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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Generalized periodic discharges (GPDs) with triphasic morphology are an electroencephalographic (EEG) pattern traditionally associated with encephalopathy and coma, although they have been observed in a wide array of neurological disorders. The clinical significance of these waveforms and their relationship to seizures and prognosis has been debated, and differentiation between interictal patterns, patterns associated with seizures, and patterns representing nonconvulsive status epilepticus can at times be a challenge. The most established literature suggests that GPDs, including those with triphasic morphology, are associated with the development of electrographic seizures, but that in the absence of clinical information, distinguishing waveforms based on morphology alone may not be clinically useful. Recent work has advocated for a more proactive approach in evaluating GPDs with triphasic morphology. Further studies of nonsedating antiseizure drugs in patients with GPDs with triphasic morphology that incorporate continuous EEG monitoring will be useful in tailoring therapy to optimize long-term clinical outcomes and recovery.

**Keywords:** Triphasic waves; Brain diseases; Generalized periodic discharges; Status epilepticus

**INTRODUCTION**

Generalized periodic discharges (GPDs) are electroencephalographic (EEG) waveforms that can be seen in a wide array of encephalopathies. By definition, they are repeated and generalized waveforms with relatively uniform morphology and duration, with a quantifiable interdischarge interval between consecutive waveforms, and recurrence of the waveform at nearly regular intervals (Fig. 1) [1]. There are different theories for their etiology and pathophysiology. Early work suggested that GPDs were due to widespread cortical destruction with relative sparing of white matter [2]. A more recent theory is that they result from either a synaptic failure of interneurons or impaired excitation of inhibitory interneurons, resulting in disinhibition of excitatory pyramidal cells. As a result of their frequent association with cardiac arrest and anoxic brain injury, it is thought that high-energy excitatory pyramidal cells may be more severely affected by hypoxic energy failure, resulting in disruption of feed forward inhibitory networks and propagation of GPDs [3]. The presence of GPDs is highly suggestive of a global encephalopathy and is seen in approximately 4% of patients in the hospital or intensive care unit setting undergoing EEG monitoring [4]. They are commonly associated
with toxic/metabolic encephalopathy, anoxia, hypothermia, infections, acute neurological injury, and nonconvulsive status epilepticus (NCSE) [5].

Triphasic waves (TWs) are likewise generalized and periodic EEG waveforms seen in a wide array of encephalopathies. TWs have specific characteristics that are thought to distinguish them from other forms of GPDs. TWs are classically described as having an initial sharp negative deflection, followed by a prominent positive deflection, and then a negative deflection. They tend to be moderate to high amplitude (100 to 300 μV) with a frequency of 1.5 to 2.5 Hz. Their location tends to be predominantly frontal (although less frequently occipital and temporal) with an anterior to posterior time lag (Table 1, Fig. 2). However, both GPDs and TWs overlap substantially with regard to their morphology and clinical associations, and the 2012 American Clinical Neurophysiology Society (ACNS) standardized EEG terminology has established the term “GPDs with triphasic morphology (GPD+TW)” [1] to replace the traditional term ‘triphasic waves.’

GPD+TW were first described in 1955, when Adams and Foley [6] noted blunt spike-and-slow wave complexes among a subset of patients with liver disease [6]. These were subsequently given the name ‘triphasic waves’ by Bickford and Butt [7] in 1955, who studied EEG patterns of patients with hepatic coma. Throughout multiple stages of mental status decline, they noted clusters of GPD+TW followed by relative quiescence, although they seemed to

Table 1. Morphologic features traditionally thought to distinguish waveforms [5,22,28,29]

<table>
<thead>
<tr>
<th>Feature</th>
<th>GPD+TW</th>
<th>GPD associated with seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of phase I of waveform</td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td>Duration of entire waveform</td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td>Angles between phases</td>
<td>Larger (blunted)</td>
<td>Smaller (sharp)</td>
</tr>
<tr>
<td>Amplitude of phase II</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Location</td>
<td>Frontocentral</td>
<td>Frontopolar</td>
</tr>
<tr>
<td>Discharge frequency</td>
<td>≤2.5 cycles/sec</td>
<td>&gt;1 Hz</td>
</tr>
<tr>
<td>Extraspike components</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Background slowing</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Likelihood of all three phases</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dominant 1st phase</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Negative polarity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Increased with stimulation</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

GPD, generalized periodic discharge; TW, triphasic wave. *Polarity refers to the dominant phase of the discharge.

