	0.821	0.89 (0.38–2.08)	0.782
Baseline Hct	1.08 (0.8–2.55)	0.610	1.1 (0.8–1.5)	0.562
Good genotype for clopidogrel metabolism	2.45 (1.13–5.32)	0.024[a]	2.69 (1.15–6.27)	0.022[a]
Baseline SBV	0.15 (0.06–0.37)	<0.001[a]		
Baseline DBV			0.91 (0.84–0.98)	0.019[a]

SBV, systolic blood viscosity; DBV, diastolic blood viscosity; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; Hct, hematocrit.
[a]Significant *P*-value.

apy were higher in those receiving clopidogrel alone ($P=0.003$), related with previous aspirin use for secondary stroke prevention. In the increased-SBV group, female sex and prior antiplatelet use were higher in the clopidogrel alone group ($P=0.023$). No differences were observed in the SBV and DBV changes among the groups.

DISCUSSION

In this study, we evaluated the propensity of a good genotype for clopidogrel metabolism and a poor genotype to reduce BV using serial BV measurements. Our study clearly demonstrated that a good genotype for clopidogrel metabolism was associated with decreased BV in patients with ischemic stroke treated with clopidogrel. Logistic regression analysis showed that CYP2C19 genotype status and baseline BV were related to decreased BV.

Several studies have revealed an association between BV and the occurrence of major thromboembolic events [16,17]. As for stroke, BV is elevated in acute ischemic stroke. After a discrete increase in the acute phase, a gradual improvement is observed in the chronic phase [18]. BV appears significantly higher in cases of lacunar or cardioembolic strokes [1,3,19]. BV may contribute to the onset of stroke subtypes in a different way and may be related to the pathogenesis of thrombus formation [1]. The major determinants of BV are the aggregation and deformability of red blood cells, Hct, and plasma viscosity [2]. When BV increases with changes in blood components, flow resistance may markedly increase in stenotic perforating arteries. This hemorheological change could be associated with thrombus formation in lacunar infarctions [1,7].

Although we reported that prior antithrombotic use was significantly associated with decreased BV within 24 hours of symptom onset in patients with acute ischemic stroke [7], there was only a trend toward decreased BV in the prior antiplatelet treatment group ($P<0.137$) in this study. BV remains uniform over a short period, and the median time from symptom onset to admission was 3.2 days in this study. One study showed that BV was significantly higher at admission but was normalized after 2 weeks of hydration [5]. Differences in BV measurement time and sample size may be plausible explanations for these discrepancies between our studies.

In our study, a good genotype for clopidogrel metabolism was positively associated with decreased-BV. BV can be modified by medical therapies, including vasodilators, statins, or antithrombotics [13,20,21]. Few studies have demonstrated the effect of an-

Table 5. Patient characteristics and laboratory indices according to SBV changes and type of antiplatelets therapy

Variable	Decreased-SBV group (n=101)			Increased-SBV group (n=73)		
	Clopidogrel plus aspirin (n=84)	Clopidogrel (n=17)	*P*-value	Clopidogrel plus aspirin (n=60)	Clopidogrel (n=13)	*P*-value
Age (yr)	64.3±10.94	68.5±12.42	0.168	67.5±10.99	72.2±10.73	0.165
Female	33 (39.3)	8 (47.1)	0.595	16 (26.7)	8 (61.5)	0.023[b]
Hypertension	57 (67.9)	11 (64.7)	0.784	37 (61.7)	11 (84.6)	0.114
Diabetes mellitus	22 (26.2)	5 (29.4)	0.770	15 (25)	6 (46.2)	0.127
Dyslipidemia	30 (35.7)	10 (58.8)	0.076	27 (45)	7 (53.8)	0.562
Stroke	5 (6)	8 (47.1)	<0.001[b]	4 (6.7)	2 (15.4)	0.289
Coronary artery disease	1 (1.2)	0	1.000	2 (3.3)	1 (7.7)	0.450
Current smoking	30 (36.7)	6 (35.3)	1.000	23 (39.3)	0	0.007[b]
Prior antiplatelets use	11 (13.1)	8 (47.1)	0.003[b]	10 (16.7)	7 (53.8)	0.009[b]
Good genotype for clopidogrel metabolism	36 (42.9)	8 (47.1)	0.750	18 (30)	2 (15.4)	0.493
BUN (mg/dL)	15.9±4.65	16.5±4.39	0.616	16.1±6.04	18.9±7.97	0.178
Creatine (mg/dL)	0.82±0.23	0.89±0.23	0.255	0.83±0.25	0.92±0.43	0.317
Change in laboratory findings[a]						
Hb (g/dL)	0.7±1.03	0.9±1.41	0.492	−0.4±1.09	−0.1±1.06	0.389
Hct (%)	1.5±2.99	1.9±4.06	0.693	−1.4±2.69	−0.2±3.45	0.313
Platelets (10^3/μL)	2.7±33.83	9.1±37.93	0.491	5±35.06	9±71.17	0.516
SBV (cP)	0.7±0.65	0.53±0.37	0.143	−0.45±0.4	−0.47±0.43	0.898
DBV (cP)	8.18±6.72	7.74±4.01	0.794	−0.86±7.03	−0.79±6.64	0.464

Values are presented as mean±standard deviation or number (%). Decreased-SBV means the SBV value in the baseline study minus the SBV value in the 180-day study was positive, and vice versa.
SBV, systolic blood viscosity; BUN, blood urea nitrogen; Hb, hemoglobin; Hct, hematocrit; cP, centipoise; DBV, diastolic blood viscosity.
[a]The changes in Hb, Hct, platelets, SBV, and DBV were calculated by subtracting the 180-day value from the baseline value; [b]Significant *P*-values.

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tithrombotics on BV [13,21,22]. Warfarin, heparin, and argatroban decrease BV [21,23]. Warfarin reduces BV significantly in patients with acute ischemic stroke with nonvalvular atrial fibrillation, compared to aspirin [21]. Regarding antiplatelet therapy, results differed depending on the study protocol. Aspirin and cilostazol do not change BV, but dipyridamole and clopidogrel decrease BV after treatment [11,13,21,24]. Clopidogrel, the P2Y12 receptor antagonist, could increase the adenosine and cyclic adenosine monophosphate plasma concentration, which have been shown to lower BV [13,25]. It is also known that clopidogrel is associated with improvement in microvascular reactivity in patients with CAD [26]. Clopidogrel may have a positive influence on hemorheological parameters. Therefore, the effect of clopidogrel on ischemic stroke prevention could be modulated not only by inhibition of platelet function but also by changes in the hemorheological profile [11,26].

The strength of this study its longitudinal design using serial BV examinations. Unlike simple cross-sectional studies, this study was used to estimate the effect of CYP2C19 genotype and BV changes in clopidogrel-treated patients with ischemic stroke. There were several limitations in this study, including small sample size. Of the 539 patients screened during the study, only 174 (32%) were enrolled. However, our study showed that 37% of participants belonged to the good genotype group for clopidogrel metabolism. These results were in concordance with those of previous studies reporting that approximately 41% of Koreans belonged to the good genotype group [27]. Second, we could not measure plasma components such as fibrinogen or C-reactive protein in all patients. BV can change according to the levels of other aggregating proteins. Third, the response to clopidogrel might have been affected by several clinical factors, including sex and smoking [10]. We could not evaluate the clinical factors associated with variability in the response to clopidogrel. Finally, clopidogrel plus aspirin was given to 144 patients (83%). Although aspirin does not change BV [13], dual antiplatelet therapy with clopidogrel plus aspirin may affect the BV changes differently. No differences were observed in BV changes between the clopidogrel plus aspirin and clopidogrel alone treatment groups in our study. However, the small sample size (144 vs. 30) limits the generalizability of our findings. These limitations should be considered when interpreting our data.

In conclusion, a good genotype for clopidogrel metabolism was associated with decreased BV in patients with ischemic stroke after clopidogrel treatment. Our findings indicate that the effect of clopidogrel treatment on ischemic stroke prevention could be modulated not only by inhibition of platelet function but also by changes in the hemorheological profile. Further studies that focus on the CYP2C19 genotype and BV are essential to evaluate the effects of clopidogrel treatment on stroke recurrence.

ARTICLE INFORMATION

Ethics statement

The Research Ethics Committee of Inje University Sanggye Paik Hospital approved the present study (IRB No. 2019-05-021). The requirement for informed consent was waived because the database was accessed only for purposes of analysis and personal information was not used.

Conflict of interest

No potential conflict of interest relevant to this article.

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Cerebral infarction caused by endocarditis in a patient with COVID-19

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CASE REPORT

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Background: Coronavirus disease 2019 (COVID-19) has become a worldwide health threat due to its highly contagious nature and severe complications. The authors experienced a case of cerebral infarction caused by endocarditis in a patient infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Case Report: A 65-year-old male patient with COVID-19 was admitted to our hospital for cohort isolation. On day 11 after admission, the patient suddenly presented right-sided hemiparesis. Computed tomography of the brain showed multiple hypodense lesions, which confirmed acute cerebral infarction. Transthoracic echocardiogram revealed a vegetation of about 5 mm on the mitral valve and endocarditis was diagnosed as the cause of cerebral infarction.
Conclusion: Cerebral infarction is one of the complications of COVID-19 and can occur at any time during the course of the disease. Hence, a neurologist has an important role in the medical team involved in COVID-19 treatment.

Keywords: COVID-19; Heart injury; Endocarditis; Cerebral infarction; Neurologist

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a newly identified infectious disease with rapid human to human transmission capacity. COVID-19 can result in several fatal complications such as acute respiratory distress syndrome, RNAaemia, acute cardiac injury, acute kidney injury, secondary infection, and septic shock [1,2]. Since February 21, 2020, the authors of this paper have been working at a hospital designated for treating COVID-19 patients and by June 15, 2020, 1,027 COVID-19 patients had been hospitalized. Our critical care team implemented a collaborative approach for intensive care unit patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection enabling simultaneous co-management of pulmonological, neurocritical, and nutritional services. Here, we report a case of multiple cerebral infarctions in a patient hospitalized with COVID-19.

CASE REPORT

A 65-year-old South Korean male patient with COVID-19 was

admitted to our hospital for cohort isolation. The patient had no underlying conditions and developed cough and sputum 5 days prior to diagnosis. On admission, the patient's vital signs were recorded as a temperature of 38.0°C, blood pressure of 135/88 mm Hg, heart rate of 78 beats per minute, respiratory rate of 22 breaths per minute, and oxygen saturation of 95% on room air. Chest computed tomography (CT) showed pneumonia in the lower lobes of both lungs. We started treatment with lopinavir/ritonavir and hydroxychloroquine, which are known to be effective against COVID-19 [1,2]. Additionally, ceftriaxone and azithromycin were simultaneously administered as empirical antibiotics to treat pneumonia.

Six days later, pneumonia gradually worsened, and the patient was put on mechanical ventilation in the intensive care unit as his blood pressure had dropped (90/60 mm Hg), heart and respiratory rate had increased (120 beats per minute and 30 breaths per minute, respectively), and oxygen saturation levels were below 85%. Based on the results of blood culture (positive for *Pseudomonas aeruginosa*) and drug sensitivity test, antibiotic treatment was changed to include piperacillin/tazobactam and levofloxacin. Inotropes were administered to raise the patient's blood pressure, and 0.4–0.6 μg/kg/hr of dexmedetomidine and 0.1–0.2 μg/kg/min of remifentanil were additionally administered during mechanical ventilation.

On day 11 after admission, when the patient's vital signs stabilized, we gradually reduced sedative administration, and the patient began to recover consciousness. However, the patient suddenly developed right-sided hemiparesis (Medical Research Council grade 3). He had a National Institute of Health Stroke Scale score of 7 (partial hemianopia, 1; facial palsy, 1; right arm motor drift, 2; right leg motor drift, 2; and dysarthria, 1). Emergency brain CT with intracranial CT angiography was performed. The brain CT showed multiple hypodense lesions with surrounding edema in different areas of the brain (Fig. 1A and B), which confirmed acute cerebral infarction. Since the intracranial CT angiography was normal, cardioembolic stroke was suspected and transthoracic echocardiogram (TTE) was performed to assess the cause of the stroke. TTE showed a vegetation of approximately 5 mm on the mitral valve (Fig. 1C and D) and endocarditis was diagnosed as the cause of cerebral infarction. Aspirin (100 mg) that was administered at the time of diagnosis of cerebral infarction was discontinued on suspicion of infectious endocarditis. Antimicrobial therapy with piperacillin/tazobactam and levofloxacin was administered based on blood culture (positive for *P. aeruginosa*) and antibiotic sensitivity test. Two weeks later, the patient was released from quarantine after two consecutive negative findings on

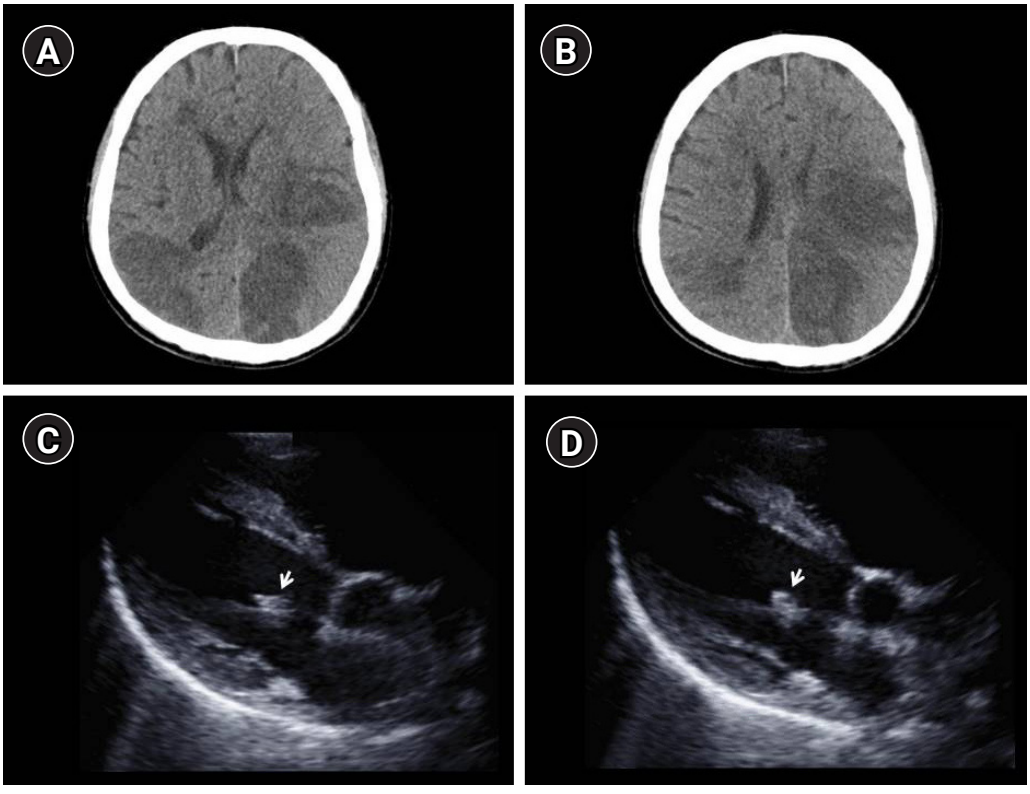

Fig. 1. Findings of brain computed tomography (CT) and transthoracic echocardiogram (TTE). (A, B) Brain CT demonstrates multiple hypodense lesions with surrounding edema in different areas of the brain. (C, D) In the TTE (supine view), a mobile and irregularly shaped echodense mass of approximately 1.0×0.5 cm is attached to the anterior mitral valve (white arrows).

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COVID-19 real-time reverse transcription polymerase chain reaction testing and was transferred to another tertiary hospital (not a COVID-19 designated hospital) for further treatment.

DISCUSSION

Recently published studies report that COVID-19 could be accompanied by acute cardiac injury (defined as blood levels of hypersensitive troponin I above the 99th percentile upper reference limit (> 28 pg/mL) or new abnormalities shown on electrocardiography and echocardiography), secondary infection, and sepsis [1,2]. The vegetation of endocarditis is initiated through bacteremia, which then binds and attaches to the damaged endothelium. Thromboplastin, which is secreted by tissue factors in the damaged endothelium, causes platelet aggregation and cleavage of fibrinogen to fibrin. Acute cardiac injury, secondary infections, and sepsis can cause endocarditis [3,4]. In our study, *P. aeruginosa* was reported in blood culture after the patient was confirmed to have COVID-19. Hence, endocarditis can occur due to complications of COVID-19 accompanied by secondary bacterial infection. Despite improved management, endocarditis remains associated with high mortality and serious complications [3]. Symptomatic neurological complications appear in 15%–30% of endocarditis patients and occur primarily due to embolism from vegetations [4]. Neurologic symptoms most occur often before or during endocarditis diagnosis, but new or recurrent events may occur after endocarditis diagnosis. Clinical presentation is variable and may include multiple symptoms or signs in the same patient. Typically, focal signs are diagnosed due to ischemic stroke. Further, transient ischemic attack, intracerebral or subarachnoid hemorrhage, brain abscess, meningitis, and toxic encephalopathy can be present, and there is evidence that 35%–60% of patients with endocarditis develop additional silent cerebral embolisms [5].

We believe that this is the first reported case of cerebral infarction caused by endocarditis in a patient with COVID-19. Several complications can result from COVID-19 and acute cerebral infarction can further potentially occur during the course of this disease [1,2,6]. Due to the lack of equipment required for neurological disease assessment and inaccessibility of medical staff in our designated hospital optimized for COVID-19 treatment, it was difficult to perform diagnosis of stroke by physical examination and evaluation. However, it is clear that neurologists have an important role besides respiratory and infectious physicians in the treatment of COVID-19.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No. 2020-09-054). Informed consent was waived by the Board.

Conflict of interest

Dr. JH Hong 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.

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Anti-Yo-associated autoimmune encephalitis after colon cancer treatment

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CASE REPORT

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Background: Anti-Yo antibodies are classically associated with paraneoplastic cerebellar degeneration in ovarian and breast cancers and are rarely seen in colon cancer. Anti-Yo-associated paraneoplastic autoimmune encephalitis in colon cancer is rare.
Case Report: A 66-year-old man presented with new-onset seizures after completion of a scheduled treatment for colon cancer. Magnetic resonance imaging showed hyperintense signals with enhancement in the left temporal lobe and insular cortex. Cerebrospinal fluid findings included pleocytosis and elevated protein levels, while Yo antibodies were detected in the serum. There was no relapse of colon cancer, nor were any new cancers found. The patient's symptoms and laboratory test results improved after the administration of high-dose steroids, intravenous immunoglobulin, and plasmapheresis with antiepileptic drugs.
Conclusion: This is a rare case of autoimmune encephalitis with anti-Yo antibodies. The appearance of new-onset seizures during the treatment of malignancy should raise suspicions for paraneoplastic autoimmune encephalitis, even after surgery and chemotherapy are completed.

Keywords: Anti-Yo antibody; Autoimmune encephalitis; Colon cancer; Seizure

INTRODUCTION

Paraneoplastic neurological syndromes occur because of immune-mediated neuronal dysfunction secondary to systemic malignancy, and the symptoms usually occur before the malignancy is discovered. Anti-Yo antibody is known to be an onconeural antibody that causes paraneoplastic cerebellar degeneration with ataxia and cerebellar dysfunction [1]. Here, we have reported a rare case of autoimmune encephalitis with anti-Yo antibodies presenting with seizures after scheduled treatment for rectosigmoid colon cancer.

CASE REPORT

A 66-year-old man presented with seizures and altered mental sta-

tus. He was previously diagnosed with stage IIIB rectosigmoid colon cancer (adenocarcinoma) and underwent treatment with laparoscopic ultra-low anterior resection of the rectum and sigmoid colon 8 months prior. Three weeks prior to consultation, the patient had successfully finished eight cycles of chemotherapy with capecitabine/oxaliplatin. Two days prior to consultation, he was noted to have somnolence. His family was not aware of any memory deficits or personality changes before the seizure. On examination, the patient was febrile (38.5°C), stuporous, and experiencing generalized tonic-clonic seizures. Brain magnetic resonance imaging (MRI) showed hyperintense signals with enhancement in the left temporal lobe and insular cortex (Fig. 1A). Analysis of the cerebrospinal fluid (CSF) showed pleocytosis (white blood cell [WBC] count, 212/μL; lymphocyte, 96.1%) and elevated protein levels (72.3 mg/dL), but no malignant cells. Electroencephalography (EEG) revealed periodic lateralized epileptiform discharges originating from the left frontotemporal area. The patient was administered intravenous (IV) acyclovir (10 mg/kg every 8 hours) and IV levetiracetam (3,000 mg/day), but no clinical improvement was noted. Hence, the patient was administered dexamethasone (20 mg/day), following which his fever and ability to obey commands improved. After he became mentally alert, he became very talkative, but speech content was incongruous. Anti-Yo antibodies were subsequently detected in the patient's serum, but other paraneoplastic and autoimmune antibodies (Hu, Ri, amphiphysin, CV2, Ma2, recoverin, SOX1, titin, NMDA, AMPA, DPPX, LGI1, CASPR2, and GABA-B) were absent, and laboratory tests for infectious agents revealed negative results. Although the CSF findings (WBC count, 14/μL; protein level, 63.0 mg/dL) began improving on day 14 after onset, the patient's electrographic seizures persisted. We then administered IV immunoglobulin (IVIG) (400 mg/kg/day) for 5 days and added valproate (1,800 mg/day) and lacosamide (200 mg/day). On day 21 after onset, he could name and recognize his wife, son, and other relatives. On day 28 after onset, follow-up MRI showed additional hyperintense signals in the left subcallosal gyrus and increased gy-

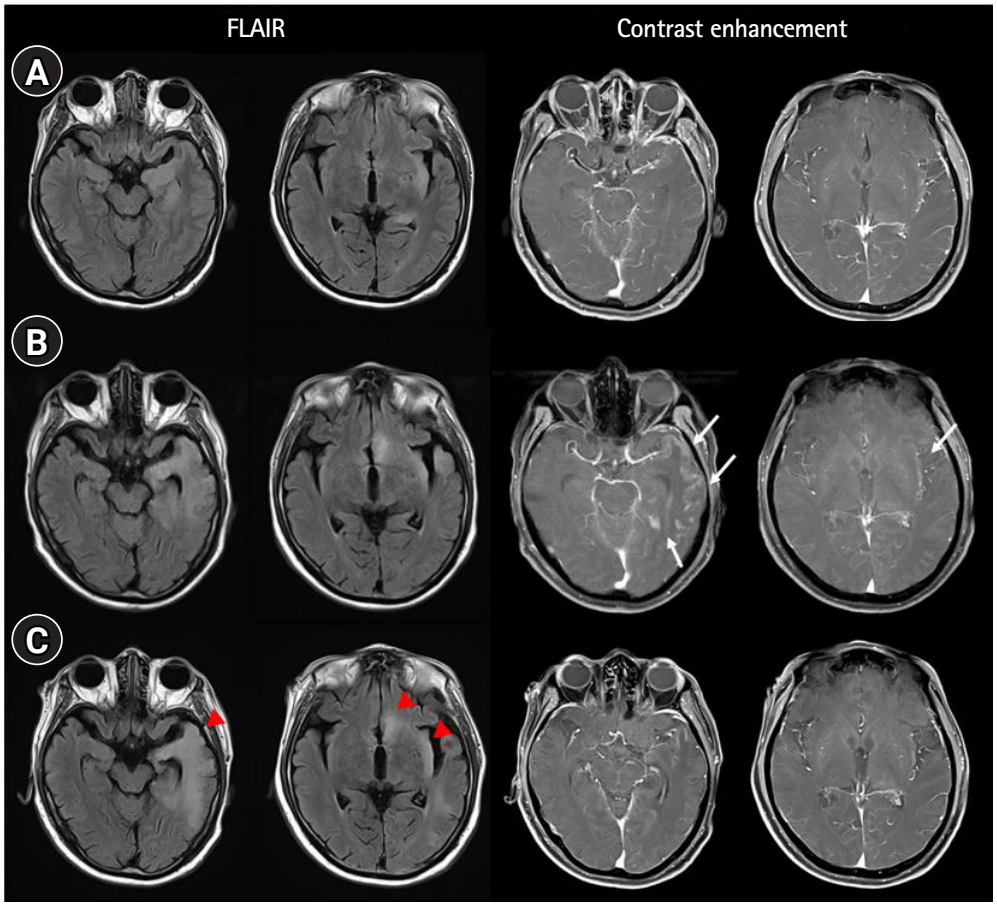

Fig. 1. Fluid-attenuated inversion recovery (FLAIR; left) and contrast-enhanced (right) magnetic resonance imaging taken on the day of onset of the seizure (A), day 28 (B), and day 53 (C). Enhancement in the left temporal lobe and insular cortex (arrows in B) decreased in images of day 53 (C). The last follow-up FLAIR images showed hyperintense signals in the left temporal lobe, subcallosal gyrus, and insular cortex (arrowheads).

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ral enhancement in the left temporal lobe (Fig. 1B). However, the patient's CSF findings (WBC count, 13/μL; protein level, 46.7 mg/dL) improved slightly. On day 36 after onset, after follow-up EEG showed no epileptiform discharges, and so the patient was discharged. He had an alert mental state but suffered from cognitive impairment including short-term memory loss, naming difficulty, and decreased verbal comprehension. Korean version of the Mini Mental State Examination was administered, but it was incomplete (5/30) because of decreased comprehension.

The patient was readmitted after 2 weeks because of aggression and agitation. His CSF WBC count was 16/μL and CSF protein level was within the normal range. MRI showed hyperintense signals in similar areas as the previous imaging result, but with decreased extent of enhancement (Fig. 1C). EEG revealed periodic lateralized epileptiform discharges in the left parietooccipital area. Anti-Yo antibodies were detected again in the patient's serum. We performed a total of five plasma exchanges and added perampanel (6 mg/day). We reduced the administration of levetiracetam and ultimately discontinued it. Although the patient still experienced cognitive impairment, poor sleep, and agitation, these were managed by antipsychotic drugs and the patient was able to walk and live at home. Given the improvements in CSF, EEG findings, and the reduction in enhancement on MRI, we did not add other immunosuppressive agents. To determine the possibility of colon cancer relapse or the appearance of a completely new type of cancer, we performed whole-body 18F-fluorodeoxyglucose-positron emission tomography 2 months after the onset of encephalitis. However, no hypermetabolic lesions were detected. Computed tomography of the chest, abdomen, and pelvis did not show any cancer recurrence or metastasis at the time of symptom onset and after 3 months.

DISCUSSION

In the present case, rapid progression of altered mental status, cognitive impairment and psychiatric symptoms, new-onset seizure, CSF pleocytosis, and encephalitis on MRI fulfilled the diagnostic criteria for autoimmune encephalitis [2]. Our patient represents a rare case of paraneoplastic autoimmune encephalitis with anti-Yo antibodies associated with colon adenocarcinoma. Most cases of paraneoplastic encephalitis are associated with small cell lung cancer and testicular cancer [3]. Colon cancer has been primarily reported in association with other paraneoplastic syndromes such as subacute cerebellar degeneration and stiff person syndrome [4,5]. In addition, anti-Yo antibodies target Purkinje cells and are associated with paraneoplastic cerebellar degeneration [1]. Cancers associated with anti-Yo-antibodies include ovarian, uterine, and breast cancers [1,6].

Initially, we considered the possibility of false-positive results with the anti-Yo antibody assay because the anti-Yo antibody did not fit the clinical presentation of the patient. However, it is reasonable to suggest a case of paraneoplastic autoimmune encephalitis because our patient had a history of recent cancer and showed improvement in symptoms and laboratory test results after the administration of high-dose steroids, IVIG, and plasmapheresis [7]. Furthermore, anti-Yo-associated autoimmune encephalitis has been rarely reported [8-10]; thus, clinical heterogeneity of anti-Yo antibody-associated paraneoplastic neurological syndromes needs to be considered. However, because almost 30%–50% of patients with paraneoplastic neurological syndromes do not have any of the well-characterized onconeural antibodies, we could not exclude the existence of other unknown antibodies [3,11].

The general prognosis of patients with autoimmune encephalitis associated with anti-Yo antibodies has not been well described because of its rarity. A previously reported case of autoimmune encephalitis associated with anti-Yo antibodies showed poor prognosis and remained in a permanent vegetative state [9]. The patient was diagnosed with colon adenocarcinoma and underwent subtotal colectomy after the onset of encephalitis. Active immunotherapy needs to be considered in patients with paraneoplastic autoimmune encephalitis associated with anti-Yo antibodies even after surgery and chemotherapy for cancer. Successful cancer treatment does not guarantee the prevention or neurologic improvement of paraneoplastic neurologic syndromes [3].