Fig. 1. Generalized periodic discharges: a 51-year-old man with a history of immunosuppression, liver disease, and heart failure with hyponatremia and sepsis. This pattern is described as a 1 Hz generalized periodic discharge pattern; note the features labeled in the figure that constitute this pattern.
be more frequent in deeper stages of coma. Consequently, it was suggested that GPD+TW were a measure of severity of hepatic coma and their presence could point towards a worse prognosis [7].

Although thought to be highly specific for hepatic dysfunction, further work showed that GPD+TW were present across a wide spectrum of disorders. They have been documented in patients with azotemia, hypoxia, hyperosmolarity, and hypoglycemia [8], and indeed, metabolic derangements appear to be a common etiology for GPD+TW [9, 10]. Beyond these, GPD+TW have been observed in Alzheimer’s disease [11] and multiple drug intoxications (baclofen [12], levodopa [13], lithium [14], ifosfamide [15], and metrizamide [16]). In addition, GPD+TW have very infrequently been seen in structural lesions, including brain stem-diencephalic lesions [17].

The exact origin of GPD+TW has been difficult to elucidate, but the predominant theory is that they result from dysfunction of the thalamocortical circuits [8]. Source localization techniques were used to understand the pathophysiology of GPD+TW in a study involving 12 patients. The density of GPD +TW was found mainly in the bilateral medial frontal regions along the cingulate cortices, making it reasonable to hypothesize that the medial frontal area plays a role in the generation of these waveforms [18]. In a study of patients with GPD+TW that examined radiographic correlates, GPD+TW were associated with the presence of white matter abnormalities [19]. However, the overlap between GPD+TW and GPD without triphasic morphology may mean that both thalamocortical circuits and cortical dysfunction are required for their formation. The necessary and sufficient biological substrate for the development of GPDs and particularly GPD+TW has not been fully elucidated.

**UPDATED TERMINOLOGY AND INTERRATER AGREEMENT**

In 2012, the ACNS released guidelines in an attempt to provide uniformity in reporting EEG, with a particular focus on abnormal periodic and rhythmic patterns encountered most commonly in critically ill patients. GPDs can vary based on location (e.g., fron-
tally predominant, occipitally predominant, midline predominant, generalized, or not otherwise specified) and frequency among a variety of additional modifiers (Table 2) [1].

These guidelines have been helpful in providing more uniformity in EEG reporting, although there continues to be some variability in the interpretation and reporting of GPD+TW. In 2014, interrater agreement (IRA) of the ACNS’ standardized terminology was examined and showed that for most terms, IRA was high. Forty-nine raters showed almost perfect agreement for seizures, terms 1 and 2 (e.g., generalized and periodic), and modifiers describe sharpness, amplitude, frequency, and the number of phases. However, the IRA for ‘triphasic morphology’ was only fair (κ of 0.67) [20]. This was similar to a study examining the IRA for EEGs of comatose patients in general [21], as well as a study specifically examining GPDs that found that among 20 patients, the IRA for ‘triphasic morphology’ was only fair (κ of 0.33) [22]. In a retrospective cohort study of 92 patients with GPDs, the IRA for ‘triphasic morphology’ was ‘substantial,’ with a κ of 0.67 [23]. However, this study utilized only two raters, where the prior IRA study for GPDs used 11 to rate EEGs; this difference could have contributed to the disparity in the IRA.