In 70%–80% of cases, neurological paraneoplastic syndrome antedates the diagnosis of cancer [1,11,12]. However, in a few cases, paraneoplastic autoimmune encephalitis occurs during chemotherapy or even after 9 years of treatment [12,13]. In our patient, the recurrence of colon cancer or the appearance of a new cancer was not observed after presentation with encephalitis. However, because we could not exclude the possibility of occult cancer, we will closely observe his clinical course. The prevalence of paraneoplastic autoimmune encephalitis after the underlying cancer is considered in remission remains unclear. Therefore, the appearance of new-onset seizures associated with a treated malignancy should raise suspicion for paraneoplastic autoimmune encephalitis as well as brain metastasis, leptomeningeal disease, infectious encephalitis, and metabolic causes. Thus, clinicians should test for paraneoplastic antibodies.

In conclusion, this is a rare case of autoimmune encephalitis with anti-Yo antibodies. The appearance of new-onset seizures during treatment for malignancy should raise suspicions for paraneoplastic autoimmune encephalitis, even after surgery and chemotherapy are completed.

ARTICLE INFORMATION

Ethics statement

This case was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 05-2020-127) and exempted from informed consent.

Conflict of interest

No potential conflict of interest relevant to this article.

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Bupropion overdose as a clinically significant confounder of the neurological examination

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CASE REPORT

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Background: Bupropion is a selective dopamine and norepinephrine reuptake inhibitor utilized in the treatment of multiple neuropsychiatric conditions. It has been implicated as a brain death mimic due to its association with a comatose examination.
Case Report: A 31-year-old man with depression and anxiety ingested bupropion as part of a multi-drug overdose in a suicide attempt. During his hospital course, he suffered two cardiopulmonary arrests approximately 24 hours after ingestion. Neurological examination was excessively poor relative to imaging studies and was notable for absent brainstem reflexes. He was treated with targeted temperature management and lipid emulsion therapy with rapid improvement. He was eventually discharged after making a complete neurological recovery.
Conclusion: Bupropion is a unique clinical confounder and may be associated with a disproportionately poor neurological examination in the setting of intoxication. Many factors should be considered in the approach to evaluation, treatment, and prognostication of these patients.

Keywords: Bupropion; Coma; Overdose; Prognosis; Neurologic examination; Brain death

INTRODUCTION

Accurate neurological prognostication after brain injury can be exceedingly challenging. In the setting of numerous confounders, such as multi-drug intoxication or overdose, predicting neurological outcomes becomes even more difficult. We describe a case of an intentional overdose of multiple medications, specifically involving bupropion, complicated by cardiopulmonary arrest, renal failure, and the loss of brainstem reflexes followed by a full neurological recovery.

CASE REPORT

A 31-year-old man with a history of longstanding depression and anxiety was brought to the emergency department with acute encephalopathy after a presumed suicide attempt. Emergency medi-

cal services found him disoriented and agitated at his residence with several empty prescription containers of mirtazapine, oxcarbazepine, fluoxetine, sustained-release bupropion (bupropion SR), gabapentin, and hydroxyzine; all bottles were confirmed by his significant other to be nearly full the night prior. Outpatient pharmacy records corroborated a recently dispensed 30 day supply of bupropion SR 200 mg to be taken every 12 hours; this suggests an approximate ingestion dose of 12 g.

Upon presentation to the hospital, vital signs were normal aside for mild tachycardia at 102 beats/min. General physical examination was notable for dry mucous membranes and decreased bowel sounds. Neurologically, he was lethargic and only arousable to pain but was able to state his name and was protecting his airway. Pupils were 7 mm, symmetric, and briskly reactive bilaterally with the remainder of the exam only significant for diffuse hyperreflexia and symmetric localization to noxious stimulation in all extremities; no myoclonus or abnormal movements were observed. Initial laboratory evaluation revealed a moderate leukocytosis (27 $\times 10^9$/L), an anion-gap metabolic acidosis (anion gap 19 mmol/L, CO_2 19 mmol/L), and an elevated lactate (6.4 mmol/L). The patient tested positive for amphetamines, benzodiazepines (which had been given pre-hospital), and cannabinoids. Other diagnostics, including an electrocardiogram (EKG) and computed tomography (CT) of the head and cervical spine, were unremarkable (Fig. 1). Activated charcoal and bowel irrigation were not utilized because of the unknown time of ingestion.

Several hours after admission the patient suffered two cardiac arrests characterized by pulseless electrical activity. Return of spontaneous circulation (ROSC) was achieved after 14 and 16 minutes, respectively, of high-quality and timely cardiopulmonary resuscitation. Resuscitation medications included multiple doses of epinephrine, sodium bicarbonate, and crystalloid solution; no sedatives or paralytics were given during the intubation. An EKG showed a new first degree atrioventricular block with slight QRS prolongation at 144 ms (Fig. 2). Serial neurological examinations immediately after the arrests and over the course of several hours consistently demonstrated absent corneal reflexes bilaterally (no blink with saline or tactile stimulation in either eye), no cough reflex with suction catheter stimulation, no oculocephalic reflex with horizontal and vertical head rotation, and no appreciable motor response to pain in any extremity; each pupil was dilated at 7 mm and unreactive to direct and indirect light. The decision was then made to administer lipid emulsion therapy and begin targeted temperature management (TTM) with a goal of 33°C Celsius. Despite aggressive measures, he deteriorated further and suffered widespread multi-organ damage evidenced by shock liver and acute non-oliguric renal failure necessitating continuous renal replacement therapy. Prior to the cooling process, a continuous electroencephalogram (cEEG) revealed a burst suppression pattern which remained unchanged over a 2-day recording period. A repeat

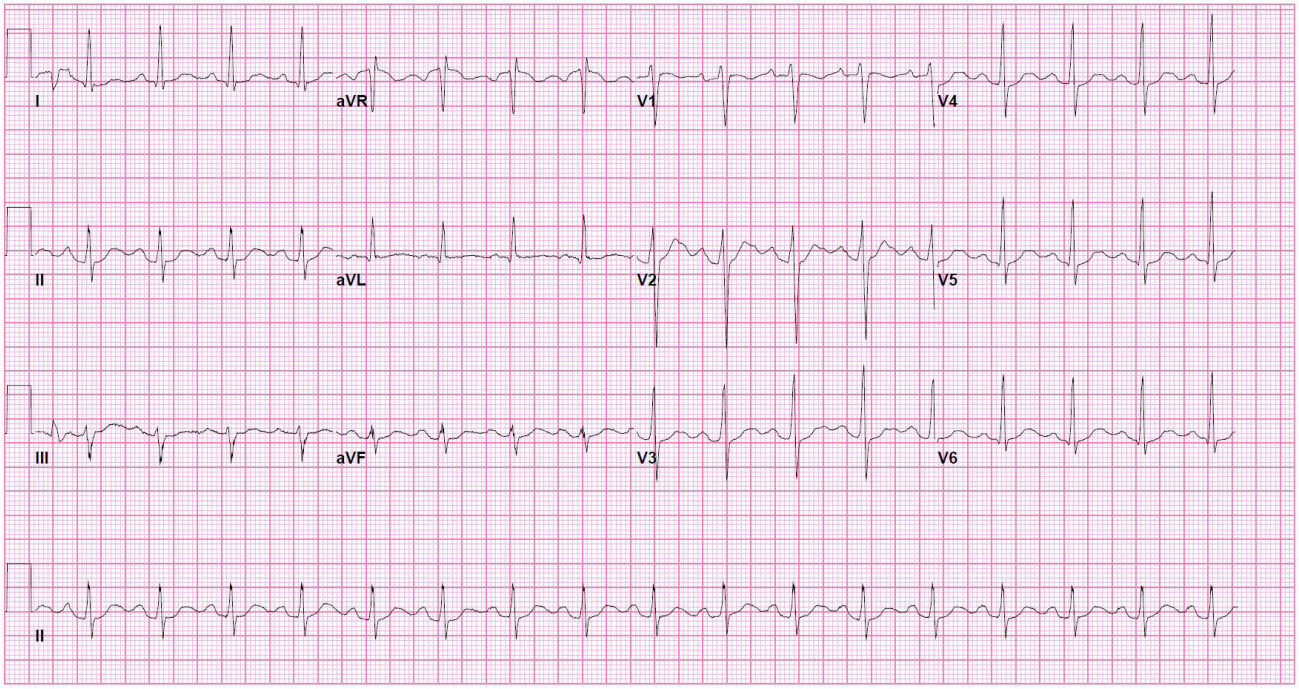

Fig. 1. Electrocardiogram on admission demonstrating normal sinus tachycardia. PR interval: 188 ms, QRS duration: 100 ms, corrected QT (QTc): 474 ms. aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot.

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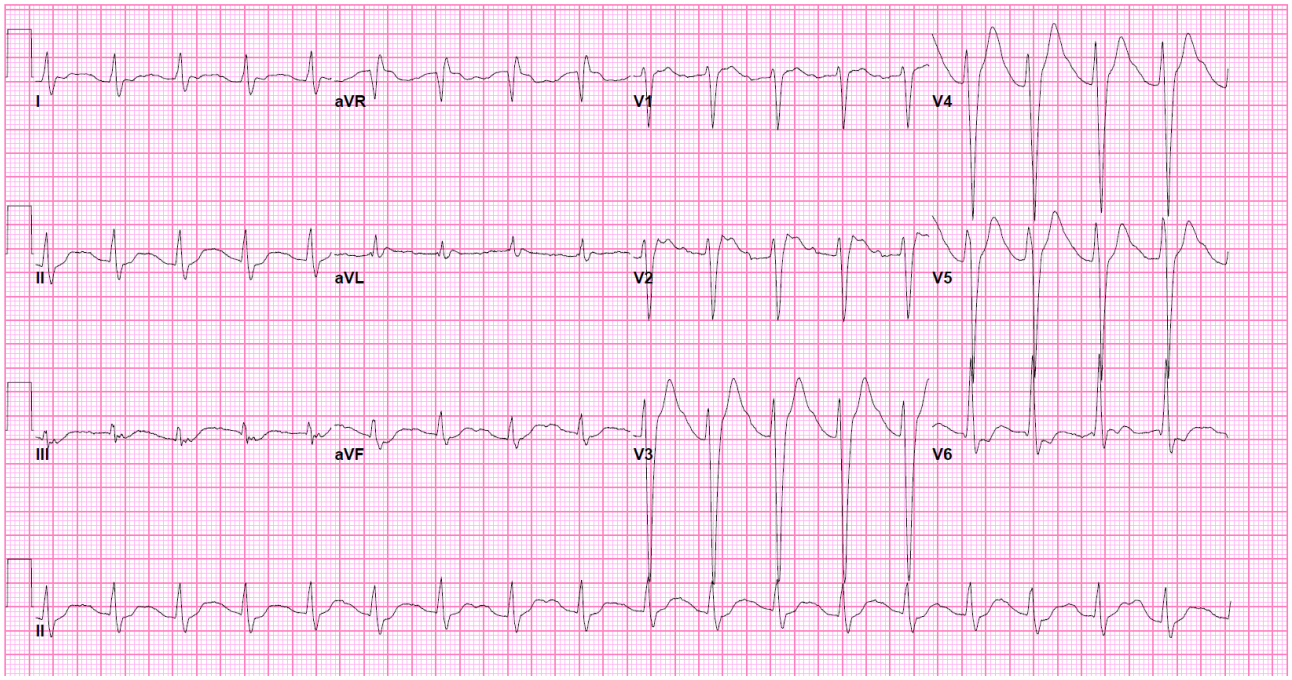

Fig. 2. Electrocardiogram immediately after cardiac arrests showing sinus tachycardia and new first degree atrioventricular block with slight QRS prolongation. PR interval: 256 ms, QRS duration: 144 ms, corrected QT (QTc): 495 ms. aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot.

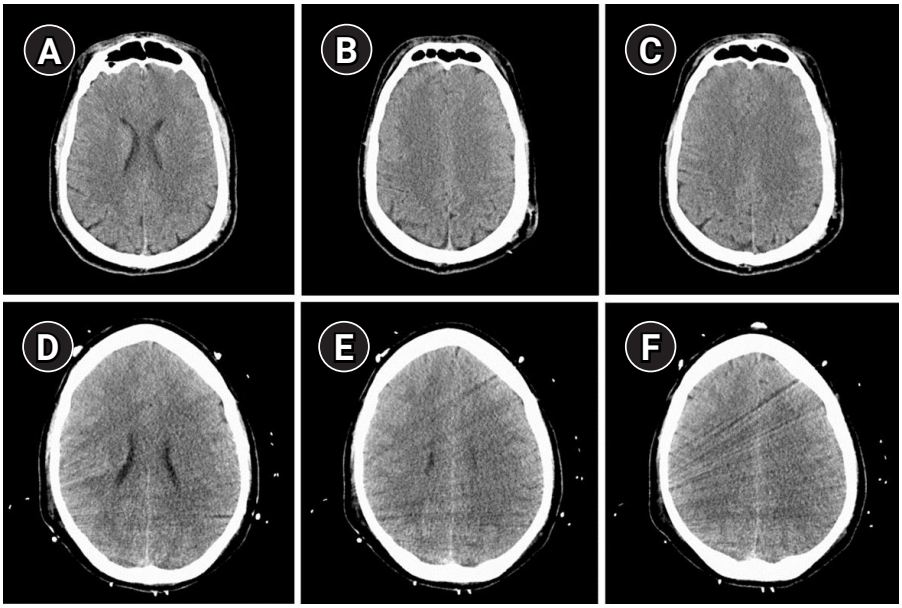

Fig. 3. Head imaging before and after cardiac arrest. (A-C) A normal non-contrast computed tomography (CT) of the head obtained at admission with slices through the corona radiata and centrum semiovale. (D-F) Non-contrast CT of the head obtained 48 hours after cardiopulmonary arrest displaying interval development of sulcal effacement and subtle changes in grey-white matter differentiation at the level of the corona radiata and centrum semiovale.

CT of the brain acquired 48 hours after ROSC was consistent with diffuse cerebral edema and exhibited interval development of sulcal and cisternal effacement and subtle blurring of the grey-white matter interface when compared to his initial scan (Fig. 3). Bedside evaluation at the initiation of TTM had been notable for persistent absence of pupillary, corneal, oculocephalic, and cough reflexes and the lack of any motor reaction to noxious stimulation as previously described. Two days after rewarming was completed

and all sedatives had been discontinued—fentanyl and midazolam infusions were utilized for TTM—no brainstem reflexes (pupillary, corneal, oculocephalic, and cough) and no motor response in any extremity could be elicited on examination. Immediate neurological prognostication and formal brain death testing were not yet pursued, however, due to the recent completion of the targeted temperature protocol and the suspected confounder of ingestion.

On hospital day (HD) 6, the patient regained bilateral corneal and pupillary reflexes. By HD 8, he was conversing and following commands without difficulty. Throughout the remainder of the admission, his overall function continued to rapidly improve. He was eventually discharged on HD 18 with a completely normal neurological examination and no evidence of cognitive impairment on formal neuropsychological testing.