### NONCONVULSIVE STATUS EPILEPTICUS AND SEIZURES

When GPDs are found, with or without triphasic morphology, it is always important to consider first whether or not they represent an ictal rhythm [5]. At any frequency and with any morphology, the appearance of motor manifestations, including myoclonic or rhythmic muscle jerking in conjunction with GPDs, indicates that the pattern is ictal, and both clinical and electrographic manifestations should be treated as with any seizure. Broadly, the diagnosis of nonconvulsive seizures or NCSE is given in patients without known epileptic encephalopathy whose EEG shows epileptiform discharges greater than 2.5 Hz, or if less than or equal to 2.5 Hz, also demonstrate EEG and clinical improvement after intravenous (IV) antiseizure drugs (ASDs) or subtle clinical ictal phenomena or typical spatiotemporal evolution. For patients with known epileptic encephalopathy, there should be an increase in prominence or frequency of epileptiform discharges from baseline as well as electrographic and clinical improvement with IV ASDs [24]. This distinguishes patterns that are slower than 2.5 Hz without motor manifestations and without evolution or response to ASD, such as ceftépine-induced encephalopathy.

There have been attempts to better classify whether or not GPD+TW in a comatose patient represent an ictal rhythm when uncertainty exists. In a retrospective study of two groups of patients with decreased consciousness, differences between GPD+TW and generalized NCSE (GNSCE) were evaluated morphologically. Among 87 EEGs with GPD+TW and 27 EEGs with GNCSE, they found several different characteristics, the most significant being that epileptiform discharges associated with GNCSE had higher frequency, shorter duration of phase one and less generalized background slowing. Administration of benzodiazepines caused a

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### Table 2. American Clinical Neurophysiology Society GPDs modifiers

| 1. Prevalence: how much of the record per epoch contains the GPDs |
| 2. Duration: how long does the GPD activity continue during the recording, in minutes or hours |
| 3. Frequency: the number of GPDs occurring in 1 second |
| 4. Number of phases: the number of baseline crossings in a typical GPD waveform |
| 5. Sharpness: the time in milliseconds for the sharpest and the most prominent phase of the GPD |
| 6. Amplitude: the highest amplitude of the GPD waveform in an anterior-posterior bipolar montage should be measured; amplitude of the GPD can also be measured relative to the background activity. |
| 7. Polarity: whether the highest amplitude of the GPD is negative, positive, or unclear |
| 8. Stimulus induced: whether the GPDs occur spontaneously or are induced with a stimulus |
| 9. Evolving or fluctuating: whether the GPDs change in frequency, morphology, or location (evolution) or whether the changes are present but not enough to be classified as evolving (fluctuating) |
| 10. Plus: whether additional features make the GPD pattern appear more epileptiform |

Other minor modifiers can also be included when describing GPDs. These include the following terms:

| 1. Quasi: used to modify the rhythmic or periodic nature of the GPDs and only if determined by quantitative computer analysis (not by visual impression) |
| 2. Sudden or gradual onset: used to describe how GPDs appear, suddenly (previously called paroxysmal) or over several seconds |
| 3. Triphasic morphology: used to describe the shape of the GPDs |
| 4. Lag of waveforms: either an anterior to posterior or a posterior to anterior lag may be seen in various components of the GPD |

GPD, generalized periodic discharge.
marked decrease of epileptiform discharges, with cessation of GNCSE in seven of the eight patients. These same medications were administered to two patients in the GPD+TW group and there were no significant or electrographical or clinical changes. Interestingly, they also found that auditory and/or noxious stimuli caused immediate increase in discharges among patients with GPD+TW, while having no effect on epileptiform discharges in the GNSCE group. In a small set of patients, well-defined sleep was detected and GPD+TW were absent during this period [25].

In the link between GPD+TW and NCSE, other authors have advocated for differentiation between “typical” and “atypical” TW. Atypical TW have been defined as “localized or lateralized sharp waves with triphasic configuration,” and when found in patients with altered mental status or depressed consciousness are more suggestive of NCSE [26]. In this case, these atypical ‘triphasic waves’ might better be classified as lateralized periodic discharges (LPDs), according to ACNS guidelines, rather than GPD+TW. Unfortunately, criteria to firmly differentiate ictal from interictal GPD patterns have not been validated [27].