DISCUSSION

Bupropion is a selective dopamine and norepinephrine reuptake inhibitor utilized in the treatment of multiple conditions including clinical depression, attention deficit/hyperactivity disorder, and seasonal affective disorder. It also has adjunct benefits for neuropathic pain, smoking cessation, and weight loss [1]. The most commonly seen side effects are dry mouth, nausea/vomiting, agitation, gastrointestinal discomfort, and dizziness. Serious complications include cardiac abnormalities such as tachycardia and arrhythmias (QRS widening, QT prolongation); cases of cardiogenic shock have also been reported [2]. Significant central nervous system effects consist of hallucinations, agitation, seizures, tremors, stupor, and coma. Bupropion demonstrates linear pharmacokinetics and is hepatically processed into several metabolites—hydroxybupropion, erythrohydrobupropion, and threohydrobupropion. These metabolites, all of which are considered active and whose concentrations rise above their parent drug level, have an elimination half-life of > 20 hours and are eventually renally excreted. Peak plasma concentrations for the SR and XL formulations are reached after 3 and 5 hours, respectively [1,3].

Management of bupropion overdose is primarily supportive and is characterized by standard emergency protocols for airway securement, oxygenation/ventilation, and hemodynamic stabilization; no known antidote exists. Seizures should be treated accordingly, and cEEG monitoring is advised for the first 48 hours since delayed onset of clinical seizures have been observed beyond 14 hours after consumption [4]. Interventions such as gastric irrigation or activated charcoal are generally recommended if ingestion occurs within an hour of presentation. Lipid emulsion therapy in bupropion overdose is an alternative but evidence is controversial and scarce though favorable outcomes have been observed; while not considered a first-line treatment, it may be beneficial in patients with delayed or prolonged deterioration and in those who suffer a cardiac arrest [2].

We acknowledge that the fixed, bilateral mydriasis and poor clinical exam could have been due to the cardiac arrests; both the intoxication and the cardiopulmonary events are undoubtedly contributors to the clinical picture. However, the rapid and complete clinical improvement may suggest a predominantly drug effect. We propose bupropion should be considered a clinically important confounder with unique and dramatic effects on the neurological examination. There have been several descriptions of comatose patients with fixed mydriasis and a burst suppression cEEG secondary to bupropion overdose but without an accompanying cardiopulmonary arrest [5-7]. This supports the notion of bupropion playing a role in a clinically comatose patient apart from any concurrent anoxic brain injury. Similarly, to what degree hypoxia versus possible delayed effects of bupropion were each responsible for the development of cerebral edema in our patient is also unclear. Normal CT findings have been documented with larger ingestion quantities, though imaging was typically obtained solely on admission in these cases; another report recorded diffuse brain edema only after a prolonged arrest [6]. Our case adds to the growing body of literature which suggests bupropion, when consumed in excessively large amounts, might be associated with a disproportionately poor neurological exam. TTM and coexisting renal failure were suspected to also play a role. Furthermore, our patient uniquely illustrates that a full neurological recovery can still be expected despite an ominous clinical course involving multiple cardiopulmonary arrests, organ failure, and the presence of a neurological insult on head imaging. The precise mechanism by which bupropion intoxication can have such a profound impact on the clinical exam is unknown but its modulatory effects on both noradrenaline and dopamine throughout the brainstem have been implicated. Noradrenergic alterations in the locus coeruleus, for example, influence pupillary size even in the absence of luminescent stimulation [8].

Although the patient ingested numerous medications in excess to bupropion, these alternatives were unlikely to be the primary culprit of his poor neurological status given their well-documented toxicology profiles. Mirtazapine has been shown to be largely benign even with overdose of extreme quantities. When consumed along with other substances, the co-ingested drugs are typically deemed the source of severe clinical symptoms [9]. Serotonin syndrome from fluoxetine, a commonly used selective serotonin reuptake inhibitor, is well described along with seizures and cardiac conduction delays [10]. Though coma and poor out-

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comes have been described with oxcarbazepine, they are infrequent and are typically the result of uncontrolled seizures or cardiac conduction irregularities [11]. Lastly, mortality secondary to acute intoxications of gabapentin and hydroxyzine have been reported but are extremely rare; no reports of clinical examinations consistent with brain death have been identified with these medications [12,13].

Our case also reiterates the value and relevance of pharmacodynamics and pharmacokinetics in the assessment of brain injury related to medication overdose. Slower absorption of delayed-release or sustained-release formulations could rationalize the use for employing bowel irrigation or activated charcoal, both of which are usually avoided in late presentations or when time of ingestion is unknown. Likewise, concurrent anticholinergic toxidromes (e.g., hydroxyzine is known to have some affinity for muscarinic acetylcholine receptors), can hinder gastrointestinal motility and absorption and further worsen drug metabolism. Utilization of the aforementioned interventions beyond the customary 1-hour time period in situations where gastric absorption might be impaired (e.g., hypothermia) therefore warrants special consideration.

Finally, the current vignette also accentuates the importance of clinical equipoise in neurological prognostication and brain death evaluations after acute intoxications. Clinicians must not only be aware of potentially significant laboratory derangements related to renal or hepatic injury but must also appreciate how damage to these organs, along with hypothermia, alter systemic metabolism and clearance. Caution must be exercised when numerous substances are involved, and providers should recognize how interventions such as renal replacement therapy may or may not facilitate toxin or medication excretion. Assuming normal hepatic and renal function, formal brain death testing is routinely delayed until at least five half-lives have passed after administration of a potential clinical confounder such as a paralytic or sedative; this time period should be extended even further in the presence of liver and/or kidney damage [14]. In instances where massive overdoses of psychotropic medications are implicated, many of which possess half-lives on the order of days, erring towards a more cautious approach is justified.

Bupropion overdose is associated with a clinical examination demonstrating the absence of brainstem reflexes and the lack of a meaningful motor response, the combination of which can be suggestive of brain death in the proper clinical setting. Despite these worrisome findings, however, a full neurological recovery can still be expected. Special consideration should be given towards the delayed use of gastric or whole bowel irrigation, activated charcoal, and lipid emulsion therapy in specific scenarios. Neurologists and intensivists should be aware of this brain death mimic and be judicious in their efforts to offer prognostication, especially in the setting of various confounders such as cardiac arrest, acute renal or hepatic failure, and TTM.

ARTICLE INFORMATION

Ethics statement

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

Conflict of interest

No potential conflict of interest relevant to this article.

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Endovascular treatment for pseudoaneurysm after carotid blowout syndrome

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CASE REPORT

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Background: Pseudoaneurysms of the carotid artery are rare and can be both a cause and consequence of carotid blowout syndrome (CBS) in patients with head and neck cancer. Surgical or endovascular treatment approaches may be useful for managing this condition.
Case Report: A 55-year-old man presented with a pulsatile mass surrounding the carotid bifurcation in the neck. He reported a history of CBS that occurred as a surgical complication while removing a benign neck cyst. Additionally, he reported a history of laryngeal cancer that underwent complete remission after surgery and radiotherapy. The mass was diagnosed as a pseudoaneurysm. Surgical treatment proved challenging owing to the patient's history of neck surgery and radiotherapy; therefore, stent-graft deployment was performed and the absence of pulsations was checked through the neck mass.
Conclusion: Endovascular treatment may be a useful therapeutic strategy in cases of post-CBS pseudoaneurysm in patients undergoing surgery and/or radiotherapy for head and neck cancer.

Keywords: Aneurysm, False; Carotid artery injuries; Stents

INTRODUCTION

Carotid artery (CA) aneurysms are rare and account for approximately 0.4%–4% of all peripheral artery aneurysms [1]. Pseudoaneurysms are the most common type of CA aneurysms [2]. Trauma is the most common cause of CA pseudoaneurysm, followed by surgery and/or radiotherapy for head and neck cancer [3]. Pseudoaneurysms are not covered by healthy, well-vascularized tissue and can therefore rupture easily [4]. Carotid blowout syndrome (CBS) is the rupture of the CA and its branches, which can cause life-threatening complications due to massive blood loss, as well as neurological complications such as cerebral infarction [5]. A pseudoaneurysm of the CA, while being one of the main known causes of CBS, can also occur as a surgical complication for CBS [1,6].

Pseudoaneurysms are treated using open surgery or with endovascular treatments, such as parent vessel sacrifice, using detachable balloons or coil embolization and stent-graft placement [7,8].

Currently, endovascular treatment is regarded as a better alternative to open surgery in selected patients [7]. We report a case of post-CBS pseudoaneurysm that was treated successfully using endovascular therapy in a patient with a history of surgery and radiotherapy for laryngeal cancer.

CASE REPORT

A 55-year-old man was diagnosed with laryngeal cancer 23 years prior to presentation; complete tumor resolution was observed after partial laryngectomy and radiotherapy. Approximately 1 year before his visit, a palpable mass surrounding the left carotid bifurcation was observed. Ultrasonography revealed a subcutaneous, solid, and well-demarcated ovoid mass that distorted the left internal jugular vein thus necessitating excision. The left internal CA (ICA) was injured intraoperatively during neck dissection which resulted in active bleeding that was managed by an emergency primary suture at the site of injury. The following day, the patient was observed to be drowsy, with an altered mental status, and with severe dysarthria. Diffusion-weighted magnetic resonance imaging revealed border-zone and cortical infarctions in the left cerebral hemisphere (Fig. 1A and B). Computed tomography angiography (CTA) showed multifocal long-segment stenosis of the left common CA (CCA) (Fig. 1C). Volume replacement was performed in addition to blood pressure control to maintain cerebral perfusion pressure. The patient showed complete recovery a month later and was discharged with aspirin (100 mg), clopidogrel (75 mg), and atorvastatin (80 mg) for multifocal stenosis extending along the CCA to the ICA. Histopathologic findings of the neck mass revealed benign soft tissue without any evidence of inflammation or tumor cells. No bleeding or abnormal vessel formation was observed at the site of CBS; the patient was therefore instructed to follow up with the outpatient department.

During follow-up, a pulsating mass was detected in the vicinity of the previous site of injury (Fig. 1D). This mass gradually increased in size and was clearly identified a year after the development of the CBS. CTA revealed a new pseudoaneurysm immediately beneath the skin in addition to multifocal long-segment stenosis of the left CCA (Fig. 1E). Because of the patient's history of partial laryngectomy and radiotherapy, we expected that performing surgical ligation would be technically challenging; therefore, a self-expandable stent graft was used to treat the post-CBS pseudoaneurysm. We inserted a 10-F sheath through the right femoral artery and an 8-F guiding catheter (Shuttle; Cook, Bloomington, IN, USA) was into the proximal portion of the left CCA. Left CCA angiography revealed a pseudoaneurysm at the carotid bulb with multifocal long-segment stenosis of the left CCA (Fig. 1F). A microcatheter (Headway 17; Microvention, Tokyo, Japan) was placed at the orifice of the external CA (ECA) and coil embolization (Tornado, Cook) of the left ECA was performed to prevent a type II endoleak after stent placement. A 0.035-inch guidewire was placed at the petrous portion of the left ICA after confirming that coil embolization had completely blocked blood flow through the ECA. A 9×60-mm self-expandable stent graft (Covera Plus; Bard Medical, Covington, GA, USA) was selected based on the dimensions of the affected CA (the graft size was at least 1 mm greater than the diameter of the CCA). The self-expandable stent graft was then advanced over the 0.035-inch guidewire and deployed to extend between the distal segment of the left CCA and the proximal ICA, ensuring that the pseudoaneurysm was completely covered. Left CCA angiography was performed after stent graft deployment and showed the absence of a pseudoaneurysm. We subsequently placed a carotid stent into the stenotic segment of the left CCA, which, if left untreated, could have served as a potential source of emboli thereby predisposing the patient to ischemic stroke. A 9×50 mm carotid stent (Carotid Wallstent; Boston Scientific, Santa Clara, CA, USA) was advanced over a 0.014-inch microwire (Transend; Stryker, Kalamazoo, MI, USA) and deployed from immediately beneath the orifice of the left proximal ICA, partially overlapping the previously deployed self-expandable stent graft. Left CCA angiography revealed no pseudoaneurysms, in-stent stenosis, or in-stent thrombosis (Fig. 1G). Carotid duplex ultrasonography was performed the following day and revealed no stenotic flow, in-stent stenosis, or thrombosis. Moreover, the patient did not show any postoperative neurological symptoms. A CTA was performed 7 days postoperatively which confirmed the disappearance of the pseudoaneurysm with good stent patency (Fig. 1H). After 3 months, the pulsatile mass disappeared completely (Fig. 1I).

DISCUSSION

A pseudoaneurysm is defined as a loss of integrity of the three layers of the arterial wall that can result in a contained rupture of blood vessels; this differs from a true aneurysm in which the three vascular walls are intact but dilated [9]. Pseudoaneurysms of the ICA are known to present as a growing pulsatile mass in the lateral aspects of the neck [10].

Radiotherapy following head and neck cancer surgery is known as an important cause of CA pseudoaneurysm that can lead to CBS [11]. The CA receives 80% of its blood supply from the vasa vasorum in its adventitia (the outermost layer of the CA) [4]; radiotherapy results in injury to the adventitia of the CA and/or its major branches, resulting in the weakening of the arterial wall

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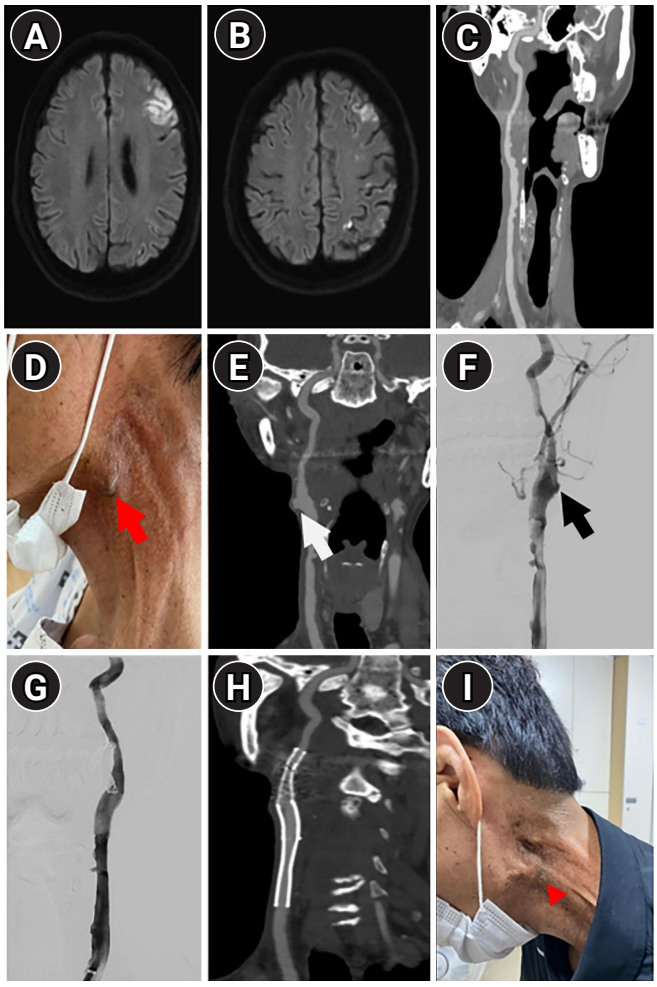

Fig. 1. (A, B) Cortical and border-zone infarctions in the left cerebral hemisphere. (C) Multifocal long-segment stenosis of the left common carotid artery extending to the proximal internal carotid artery on computed tomography angiography. (D) A pulsating mass in the vicinity of the previous injury site of the carotid artery (red arrow). (E) Pseudoaneurysm immediately beneath the skin (white arrow). (F) Pseudoaneurysm (black arrow) with long-segment stenosis of the left common carotid artery on digital subtraction angiogram. (G) Non-visualization of pseudoaneurysm after deployment of a self-expandable stent graft. (H) The disappearance of the pseudoaneurysm with good stent patency on computed tomography angiogram 7 days after endovascular treatment. (I) The disappearance of the pulsatile mass in the vicinity of the previous injury site of the carotid artery (red arrowhead) after 3 months.

[5,12]. Thus, radiotherapy itself can be the main cause of pseudoaneurysm formation in CA. In addition, weakening of the arterial wall due to radiotherapy after head and neck cancer surgery can increase the risk of pseudoaneurysm formation after surgical repair for CBS.

Treatment modalities for pseudoaneurysms can be categorized into surgical repair and endovascular treatment [7,8]. Surgical repair involves surgical ligation of the affected ICA followed by vascular bypass or anastomosis; this procedure sacrifices the ICA. Furthermore, surgical ligation can predispose patients to cerebral ischemia, and bypass or anastomosis cannot be performed when the aneurysms are located near the skull base. Additionally, the open access approach is challenging in patients who previously underwent surgery or radiotherapy for head and neck cancer [8].

Endovascular treatment involves deconstructive methods, such as occlusion of the affected ICA using a balloon or coil, and reconstructive methods, such as stent-graft placement [5,7]. Because stent-graft placement is less invasive and has lower complication rates [13], it may be a useful strategy for managing post-CBS aneurysms especially in patients with a history of surgery and/or radiotherapy for head and neck cancer. Nevertheless, the following factors should be considered prior to stent-graft placement for CBS: (1) it is necessary to assess the patient's anatomical suitability for the procedure, as this method is only feasible in patients without excessive vascular tortuosity, to ensure easy access for the stent delivery system, and in those with patent femoral or iliac arteries to ensure placement of a large-caliber (10–11F) vascular sheath [14]; (2) stent-grafts are more thrombogenic than bare stents and warrant long-term aggressive antiplatelet therapy which involves a high risk for bleeding complications [15]; and (3) endoleak is a common complication of stent-graft placement. Specifically, reconstitution of the proximal branches of the ECA for lesions in the vicinity of the carotid bifurcation is associated with a risk for developing a type II endoleak from collateral vessels [16]; however, embolization of the main trunk of the ipsilateral ECA can reduce this risk [14].

In our case, the patient was relatively young and had a favorable vascular anatomy and was therefore considered to be a suitable candidate for endovascular treatment. In addition, severe adhesions were detected intraoperatively between the CA and the surrounding connective tissue, which occurred at the time of CBS development. Based on these findings, we performed endovascular treatment for a post-CBS pseudoaneurysm. Furthermore, we performed ECA embolization to prevent a type II endoleak.

In conclusion, the anatomical constraints associated with surgical treatment of post-CBS pseudoaneurysm make endovascular treatment an appealing alternative. This case illustrates the usefulness of stent-graft placement in treating post-CBS pseudoaneurysms.

ARTICLE INFORMATION

Ethics statement

This study was reviewed and approved by the Institutional Re-

view Board of Keimyung University Dongsan Hospital (IRB No. 2020-09-068). The requirement to obtain informed consent was waived by the Board.

Conflict of interest

Dr. JH Hong 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.

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Conceptualization: HP, Data curation: CHC, YNR, SHL, YSJ, JHH, SIS, Writing–original draft: CHC, HP, Writing–review & editing: HP.

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Central skull base osteomyelitis due to nasopharyngeal *Klebsiella* infection

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CASE REPORT

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Background: Skull base osteomyelitis (SBO) is a rare but life-threatening disease occurring as a complication of malignant otitis externa, and accompanied by venous sinus thrombosis, meningitis, abscess, cranial neuropathies, and carotid invasion as complications. Central SBO may originate from a paranasal infection, such as sphenoidal or ethmoidal sinusitis without associated external otitis.
Case Report: We describe a 36-year-old Sri Lankan male with central SBO presenting with multiple embolic infarctions and meningitis caused by a nasopharyngeal *Klebsiella* infection that had invaded the left internal carotid artery. Despite complications, such as endogenous endophthalmitis, abscesses in the brain parenchyma, and mycotic aneurysms in cerebral vessels, the patient recovered after 8 weeks of intensive antibiotics treatment except for a remnant mycotic aneurysmal dilatation in the internal carotid artery.
Conclusion: This is the first report of central SBO caused by a nasopharyngeal *Klebsiella* infection, which invaded the left internal carotid artery and led to multiple complications.

Keywords: Skull base osteomyelitis; Infarction; *Klebsiella*

INTRODUCTION

Skull base osteomyelitis (SBO) is a rare but life-threatening disease usually seen as a complication of otitis externa [1]. It initially involves the lateral part of the temporal bone and extends to the petrous apex and clivus [2], accompanied by bone erosion, thrombophlebitis, and hematogenous seeding [3]. Thus, patients with SBO typically present with otalgia, otorrhea, hearing loss, and cranial nerve dysfunction in the immunocompromised, particularly older diabetic patients [4].

Although SBO typically evolves as a complication of malignant otitis externa, atypical or central SBO without associated external otitis has occasionally been reported [5,6]. Central SBO is generally caused by paranasal infections, such as sphenoidal or ethmoidal sinusitis; thus, patients with central SBO usually experience headaches, atypical facial pain, and cranial nerve palsies at the time of initial presentation [7,8]. Furthermore, compared to the known complications of SBO, including venous sinus thrombosis, meningitis, abscess, cranial neuropathies, and carotid invasion with or without ischemic stroke [1], the pattern of complica-

tions in central SBO is different. This is because the inflammation in the cavernous sinus can easily spread to the carotid siphon, causing inflammatory arteritis and, in turn, leading to stroke by carotid artery occlusion or septic embolism [9].

We describe a case of central SBO who initially presented with severe headache, fever, aphasia, and right hemiparesis due to multiple embolic infarctions and meningitis, caused by a nasopharyngeal *Klebsiella* infection that invaded the left internal carotid artery (ICA), which led to septic embolism and mycotic aneurysmal formation.

CASE REPORT

A 36-year-old Sri Lankan male was transferred to our emergency department with the chief complaints of headache, fever, and aphasia emerging after 3 weeks of sore throat and cough without a preceding history of otitis externa. He had been diagnosed with type 2 diabetes mellitus 3 years before but had discontinued medication 3 months prior to the current presentation. On neurological examination, his mental status was alert, and cranial nerve examinations revealed unremarkable findings. However, he showed global aphasia and right hemiparesis, equivalent to a score of 9 points in the National Institutes of Health Stroke Scale (NIHSS), with neck stiffness. Otorhinolaryngological examination revealed left nasopharyngeal mucosal swelling with purulent discharge and otitis media with effusion. Laboratory data showed elevated leukocyte count (15,150/μL), erythrocyte sedimentation rate (ESR; 105 mm/hr), C-reactive protein (CRP; 15.76 mg/dL), and glycated hemoglobin (12.3%).

Brain magnetic resonance imaging (MRI) showed multiple embolic infarctions, particularly in the territory of the left middle cerebral artery, and abnormally increased gadolinium enhancement in the left parapharyngeal space invading the left infratemporal fossa and skull base. In addition, increased sulcal effacement suspicious of leptomeningitis was detected in both frontal and parietal lobes. Computed tomographic angiography revealed luminal narrowing with filling defects in the petrous portion of the left ICA (Fig. 1A and B). These findings were compatible with the invasion of nasopharyngeal infection into the carotid artery and skull base, which, in turn, led to multiple embolic cerebral infarctions. Cultures of peripheral blood and nasopharyngeal discharges revealed the presence of *Klebsiella pneumoniae*. Thus, the patient was initially treated with intravenous antibiotics, including ceftazidime and vancomycin as the empirical regimen and then treated with a modified regimen, including ceftriaxone and vancomycin targeting the *Klebsiella* for 8 weeks of schedule.

On the 3rd day after admission, the patient suddenly developed a blurring vision accompanied by eyeball pain, chemosis, and conjunctival injection in his left eye. On ophthalmologic examination, bacterial endophthalmitis was diagnosed due to septic embolism from the invaded ICA. Subsequently, intravitreal injection of vancomycin and ceftazidime was administered and vitrectomy was performed. Follow-up brain MRI and magnetic resonance angiography (MRA) after 2 weeks of treatment showed a newly developed brain abscess within prior ischemic lesions and mycotic aneurysmal formation in the left cervical ICA (Fig. 1C). Sequential follow-up of brain MRI and MRA at 4 weeks and 8 weeks of antibiotic treatment showed an improving course of prior lesions with a decreased size of brain abscess and decreased gadolinium enhancement in the left infratemporal fossa and skull base, but an increased size of the aneurysm in the left cervical ICA (Fig. 1D). After completing 8 weeks of intravenous antibiotic treatment, the patient showed an improvement in neurological deficit except for a remnant mild degree of facial palsy (NIHSS 1) with normalized serum levels of ESR and CRP and non-detectable pathogen on repeatedly performed blood cultures. Although we considered a rescue treatment with stent-assisted coil embolization to manage the worsening aneurysmal dilation in the left ICA, the patient was required to return to his own country due to the expiration of his visa.

DISCUSSION

We describe a case of a 36-year-old Sri Lankan male with central SBO caused by a nasopharyngeal *Klebsiella* infection that invaded the left ICA and led to multiple embolic infarctions and meningitis, followed by endogenous endophthalmitis, brain abscess, and mycotic aneurysms despite antibiotic treatment. Central SBO originating from nasopharyngeal infection is rarely reported and difficult to diagnose as the radiological findings frequently mimic nasopharyngeal carcinoma with skull base involvement [7]. SBO is a rare but life-threatening disease if not properly diagnosed and treated. A recent systematic retrospective study showed that 42 patients with central SBO had a 9.5% mortality rate, with long-term neurologic sequelae seen in an additional 31% of cases despite aggressive treatment [5,10]. Therefore, prompt commencement and selection of appropriate antibiotics are crucial for the treatment of central SBO, and close monitoring is essential for early detection of multiple complications, such as septic embolism and mycotic aneurysmal formation even during the antibiotic treatment.

Central SBO mainly involves the sphenoid and occipital bones and usually occurs due to the direct spread of infection from the paranasal sinuses, mastoid process, middle ear, or oral cavity [10].

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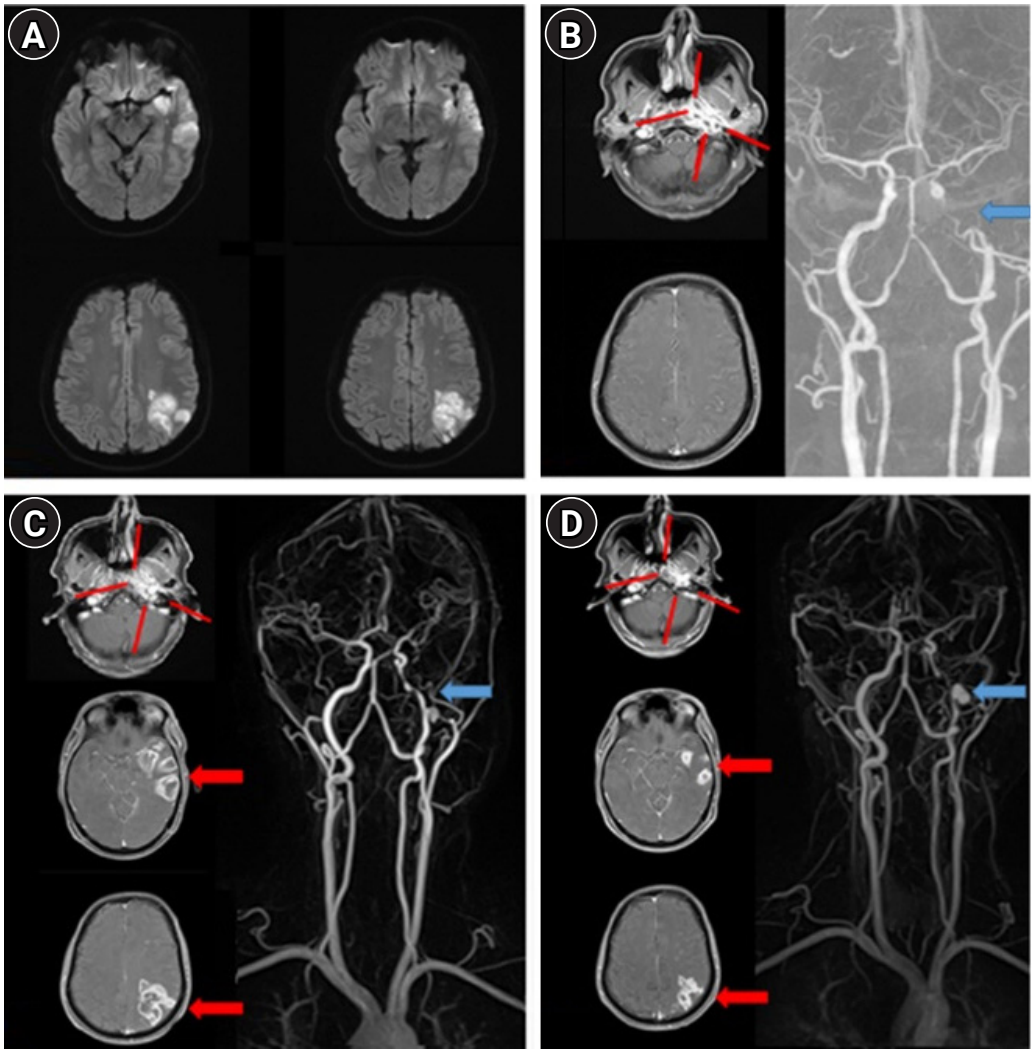

Fig. 1. Brain magnetic resonance imaging (MRI) and computed tomography angiography (CTA) findings at admission (A, B), at 2 weeks of hospitalization after the onset of endogenous endophthalmitis (C), and at 8 weeks of hospitalization after completion of the antibiotic treatment (D). (A) Baseline MRI revealed multiple embolic infarctions on diffusion weighted image sequence in the region of the left middle cerebral artery. (B) Baseline MRI revealed an increased gadolinium enhancement in the left infratemporal fossa and skull base (red lines) and sulcal enhancement in the hemispheres (left), and baseline CTA (right) revealed a narrowing in the left petrous portion of the internal carotid artery (ICA; blue arrow), compatible with osteomyelitis due to the extension of a deep neck infection into the ICA. (C) Follow-up MRI revealed an increased enhancement in the left infratemporal fossa and skull base (red lines) and newly developed ring enhancement in the infarct area (suspicious of brain abscess formation; red arrows), and follow-up magnetic resonance angiography (MRA) revealed an interval improvement of the left distal ICA stenosis with a newly developed aneurysmal formation (mycotic aneurysm, blue arrow). (D) Follow-up MRI revealed an improvement in the inflammation in the left skull base and neck (red lines) and brain abscess (red arrow), and follow-up MRA revealed an increased size of the aneurysm in the ICA (blue arrow).