GPDs with or without TW that do not fulfill the criteria for nonconvulsive seizures or NCSE remain highly associated with the development of electrographic seizures. In a matched case-control of patients with and without GPDs, nonconvulsive seizures were seen in 26.5% (vs. 8% in controls without GPDs), of whom nearly half had focal seizures. Seizures occurred after the development of GPDs in 42% and in 14.5% of patients, seizures occurred after 48 hours [4]. In a cohort of 4,772 patients undergoing continuous EEG (cEEG) interpreted by experienced raters using the ACNS standardized terminology, LPDs, lateralized rhythmic delta activity, and GPDs were associated with seizures, while generalized rhythmic delta activity was not. Among GPDs specifically, those with frequencies between 1.5 to 2 Hz had a higher association with development of seizures (odds ratio, 2.31; 95% confidence interval, 1.25 to 4.11), suggesting that longer EEG monitoring may be warranted when GPDs are encountered [28].

Morphologic features do not appear to accurately stratify GPDs based on their association seizures. One retrospective study found that the amplitude and duration of the waveform were associated with the development of seizures or status epilepticus, but this was not specific enough for clinical purposes [29]. In an interrater agreement study, raters judged GPDs with or without TW based on their clinical knowledge. Raters tended to judge a waveform as ‘triphasic’ based on traditional morphologic features (Table 1) and in the absence of clinical information, agreed 93% of the time that seizures would develop based purely on their assessment of the waveform. However, this correlated only weakly with the actual appearance of seizures; in fact, both GPDs and GPD+TW were equally likely to be associated with seizures regardless of waveform or the presence of classically ‘triphasic’ features such as anterior-posterior time lag [22]. Fig. 2 demonstrates a classic ‘triphasic wave’ pattern (GPD+TW) in a patient with hepatic failure; within 24 hours of this recording, he developed focal seizures arising from the right parietal region that were subsequently treated with two conventional ASDs.

In another retrospective cohort study, 92 patients were divided in two groups: those with seizures and those without seizures. The cEEG data and clinical features were then analyzed to predict the development of seizures. Variables with a statistically significant risk of having seizures included focality on EEG, interburst suppression, history of epilepsy, an abnormal neuroimaging test, and generalized pattern without triphasic morphology. GPD+TW had a statistically significant decreased risk of seizures [23]. However, others have noted that their definition of GPD+TW does not appear in line with ACNS guidelines and this may have influenced their findings [30].

**CLINICAL OUTCOMES**

The presence of GPDs with or without TW was historically thought to be a poor prognostic marker. A retrospective case-control study was performed involving 200 patients with GPDs and 200 controls matched by age, etiology, and level of consciousness. GPDs were not independently associated with worse outcome, whereas coma, sepsis, cardiac arrest, and NSCE were associated with worse outcome after matching for controls [4].

In the postcardiac arrest setting, GPDs are commonly encountered; however, prognosis in these cases may be linked to the presence or absence of background EEG activity. GPDs on a completely suppressed background have been associated with worse outcomes, whereas if they surface out of a normal background EEG, the prognosis was improved [31]. In 47 patients with postanoxic encephalopathy and generalized epileptiform activity, those with good clinical outcomes (defined by a score of 1 to 2 on the cerebral performance category) had higher background continuity, lower relative discharge power, and lower discharge periodicity [32]. This suggests that the relationship between the GPDs and their background is critically important in prognostic interpretation.

Interestingly, the same may be true in nonhypoxic coma. In a 9-year cohort study evaluating outcomes among patients with acute encephalopathy and TW excluding cardiac arrest, a lack of EEG background reactivity was independently associated with death [19]. Interestingly, in the case-control study of patients with and without GPDs, there was a statistically significant asso-
Association between GPDs and mortality when patients with cardiac arrest were excluded [4]. Background reactivity has been shown to be prognostically important in both nonanoxic [33] and anoxic [34] patient populations. There is debate about whether or not GPDs after cardiac arrest represent ischemic brain injury (i.e., are an epiphenomenon, or create further injury through an imbalance between the supply and demand of the injured brain). The Treatment of Electroencephalographic Status Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial, which is currently in the recruitment phase, will assess postarrest patients with status epilepticus including GPDs and their clinical neurological outcomes, randomizing them to either receive aggressive medical treatment with ASDs to suppress all epileptiform activity or best medical care [35].