Underlying diabetes mellitus and immunodeficiency are common predisposing factors [4]. Headache and/or facial pain and cranial nerve palsies are common at initial presentation, followed by nasal congestion/discharge and fever. According to the previous literature, *Pseudomonas aeruginosa* is the most common pathogen causing central SBO, while fungal or mixed bacterial infections have also been reported [7]. Although standard protocol has not been proposed regarding the duration of antibiotic therapy in central SBO, currently, 6–20 weeks of broad-spectrum antimicrobial agents are recommended [11]. Our patient also recovered after 8 weeks of intensive antibiotic treatment with ceftriaxone and vancomycin targeting the *Klebsiella* infection. Central SBO caused by *Klebsiella* has been reported in patients with sphenoid sinus cholesteatoma [12] and a history of previous ear infections [11,13]. Thus, to our knowledge, this is the first report of a central SBO case caused by nasopharyngeal *Klebsiella* infection. In this case, the nasopharyngeal *Klebsiella* infection led to SBO by invading the ICA, which, in turn, led to multiple embolic infarctions, men-

ingitis, endophthalmitis due to septic embolism, and mycotic aneurysms.

ARTICLE INFORMATION

Ethics statement

Approval for this study was waived by the Institutional Review Board of Pusan National University Yangsan Hospital because of the usual practice, and informed consent was obtained from the patient to publish his case.

Conflict of interest

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

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Multiple embolic infarctions and intracranial hemorrhage in a patient with gestational trophoblastic disease

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CASE REPORT

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Background: Choriocarcinoma is a subtype of gestational trophoblastic disease (GTD) that can spread to multiple organs, including the central nervous system. Most cases of GTD affecting the central nervous system can cause intra- or extra-axial hemorrhages. Herein, we describe a rare case of multiple embolic infarctions and intracranial hemorrhages in a patient with GDT.
Case Report: A 36-year-old woman with sudden headache and right homonymous hemianopsia was admitted to our hospital 19 hours from symptom onset. Brain magnetic resonance imaging revealed small acute infarctions in the territories of the left posterior cerebral artery and both middle cerebral arteries. Furthermore, intracerebral hemorrhage in the left occipital lobe, small amounts of intraventricular hemorrhage, and subarachnoid hemorrhage were observed. In the past, she gave birth to her child through cesarean section 6 months ago. D-dimer level was elevated with a value of 1.61 μg/mL (reference range <0.5 μg/mL). Her urine beta-human chorionic gonadotropin (hCG) was positive, and her serum beta-hCG level was >1,000 IU/mL. She was diagnosed with GTD and underwent chemotherapy.
Conclusion: The precise pathogenesis of the coexistence of multiple embolic infarctions and intracranial hemorrhage remains unclear. Cancer-related coagulopathy, micro-tumor emboli, or both could be involved in the pathogenesis of the rare presentation of this patient.

Keywords: Gestational trophoblastic disease; Stroke; Intracranial hemorrhage

INTRODUCTION

Gestational trophoblastic disease (GTD) is a clinical spectrum consisting of benign hydatidiform mole, invasive mole, and highly malignant choriocarcinoma. Choriocarcinoma can spread rapidly through the bloodstream to the lungs, vagina, liver, kidney, ovaries, and brain. Approximately 20% of patients with choriocarcinoma have central nervous system (CNS) involvement, with diverse symptoms [1]. Most cases affecting the CNS include intra- or extra-axial hemorrhages due to oncotic aneurysm formation and its subsequent rupture [2]. Herein, we report a case of a patient with GTD with rare multiple embolic infarctions and intracranial hemorrhage.

CASE REPORT

A 36-year-old woman with sudden headache and right homonymous hemianopsia that occurred 19 hours before presentation was admitted to the emergency room (ER) on November 25, 2016. She had experienced facial palsy in the left side and clumsiness in the left arm 3 months before presentation, but spontaneously recovered within a week. One month later, she experienced weakness and numbness in her left hand. She experienced intermittent headaches intermittently for 15 days. The headache worsened and was accompanied by nausea and vomiting from the day before the ER visit.

In the past, she gave birth to her child through cesarean section 6 months ago. She had no family history of stroke. Brain magnetic resonance imaging (MRI) revealed small acute infarctions in multiple vascular territories, including the left posterior cerebral artery and both middle cerebral arteries (MCAs). Furthermore, intracerebral hemorrhage (ICH) in the left occipital lobe, small amounts of intraventricular hemorrhage (IVH), and subarachnoid hemorrhage (SAH) were observed. There was no significant vascular derangement on her magnetic resonance angiography (Fig. 1). Initial blood pressure and body temperature were 188/89 mmHg and 36.8°C, respectively. We performed an emergency transthoracic echocardiography to assess infective endocarditis. There was no evidence of vegetation or any embolic source, such as patent foramen ovale, ischemic heart disease, or valvular disease. Normal sinus rhythm was observed on electrocardiography. Complete blood counts, erythrocyte sedimentation rate, urinalysis, plasma electrolyte, kidney, liver, and thyroid function tests were normal. D-dimer level was elevated with a value of 1.61 μg/mL (reference range < 0.5 μg/mL). We performed chest and abdominal computed tomography (CT) to rule out malignancy. Chest CT revealed clustered nodular and tubular opacities, and tree-in-bud appearances were observed in both lungs, which were indicative of pulmonary tumor thrombotic microangiopathy (PTTM) (Fig. 2). There were no abnormal findings on her abdominal CT. Her urine beta-human chorionic gonadotropin (hCG) was positive, and serum beta-hCG level was > 1,000 IU/mL. The elevated level of beta-hCG in her serum and the presence of PTTM in a patient of reproductive age strongly suggested GTD. However, the pathology result of the endometrial biopsy was nonspecific.

With intravenous nicardipine and labetalol administration, her systolic blood pressure was lowered immediately to 140 mmHg or less to prevent hematoma expansion. She was administered a dose of mannitol (40 g; 2 bottles of 20% mannitol; 100 mL) four times a day for 5 days and then tapered off over 4 days. Combinations of nonsteroidal anti-inflammatory drugs and opioids have also been used to control headache. Her follow-up CT confirmed that there was no hemorrhage expansion and rebleeding. After mannitol tapering, she was transferred to the department of oncology. At that time, she complained of a mild headache and right homonymous hemianopsia, and there was no other neurological

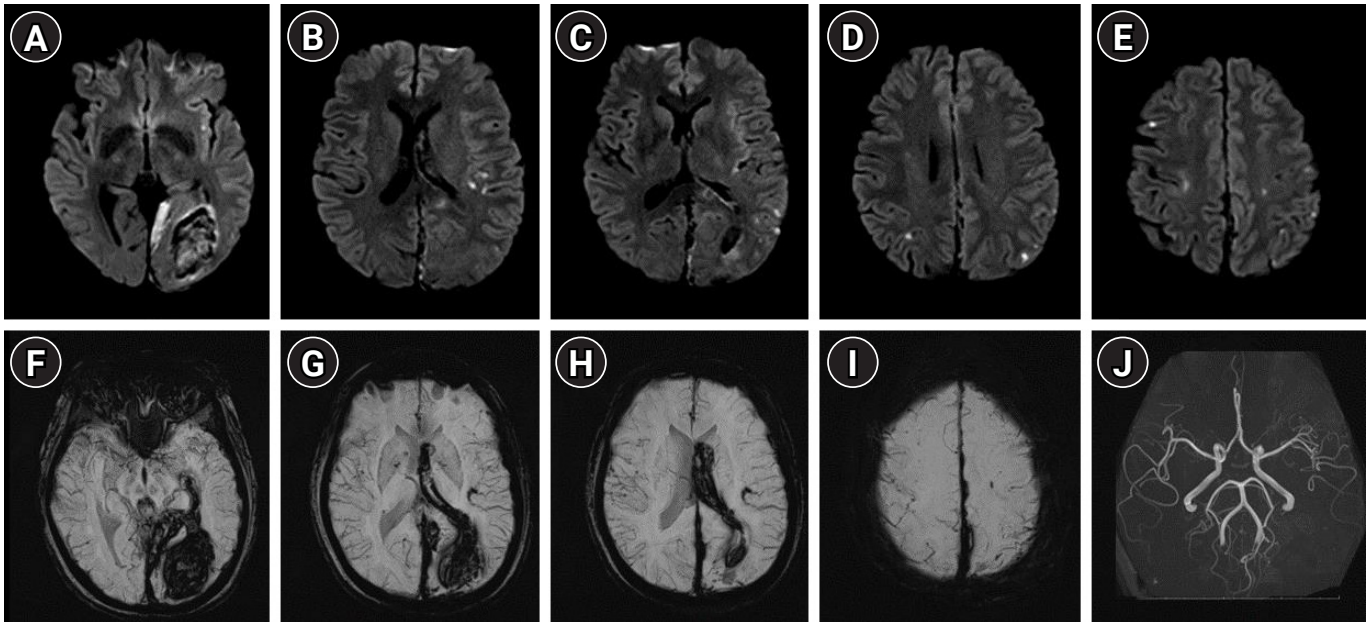

Fig. 1. Initial brain magnetic resonance imaging shows multiple embolic infarctions in the multiple vascular territories (A-E). Intracerebral hemorrhage in the left occipital lobe and adjacent intraventricular, subdural and subarachnoid hemorrhages are also observed on susceptibility-weighted images (F-I). No significant vascular derangement is seen on the magnetic resonance angiography (J).

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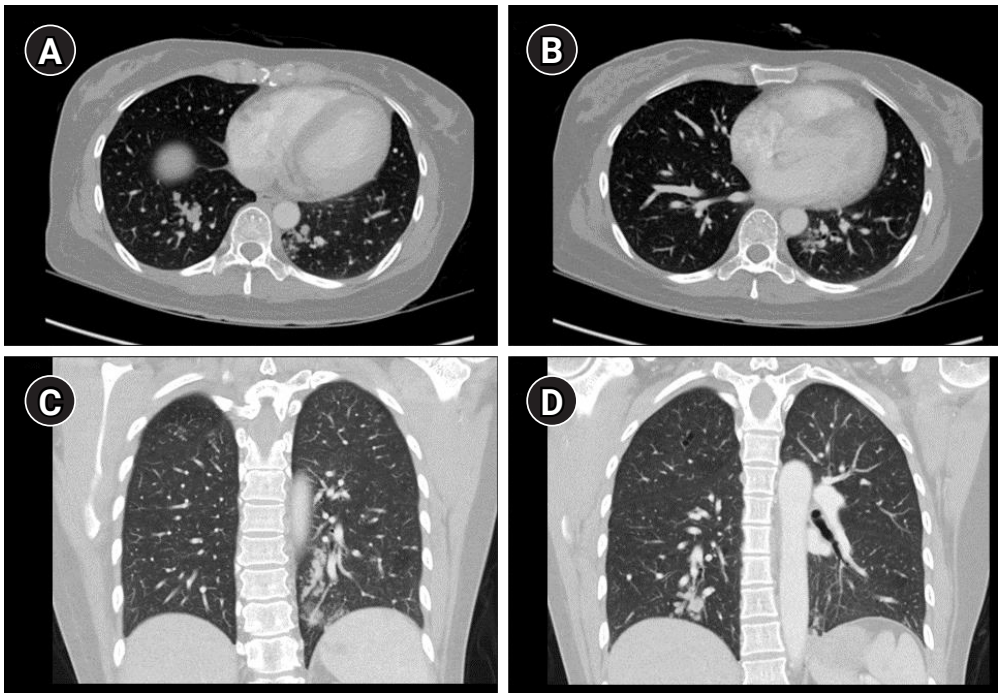

Fig. 2. Axial (A, B) and coronal (C, D) views of the chest computed tomography show clustered nodular and tubular opacities, as well as tree-in-bud appearances in both the lungs.

deficit on her neurological examination. She started chemotherapy with etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine on December 5, 2016. The level of beta-hCG decreased dramatically to the normal range (8.0 IU/mL on January 16, 2017). Cerebrospinal fluid (CSF) analysis was performed on December 19, 2016. The white blood cell and red blood cell counts in the CSF were 0 /mm^3 and 3 /mm^3, respectively. The CSF protein level was in the normal range (32.2 mg/dL). There was no evidence of malignancy on CSF cytology. The patients completed chemotherapy on November 7, 2017. Follow-up brain MRIs on November 14, 2016, January 1, 2017, and February 27, 2017, revealed no recurrent stroke. Brain MRI has been performed every year to check for recurrent brain lesions. Lately, she underwent brain MRI on July 24, 2020, and there was no evidence of recurrence. To date, there have been no neurological deficits other than visual field defects.