**TREATMENT AND FUTURE DIRECTIONS**

Recent work has found that the use of short-acting benzodiazepines or nonsedating ASDs may be useful to discern the potentially ictal nature of periodic or rhythmic patterns that do not fulfill criteria for nonconvulsive seizures or NCSE, such as GPD+TW. In a retrospective case series of patients with GPD+TW, 18.9% of patients had positive clinical responses to a benzodiazepine, compared to 42.2% who responded after a trial of nonsedating ASDs such as levetiracetam. Positive responses were defined as a resolution of EEG pattern and either unequivocal improvement in encephalopathy or appearance of previously absent normal EEG patterns. In addition, responses were categorized by time frame—immediate, delayed (> 2 hours) but unequivocal, delayed equivocal (cases where improvement could potentially be attributed to something other than the ASD trial) or no response. Patients who responded to benzodiazepines did so immediately, whereas patients receiving nonsedating ASDs tended to have delayed responses [36]. Fig. 1 above shows a GPD pattern that was treated with 1 mg lorazepam after which there was clear clinical improvement, constituting a positive response and suggesting that the pattern represented an ictal discharge warranting treatment.

A rapidly-acting nonsedating ASD could be of particular benefit in patients who either can’t receive benzodiazepines or who don’t initially respond to benzodiazepines. Consideration should be given to the time course of responses, as there is often overlap between NCSE and toxic-metabolic encephalopathies and improvement cannot always be attributed definitively to the nonsedating ASD trial. “ASD responsiveness” may be a useful descriptor among these GPD+TW patients. In contrast, others have argued that the risk of a benzodiazepine and/or nonsedating ASD for all patients with GPD+TW opens up risks for unnecessary medication overuse, side effects, interactions and potentially higher mortality and longer hospital stays [37]. The decision to treat should follow an individualized approach; recognition of the association between GPD+TW and seizures should raise concern and warrant at the very least serial or cEEG monitoring.

**CONCLUSION**

GPD+TW continue to be a debated pattern. Their association with seizures is now clear, but the interpretation of GPDs as having ‘triphasic morphology’ and the perception that these are not associated with seizures is often subjective, based on clinical history rather than the objective nature of the discharges. The presence of GPD+TW should prompt additional monitoring, ideally using cEEG and may, when uncertainty exists, warrant evaluation using a short-acting benzodiazepine or nonsedating ASD in order to discern the effects of the pattern on the patient’s clinical exam and EEG. Ultimately, GPD+TW likely do not contribute to poor outcome independent from the patient’s underlying diagnosis; however, seizures likely do contribute and; therefore, the two entities should be distinguished by clinicians wherever possible.

**ARTICLE INFORMATION**

**Conflict of interest**

No potential conflict of interest relevant to this article.

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Coagulopathy may be defined as the loss of balance between hemostatic and fibrinolytic processes resulting in excessive bleeding, intravascular thrombosis or abnormalities in coagulation testing. It is frequently encountered across a wide range of conditions seen in the neurocritical care unit and can contribute to poor outcomes. Early recognition and appropriate management are key, with traumatic brain injury, acute ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage presenting unique challenges to the neurointensivist. We will discuss techniques to assess coagulopathies as well as treatment strategies for the brain injured patient.

Keywords: Anticoagulants; Platelet aggregation inhibitors; Blood coagulation disorders; Thrombelastography; Subarachnoid hemorrhage; Brain injuries, traumatic

INTRODUCTION

Normal coagulation is a balance between hemostatic and fibrinolytic processes, the loss of which may result in either excessive bleeding or intravascular thrombosis, which defines coagulopathy. Abnormalities in coagulation testing may also be considered evidence of coagulopathy, even in the absence of clinical sequelae of bleeding or thrombosis.

There is limited data on the incidence of coagulopathy in neurocritical care units; however, it is commonly seen in critically ill patients with incidences ranging widely from 14% to 81% [1,2]. Coagulopathies may be acquired through a variety of conditions including trauma, organ failure and the use of medications, and may confer an increased risk of secondary hematoma expansion, poor functional outcome, and death across the spectrum of neurocritical illnesses [3-6]. An aging patient population and increased use of antithrombotic and anticoagulant agents demand unique considerations [3,7,8]. Timely, appropriate assessment and treatment are warranted to mitigate hematoma expansion and to facilitate emergent neurosurgical intervention when indicated. We discuss herein techniques in the assessment and management of coagulopathies for the patient with an intracranial hemorrhage, in line with the most recent guidelines adopted by the American Heart Association (AHA), American Stroke Association (ASA), Neurocritical Care Society (NCS), and Society of Critical Care Medicine (SCCM) [3,9]. We include updates from clinical trial findings that
Coagulation Assessment

Conventional coagulation tests
Common (or conventional) coagulation tests (CCT) include prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), platelet count, D-dimer, and fibrinogen levels. The PT is a laboratory test developed to assess the function of the "extrinsic pathway" whereby calcium and tissue factor (TF) are added to citrated blood and the time to coagulation is measured. To correct for interlaboratory differences in TF preparations, the INR was developed and is only intended for monitoring the effect of warfarin therapy [10]. Abnormalities in PT may reflect coagulopathy seen in liver failure, disseminated intravascular coagulopathy (DIC), trauma as well as in the case of some medications such as factor Xa inhibitors. The aPTT was developed historically to assist in the diagnostic process for patients who exhibit signs consistent with hemophilia [11]. In modern clinical practice, it is commonly used to assess the "intrinsic pathway" of hemostasis and is performed by adding calcium, phospholipid, and an activator such as kaolin to citrated blood, and the time to coagulation is measured. It is most useful for monitoring the effect of unfractionated heparin (UFH); however, it cannot reliably reflect the effect of other anticoagulants [12].

CCTs present limitations in our patient population as they are plasma-based, and hence cannot measure interactions between clotting factors, TF, and platelets, and were not designed to assess hemostatic integrity in the trauma or preoperative patient [11,13]; they simply reflect a static evaluation of the coagulation cascade with clot formation as their endpoint rather than assessing the whole coagulation system [13]. They have also been shown to correlate poorly with clinical bleeding and transfusion requirements, lack accuracy in detecting deficiencies in coagulation factors, fail to detect the effects of novel anticoagulation agents or antiplatelet therapy (APT), and do not describe platelet function and fibrinolysis.

Viscoelastic hemostatic assays
Shortcomings of CCTs have led to increased utilization of viscoelastic hemostatic assays (VHAs), which offer a better depiction of the successive steps that comprise the cell-based theory of hemostasis, i.e., initiation, amplification, propagation, and termination through fibrinolysis. VHAs are performed by placing whole blood in a cup with a suspended pin, which transduces changes in tension during clot formation and breakdown with rotation (Fig. 1) [14].

Thrombelastography (TEG) is a VHA commonly used in North America. TEG measures different phases of the coagulation cascade including time to initiate clot formation (reaction time [R]), rate of clot formation (kinetics [K], α angle), maximum clot strength (maximum amplitude [MA]), and clot stability (fibrinolysis; Ly30). When compared with CCT, TEG has been shown to be a better predictor of significant bleeding, the need for massive transfusions as well as mortality at 24 hours and 30 days following trauma [15]. Furthermore, there is a reported mortality benefit to TEG-directed hemostatic resuscitation in trauma patients requir-

![Fig. 1](https://doi.org/10.18700/jnc.190086)
ing massive transfusions when compared to interventions dictated by CCTs [16-18]. An example of CCT and TEG guided transfusion recommendations implemented at our institution is shown in Table 1.