DISCUSSION

Choriocarcinoma is a very aggressive, malignant variant of GTD, which grows rapidly and metastasizes to the lung, liver, and, less frequently, to the brain. The metastatic involvement of the lung in our case suggested that the clinical pathologic form of this patient was choriocarcinoma. Most cases of choriocarcinoma involving the CNS present with both intra- and extra-axial hemorrhage. These were manifested by vascular fragility and rupture of oncotic aneurysms. Arterial infarctions due to direct tumor emboli are also possible, but there was no evidence of vascular tumor invasion on serial contrast-enhanced MRI [2]. If the ratio of serum to CSF hCG is less than 60, CNS metastasis is strongly suspected. Unfortunately, we performed CSF analysis two weeks after chemotherapy because increased intracranial pressure was assumed during the period of acute ICH, IVH, and SAH. The ratio of serum to CSF hCG could not be obtained [3]. Acute cerebral infarctions in multiple vascular territories and elevated level of D-dimer (1.61 μg/mL) were observed in this case. These findings suggest that the main cause of multiple cerebral infarctions and hemorrhage could be cancer-associated hypercoagulability rather than direct tumor emboli. A previous study showed that concealed cancer should be considered in patients with ischemic lesions in multiple vascular territories on diffusion-weighted imaging (DWI). The level of D-dimer, a specific derivative of cross-linked fibrin, has been used in many previous studies as a measure of hypercoagulability [4]. The DWI pattern of ischemic lesions in multiple vascular territories and elevated D-dimer level (> 1.11 μg/mL) was independently associated with cancer-related coagulopathy (CRC) [5,6]. In these scenarios, ICH could occur in the preexisting infarct area. There have been a few case reports of metastatic choriocarcinoma as a cause of ischemic and hemorrhagic stroke [7-9]. The case reported by Bonnet et al. [7] was very similar to our case in terms of

the concomitant presence of multiple ischemic stroke and lobar hematoma. In this case, a local thrombus in the left atrium was detected on transesophageal echocardiography (TEE). It could be considered that thrombotic embolus was the most plausible diagnosis. However, there was no evidence of hypercoagulability in her laboratory findings [7]. Another case had multiple distributed, small, and large infarctions. Her neurological state deteriorated 3 days later. Hemorrhagic transformation of the large infarction in the left MCA territory was observed [9]. The precise pathogenesis of multiple small and large infarctions remained uncertain. In our case, D-dimer levels were elevated, suggesting hypercoagulability. Although we could not perform TEE, there was no evidence of non-bacterial thrombotic endocarditis on TTE. Several cases of choriocarcinoma with pulmonary thromboembolism have been reported previously [10]. The effects of thrombolytic therapy, embolectomy, and/or anticoagulant therapy were uncertain in these cases. The literature highlights the importance of early diagnosis and timely appropriate chemotherapy in the management of this condition [10]. In our case, the patient was diagnosed with PTTM. The pathomechanism of PTTM involves tumor cells entering the pulmonary circulation; this occludes small arterioles and expresses vascular endothelial growth factor and tissue factor that lead to proliferation of intimal myofibroblasts and luminal stenosis. The coexistence of the PTTM and stroke suggested that the pathomechanisms of these were similar [11]. The arterial tumor emboli could have occurred when the metastatic pulmonary neoplasm invaded the heart through the pulmonary vein. Although there was no evidence of brain metastasis on the serial contrast-enhanced MRI and CSF analysis, there were possibilities of micro-thromboembolism, micrometastasis, or micro-tumor embolism, which cannot be detected on MRI. Choriocarcinoma may metastasize to the cerebral blood vessels, resulting in ischemic stroke or intraparenchymal hemorrhage [8,12].

Furthermore, the coexistence of micro-tumor embolism with CRC could not be excluded in our case. The ratio of serum to CSF hCG before chemotherapy may be important to confirm CNS metastasis. However, we checked the CSF after the initiation of chemotherapy because of the presence of increased intracranial pressure. Timely appropriate chemotherapy was very important in this condition.

This is a rare case of multiple embolic infarctions and intracranial hemorrhages in a patient with GTD. The precise pathogenesis of coexisting ischemic and hemorrhagic strokes is not clear. CRC, micro-tumor emboli, or both could be the pathogenesis of this rare presentation.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (IRB No. 2020-12-032). Informed consent was waived by the Board.

Conflict of interest

No potential conflict of interest relevant to this article.

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Normal pressure hydrocephalus after gamma knife radiosurgery in a patient with vestibular schwannoma

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CASE REPORT

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Background: Vestibular schwannoma is a benign, usually slow-growing tumor, which develops from Schwann cells of the eighth cranial nerve.
Case Report: The treatment options for the schwannoma are surgical removal or gamma knife radiosurgery. The treatment of choice depends on the size of the tumor and the level of hearing in the affected ear. After gamma knife radiosurgery, there may be some neurological complications including headache, dizziness, motor or cranial nerve deficits, seizure, carotid artery stenosis, and increased intracranial pressure. Hydrocephalus is a rare complication of gamma knife radiosurgery for vestibular schwannoma.
Conclusion: Here, we report a case of normal pressure hydrocephalus after gamma knife radiosurgery in a patient with vestibular schwannoma.

Keywords: Acoustic neuroma; Radiosurgery; Gait disturbance

INTRODUCTION

Vestibular schwannoma (VS) is a benign tumor that grows in Schwann cells of the eighth cranial nerve, and it can be treated by surgical removal or stereotactic radiosurgery including gamma knife surgery. Stereotactic radiosurgery for VS was first attempted in 1969 and has been one of the most active treatments in the last 40 years. The main side effects include facial paralysis, hearing loss, trigeminal neuralgia, and hemifacial spasm [1]. In addition, hydrocephalus is a potential concomitant disease [2-4]. In this article, we report a case of normal pressure hydrocephalus (NPH) in VS that has undergone gamma knife radiosurgery.

CASE REPORT

A 67-year-old woman visited the clinic with hearing loss in the left ear. The symptom began 1 month previously. She did not have a specific medical history, except for myasthenia gravis. Vital signs were within normal ranges. Rinne test was normal on both sides. However, the Weber test detected sensorineural hearing loss on the left side. No other abnormalities were observed during other neurological examinations. Magnetic resonance imaging revealed

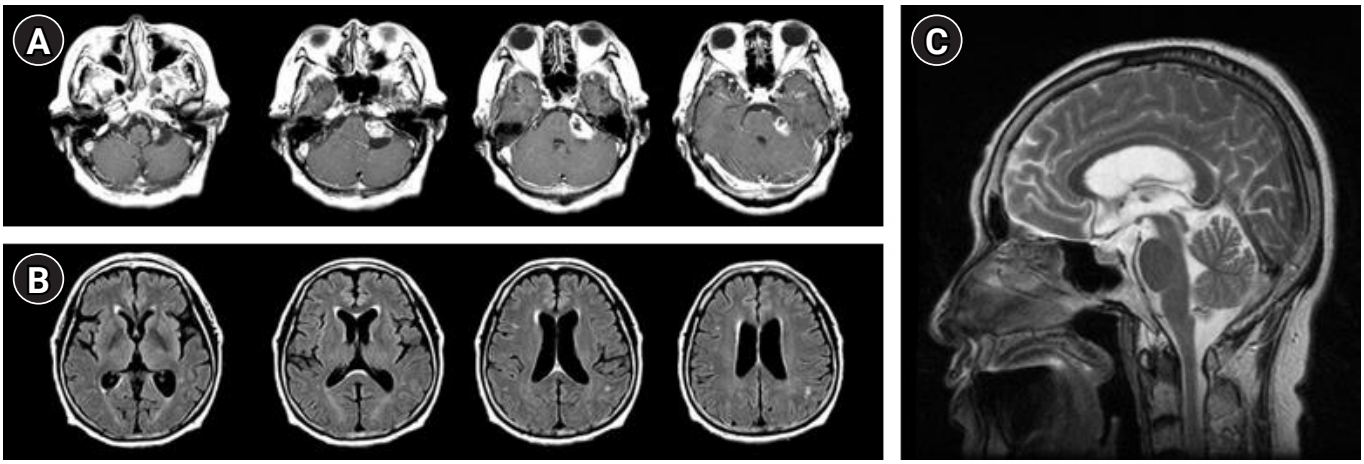

Fig. 1. (A) T1-enhanced images show a mass in the left cerebellopontine angle. (B) Fluid-attenuated inversion recovery images reveal a normal-sized ventricle. (C) T1 midsagittal view does not show any evidence of non-communicating hydrocephalus.

a high signal intensity mass measuring 2.7 cm × 3.0 cm with fine enhancement on the left cerebellopontine angle (Fig. 1). This lesion was diagnosed as VS, and gamma knife surgery was performed.

Three months after, the patient visited the clinic again, complaining of progressive cognitive decline, gait disturbance, and urinary incontinence. Neurologic examination revealed normal cranial nerve functions. Motor and sensory functions were intact. Finger-to-nose and heel-to-shin tests were normal. However, she had a magnetic gait with a wide base. Additionally, she kept on losing her balance as she walked. The Timed Up and Go test was measured at 26 seconds. The patient had 2 years of education. Her Korean Mini-Mental Status Examination (K-MMSE) score was 17/30. Moreover, Seoul Neuropsychological Screening Battery (SNSB) showed impaired attention, verbal and visual memory, and executive function (Table 1).

On follow-up computed tomography (CT) scan, the size of the VS decreased from 2.7 cm × 3.0 cm to 1.6 cm × 2.8 cm, reducing the mass effect to the surrounding brain stem. However, newly developed bilateral ventricular dilatation was observed (Fig. 2). The Evans ratio was 0.37. Cerebrospinal fluid (CSF) drainage was performed, and the pressure was measured at 10 cm H_2O. Leukocyte count was 0/mm^3, erythrocyte count was 0/mm^3, protein concentration was 58 mg/dL, and sugar level was 88 mg/dL (blood sugar, 97 mg/dL), demonstrating mild increases in protein level. After CSF drainage, the patient's gait and urinary incontinence improved. The Timed Up and Go test was measured again, and the result decreased from 26 to 22 seconds. A ventriculoperitoneal shunt was inserted, resulting in subjective improvements in the gait disturbance. Her follow-up K-MMSE score improved to 22, and visual memory and executive function in the SNSB, performed after 3 months, also improved (Table 1). Another CT scan was conducted, and it revealed that the size of the ventricle had decreased, and the Evans ratio measured 0.21 (Fig. 2).

DISCUSSION

Hydrocephalus has been reported repeatedly in patients with VS who undergo gamma knife radiosurgery [1-5]. A causal relationship, however, has not been identified, and the mechanism remains unclear. The most likely hypothesis for the relationship between gamma knife radiosurgery and hydrocephalus involves tumor necrosis, which causes the protein to deposit in arachnoid granulation and interfere with CSF absorption [3]. In this case, the level of protein was slightly increased, supporting this hypothesis. In addition, fourth ventricle compression [6] or CSF flow alteration in basilar cisterns [7] is considered to be another potential mechanism. However, whether these side effects occur only in radiosurgery, including gamma knife, is still controversial [8,9].

According to a 2012 study [9], 19.9% of patients who underwent gamma knife surgery were diagnosed with hydrocephalus. However, 12.8% were diagnosed before gamma knife surgery and 7.6% occurred after surgery. In the same study, there was a statistically significant risk of the development of hydrocephalus, especially in patients with large tumor masses or who are female. With this in mind, the patient in this case was diagnosed with newly developed NPH, characterized by the traditional triad of gradual memory loss, gait disturbance, and urinary incontinence 3 months after gamma knife surgery. The causal relationship between NPH and gamma knife radiosurgery is further supported by the patient's symptom recovery with the insertion of a ventricular abdominal shunt.

Table 1. Results of the neuropsychological test (SNSB) of pre- and post-ventriculoperitoneal shunt

Variable	Preoperative		Postoperative	
	Raw score	%Score	Raw score	%Score
K-MMSE	17	0.27	23	0.15
Digit span				
Forward	4	26.11	4	26.11
Backward	0	0.01	2	11.51
K-BNT	24	0.4	25	0.71
RCFT				
Copy	1	0.01	18	10.56
Immediate recall	NA	NA	0.5	5.48
20-Minute-delayed recall	NA	NA	0	3.92
Recognition	13	0.82	15	5.94
SVLT				
Immediate recall	11	12.51	12	17.88
20-Minute-delayed recall	0	0.15	2	3.14
Recognition	13	0.06	17	9.01
Frontal/executive function				
Contrast program	6	<16	17	<16
Go-no-go test	3	<16	14	>16
Fist-edge-palm test	Abnormal		Abnormal	
Alternating hand movement	Abnormal		Normal	
Alternating square and triangle	Preservation		Preservation	
Luria loop	Preservation		Preservation	
COWAT				
Animal	5	0.37	13	33
Supermarket	3	0.26	9	6.55
ㄱ	0	1.25	0	1.25
ㅇ	0	5.59	1	13.35
ㅅ	0	4.27	0	4.27
Phonemic total score	0	1.13	1	1.79
K-CWST				
Word reading: number of correct response	45	<16	59	<16
Word reading: number of error	8	<16	4	<16
Word reading: response time	120		120	
Color reading: number of correct response	10	0.01	25	0.18
Color reading: number of error	28	0.01	19	0.01
Color reading: response time (sec)	120		120	
CDR				
Score	1		0.5	
Sum of boxes	5		2	
GDS	NA		2	
B-ADL	13		19	

SNSB, Seoul Neuropsychological Screening Battery; K-MMSE, Korean Mini-Mental Status Examination; K-BNT, Korean-Boston Naming Test; RCFT, Rey Complex Figure Test; NA, not applicable; SVLT, Seoul Verbal Learning Test; COWAT, Controlled Oral Word Association Test; K-CWST, Korean-Color Word Stroop Test; CDR, Clinical Dementia Rating; GDS, Global deterioration scale; B-ADL, Basic Activity of Daily Living.