**Platelet function**

While CCT identifies patients at increased risk of bleeding due to thrombocytopenia, it does not indicate; however, qualitative platelet dysfunction due to the use of APT, renal insufficiency or other factors. Bleeding time has grown out of favor for this purpose due its operator-dependence and lack of sensitivity [19]. Light transmission aggregometry in platelet-rich plasma or whole blood is considered the gold standard for assessment of platelet function, but availability may be limited due to poor standardization and time consumption [20]. Commercially available point-of-care platelet function assays overcome some of these obstacles and include the platelet function analyzer (PFA-100, Siemens Medical Solutions, Malvern, PA, USA), VerifyNow (Accumetrics, San Diego, CA, USA) ASA and P2Y12 assays. These tests detect dysfunction secondary to the use of antiplatelets and can provide measures of patient response to these agents as well as adequacy of efforts to reverse them. Standard TEG testing unreliably detects the presence of single APT use; however, it may detect coagulopathy seen in combination APT use [21]. TEG with platelet mapping (TEG-PM, Haemoscope Corp., Niles, IL, USA) is a specific VHA that has been shown to correlate with platelet aggregometry and is able to detect platelet dysfunction due to APT and other coagulopathies in acute brain injury [22-24].

**COAGULOPATHY IN ACUTE BRAIN INJURY**

Historically, reports dating back to the 1970s described baseline hypercoagulability based on TEG in patients with acute ischemic stroke (AIS) and SAH [25,26]. The more recent use of TEG in the neurocritical care unit has allowed investigators to better elucidate coagulopathies seen in different types of acute brain injury. In general, patients with acute brain injuries present with hypercoagulable states compared with normal controls. The impact of this response, variations in this response between patients with the same type of injury, and potential therapeutic implications largely remain unclear.

**Acute ischemic stroke**

Patients with AIS have been reported to present with a hypercoagulable state when compared with normal controls. In a study of patients with AIS presenting within the window of administering tissue plasminogen activator (tPA) (i.e., within 3 hours), TEG demonstrated a hypercoagulable state based on shorter R and K times with greater α angle. After treatment with tPA, significant changes in MA, G, and Ly30 were demonstrated within 10 minutes [27]. However, the same group was unable to predict a clinical response to tPA treatment using TEG values [28].

Admission TEG values have been associated with outcomes after AIS. In another study utilizing TEG in patients with AIS, MA was found to be an independent predictor of poor outcome (modified Rankin Score ≥ 2) at 1 year. Recurrence rate of ischemic events were found to be higher in the 3rd MA tertile group, despite higher rates of treatment with dual APT. Higher tertile of MA was also associated with stroke severity (higher National Institutes of Health Stroke Scale scores on admission and longer hospital stay) [29]. Although MA appears to be a marker of stroke severity and may portend worse outcome, it is unclear if this may be a potential target for intervention.

**Intracerebral hemorrhage**

Studies utilizing TEG in patients with ICH have illustrated its potential in predicting the clinical course. In a study by Kawano-Castillo et al. [30], patients with ICH demonstrated faster and stronger clot formation at baseline (shorter R and delta) and stronger clot strength (higher MA and G) at 36 hours compared with normal

---

**Table 1. Memorial Hermann Hospital transfusion recommendations based on abnormal coagulation testing in bleeding patients**

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Blood product transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT &gt;128</td>
<td>FFP and RBCs</td>
</tr>
<tr>
<td>r &gt;1.1</td>
<td>FFP and RBCs</td>
</tr>
<tr>
<td>k time &gt;2.5</td>
<td>Cryoprecipitate/fibrinogen/FFP</td>
</tr>
<tr>
<td>α angle &lt;56</td>
<td>Cryoprecipitate/fibrinogen/platelets</td>
</tr>
<tr>
<td>MA &lt;55</td>
<td>Platelets/cryoprecipitate/fibrinogen</td>
</tr>
<tr>
<td>Ly30 &gt;3%</td>
<td>Tranexamic acid</td>
</tr>
<tr>
<td>PT &gt;18.0 sec</td>
<td>FFP</td>
</tr>
<tr>
<td>αPTT &gt;35 sec</td>
<td>FFP</td>
</tr>
<tr>
<td>INR &gt;1.5</td>
<td>FFP</td>
</tr>
<tr>
<td>Platelet count &lt;150×10^3/L</td>
<td>Platelets</td>
</tr>
<tr>
<td>Fibrinogen &lt;180 g/L</td>
<td>Cryoprecipitate/fibrinogen</td>
</tr>
</tbody>
</table>