As mentioned above, there have been several reported cases of hydrocephalus developing after radiosurgery for VS. However, in this case, the patient complained of a sudden decline in cognitive function, gait disturbance, and urinary frequency after gamma knife surgery, and the recovery of cognitive function after the shunt operation was confirmed through subjective reports by patients and guardians, as well as objective neuropsychiatric tests. This case is meaningful in emphasizing that neurologists should

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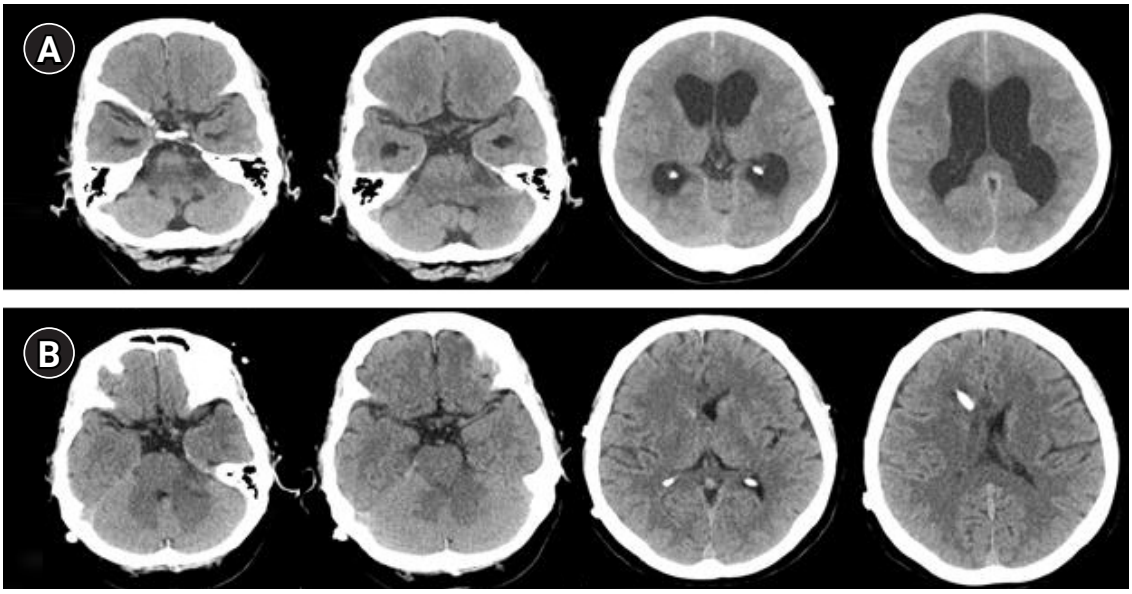

Fig. 2. Non-contrast computed tomography (CT) images of the patient. (A) Three months after gamma knife surgery, follow-up CT scans revealed enlarged ventricles. (B) After ventriculoperitoneal shunt insertion, the size of the ventricles normalized.

actively discriminate and exclude secondary correctable causes, such as NPH, when rapid progressive cognitive decline and gait disturbances occur in patients with a history of brain radiosurgery, especially considering its reversibility.

ARTICLE INFORMATION

Ethics statement

The requirements for approval of the Institutional Review Board and informed consent were waived due to the retrospective nature of this study.

Conflict of interest

No potential conflict of interest relevant to this article.

Author contributions

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Radiculopathy caused by lumbar epidural varix

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CASE REPORT

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Background: Lumbar epidural varix (LEV) is a very rare condition caused by dilatation of the vertebral venous plexus. LEV can result in lumbosacral radiculopathy, which is often mistaken for lumbosacral herniated intervertebral disc (HIVD).
Case Report: A 72-year-old man visited the emergency department (ED) with radiating pain of the right leg that had developed 3 weeks previously. Before the ED visit, he was diagnosed with lumbosacral radiculopathy due to HIVD based on lumbar X-rays at an outpatient clinic. Despite conservative treatment, his symptoms deteriorated. On magnetic resonance imaging at the ED, an epidural cystic mass in the right L5–S1 with multiple HIVDs was observed. The mass was surgically removed, and the histological findings showed a dilated vessel with a thrombus, which led to the final diagnosis of LEV.
Conclusion: In lumbosacral radiculopathy, LEV should be considered as a possibility even if degenerative spine disease is observed on lumbar X-rays.

Keywords: Radiculopathy; Spine; Varicose veins

INTRODUCTION

Lumbar epidural varix (LEV) is a very rare condition caused by dilation of the internal vertebral venous plexus, and can result in lumbosacral radiculopathy by irritating or compressing the epidural or intervertebral foramen [1]. According to previous studies, 0.067% to 1.2% of patients with lower back pain or leg paresthesia are diagnosed with LEV [2]. Clinically, LEV is often confused with lumbosacral herniated intervertebral disc (HIVD), a common cause of lumbosacral radiculopathy, and it is usually diagnosed during or after surgery [3]. Here, we report a rare case of a patient diagnosed with LEV who presented with lumbosacral radiculopathy.

CASE REPORT

A 72-year-old man with past history of hypertension, diabetes mellitus, and hyperlipidemia visited the emergency department (ED) of Jeju National University Hospital with a complaint of radiating pain of the right leg that had developed 3 weeks previously. He visited an outpatient clinic 10 days before presenting to the ED. At that time, lumbar X-rays showed compression fractures in

the T12 and L2 vertebral bodies and L4–5 disc space narrowing on lumbar X-rays, and the patient was diagnosed with lumbosacral radiculopathy due to HIVD. He was prescribed nonsteroidal anti-inflammatory drugs and underwent a nerve block injection, but his symptoms steadily worsened. On the day of the patient's ED visit, his symptoms were so severe that he could not walk.

The patient also stated that he had suffered from lower back pain for 1 month and reported no history of urinary or fecal incontinence, febrile sensation, or rash. He reported no history of trauma or intense exercise. A neurologic examination at the ED showed that his muscle power had been reduced to Medical Research Council grade 4 for right big toe extension. A sensory deficit was documented over the right L4 to S1 dermatome levels. The deep tendon reflex was hypoactive on the right knee and ankle, and Babinski reflexes were negative. In the complete blood count, the levels of white blood cells, platelets, and hemoglobin were 11,700/mm^3 (normal range, 4,000–10,000/mm^3), 385,000/mm^3 (normal range, 150,000– 450,000/mm^3), and 12.6 g/dL (normal range, 13–17 g/dL), respectively. In the coagulation test, the prothrombin time-international normalized ratio and activated partial thromboplastin time were 0.98 (normal range, 0.88–1.20) and 26 seconds (normal range, 20.0–36.0 seconds), respectively: both values were within the normal range. Lumbar magnetic resonance imaging (MRI) showed multiple bulging intervertebral discs. An epidural cystic mass measuring 18 × 11 × 19 mm was also observed in the right L5–S1 intervertebral foramen and the right epidural space. The mass presented as hyperintense on T1-weighted images, hypointense on T2-weighted images, and heterogeneously enhanced on T1 gadolinium-enhanced images (Fig. 1). Emergent partial hemilaminectomies were performed. The ligamentum flavum showed hypertrophy, had turned black, and compressed the right L5 root. A black cystic epidural mass was identified in the shoulder of the right S1 root during surgery. The mass was grossly removed and was shown to be a dilated vessel wall with an organized thrombus on the histological examination (Fig. 2). Finally, the mass lesion was diagnosed as LEV.

The patient's symptoms gradually improved starting on the second day after surgery, Two weeks after surgery, although hypoesthesia in the sole of the right foot was observed, the radiating pain in the right leg had disappeared entirely, and the muscle power of the right big toe was also normal.

DISCUSSION

Our patient was initially diagnosed with lumbosacral radiculopathy caused by HIVD and conservatively treated at an outpatient clinic, but the symptoms worsened, prompting him to visit the

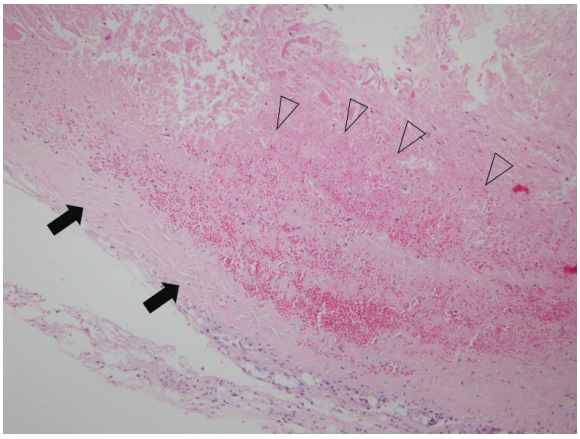

Fig. 2. Dilated and tortuous vessel wall (arrows) with an organized thrombus (arrowheads) in the histological examination (H&E, ×100).

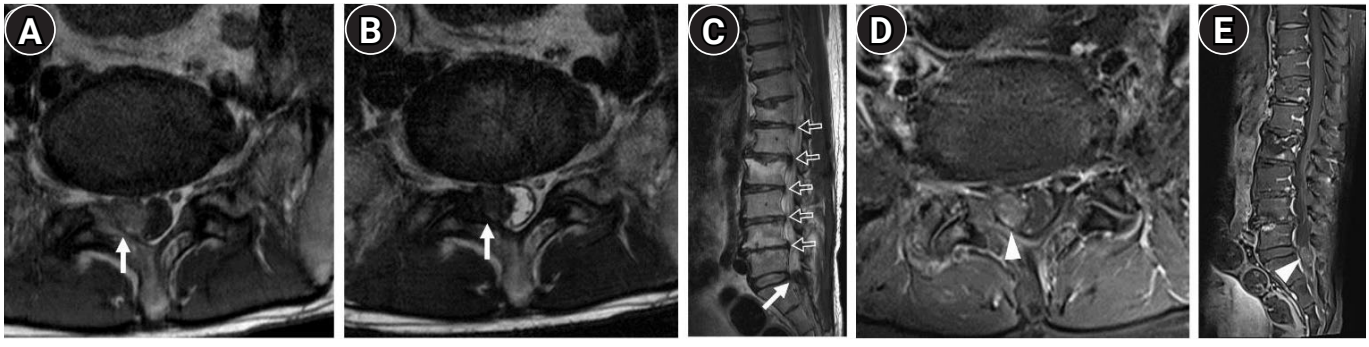

Fig. 1. Preoperative lumbar magnetic resonance images. Axial T1-weighted (A) and T2-weighted (B), and sagittal T2-weighted (C) images show an irregular mass lesion (closed arrows) involving the right facet joint at L5–S1 and the right epidural space at the L5–S1 level. Multiple bulging discs (open arrows) with compression fractures in the T12 and L2 vertebral bodies are also shown on sagittal T2-weighted images (C). Heterogeneous enhancement of the mass is shown on gadolinium-enhanced T1-weighted axial (D) and sagittal images (E) (arrowheads).

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ED. A mass lesion around the epidural space at L5–S1 with multiple spinal degenerative changes was observed on lumbar MRI performed at the ED. The mass was finally diagnosed as LEV after surgical removal.

LEV is challenging to diagnose because of clinicians' unfamiliarity with the disease and its variable findings on MRI, which are attributed to diversiform thrombosed or flowing blood states. Three core MRI findings have been proposed in the literature: an epidural mass of intermediate signal intensity, serpiginous dilated veins, and notable lumbar segmental veins [4]. Slin'ko and Al-Qashqish [1] described the MRI findings more specifically. According to those researchers, normal epidural veins are generally indistinguishable on MRI. Instead, the epidural varix can be visualized in the form of a signal void, or with moderate blood flow, the signal intensity is low on T1-weighted images. On T2-weighted images, the signal intensity is low with high blood flow and high with low blood flow. A pattern of spottiness is rarely seen in partial thrombosis of varicose veins. In some cases, the mass can be enhanced heterogeneously or intensively [1]. These various patterns of MRI findings are often confused with HIVD, synovial cyst, schwannoma, abscess, or a metastatic tumor [5]; therefore, LEV is often diagnosed during or after surgery.

If a clinician suspects LEV, venography can be performed in addition to MRI. If this test shows evidence that is strongly suggestive of LEV, the surgeon has microsurgical treatment options, such as whether to incompletely interrupt the blood flow related to the mass with regard to the collateral flow. Slin'ko and Al-Qashqish [1] suggested spinal venography as a helpful examination, using contrast injection through transdural or spinous process approaches. Based on computed tomography (CT), CT myelography, and MRI, the researchers performed venography in all cases that were assumed not to be typical disc herniation or spinal stenosis. However, only 51 out of 433 patients who underwent venography were identified as having LEV, and of those, 43 cases were surgically confirmed. However, selective spinal angiography is not helpful to identify epidural venous plexus.

The spinal epidural venous system is valveless, connecting the spinal venous flow with the inferior vena cava (IVC). It comprises internal and external venous networks. The internal vertebral venous system consists of anterior and posterior divisions. LEV is known to be associated with the anterior division since it lies before the posterior margins of the vertebral bodies and intervertebral discs [6]. The pathophysiology of LEV formation is not fully understood. Excessive intraabdominal pressure caused by pregnancy, an abdominal tumor, or trauma can keep spinal venous blood from returning to the heart through the IVC, resulting in engorgement of the valveless spinal venous plexus [7,8]. There have also been reports of LEV in patients with coagulopathy (e.g., protein C deficiency) or vasculitis (e.g., Behçet disease) [7].

Some researchers have proposed that degenerative spine diseases, including HIVD, may cause varix by directly irritating the venous endothelium [1,9]. Interestingly, it has been reported that 48 of 1,091 patients who underwent surgery for HIVD turned out to have LEV [10]. Therefore, it should be noted that although LEV can occur independently, it can also be accompanied by degenerative spine diseases such as HIVD, a common cause of lumbosacral radiculopathy. Unfortunately, blood tests for coagulopathy or vasculitis were not performed in our patient, but there was no condition that could increase intraabdominal pressure. However, it is cautiously assumed that the multiple HIVDs observed on lumbar X-ray images may have caused LEV in this patient. As far as is known, the optimal treatment of LEV is surgical resection and decompression, although Tofuku et al. [11] published a case of lumbar LEV that spontaneously regressed in 2 weeks. Whether to remove all perilesional epidural veins is not well established.

In conclusion, LEV is easy to misdiagnose and underestimate. When physicians encounter patients with lumbosacral radiculopathy, they should always be mindful of the possibility of LEV, even if degenerative spine diseases such as HIVD are strongly assumed to be present based on lumbar X-rays. Lumbar X-rays can show bony structural abnormalities, but cannot be used to evaluate the condition of soft tissues around bones (e.g., blood vessels and nerves); therefore, X-ray examinations have low effectiveness in discriminating the cause of radiculopathy. Finally, the exact mechanisms involved in the pathogenesis of LEV remain unclear; systematic research is therefore needed to establish these mechanisms conclusively.

ARTICLE INFORMATION

Ethics statement

This study was conducted with permission from the Institutional Review Board and Ethics Committee of Jeju National University Hospital (IRB No. 2020-10-015). The informed consent was waived due to the retrospective nature of the study.

Conflict of interest

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

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Journal of Neurocritical Care

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- Articles in academic journals

1. Kang J, Kang CH, Roh J, Yeom JA, Shim DH, Kim YS, et al. Feasibility, safety, and follow-up angiographic results of endovascular treatment for non-selected ruptured intracranial aneurysms under local anesthesia with conscious sedation. J Neurocrit Care 2018;11:93-101.
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3. Di Luca DG, Mohney NJ, Kottapally M. Paroxysmal sympathetic hyperactivity with dystonia following non-traumatic bilateral thalamic and cerebellar hemorrhage. Neurocrit Care 2019 Feb 6 [Epub]. https://doi.org/10.1007/s12028-019-00677-9.

- Book & book chapter

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

- Online source

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

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