Adapted from Holcomb et al. [16], with permission of Wolters Kluwer Health.

ACT, activated clotting time; FFP, fresh frozen plasma; RBC, red blood cells; MA, maximum amplitude; Ly30, percentage of lysis 30 minutes after MA; PT, prothrombin time; αPTT, activated partial thromboplastin time; INR, international normalized ratio.
controls. Patients with hematoma expansion had significantly longer baseline K and delta compared with nonexpanders, indicating that the former group had slower clot formation [30]. Other reports have also demonstrated greater baseline hypercoagulability in patients with ICH [31,32].

Although patients with ICH often present with a hypercoagulable state compared with controls, hypercoagulability may have a powerful impact on outcome from ICH. Hypercoagulability by TEG has been associated with worse functional outcome, higher rates of cerebral herniation, and mortality from ICH and isolated TBI [33]. Detection of hypercoagulability could represent an application of TEG in terms of therapeutic implications in ICH.

Subarachnoid hemorrhage
Like AIS and ICH, baseline coagulation disturbances are common in the spontaneous SAH population. In animal models of SAH, hypercoagulability is demonstrated as early as 30 minutes following the injury [34]. In patients with SAH, early hypercoagulability and platelet dysfunction has been identified by TEG and shown to correlate with poor outcomes, including an increased incidence of delayed cerebral ischemia and worse modified Rankin Scores at 3 months [22]. Similar to AIS, there is an association noted between elevated MA values and poor outcomes, independent of other inflammatory biomarkers, age, and Hunt-Hess grade [35].

Traumatic brain injury
Trauma population studies have elucidated some of the complex coagulation disturbances which occur in the setting of traumatic injury. Furthermore, more widespread use of TEG has enhanced the ability to detect coagulation differences. In general, hypercoagulability by TEG is the most commonly observed pattern in trauma and may be observed in up to 65% of patients [36]. However, a subset of patients may present with an acute traumatic coagulopathy. Hypercoagulability on admission is associated with a severalfold increase in morbidity and mortality [37]. Findings seen most often with severe injuries include elevated PT/partial thromboplastin time, low platelet counts, and fibrinogen levels on CCT. TEG has demonstrated hypercoagulability in severe trauma through changes in the values of R, α angle, and MA. Hyperfibrinolysis, while only seen in 2% to 6% of patients, may have a powerful impact on outcome from major trauma. Ly30 values greater than 3% have been associated a two-fold increase in mortality in trauma patients [15]. Patients with massive tissue injury have also demonstrated evidence of hyperfibrinolysis, such as elevated D-dimer and fibrin degradation products on CCT [38]. As previously discussed, TEG based protocols may now be used to guide transfusion therapy in the setting of traumatic injury.

Coagulopathy following TBI is associated with the severity of injury. In one report, it was present in up to one-third of patients with isolated TBI and up to 60% of patients with severe TBI, although there have been reports of lower rates [39]. The brain is rich in TF and it is postulated that its release activates the extrinsic pathway, which in turn leads to a consumptive coagulopathy and hyperfibrinolysis. Evidence of coagulopathy on TEG (e.g., increased R or decreased MA) following isolated TBI has been shown to be associated with considerably higher rates of mortality when compared to TBI patients without evidence of coagulopathy (66% vs. 16.6%) [40]. Hyperfibrinolysis also continues to play an important role in predicting poor outcome in patients with TBI, with D-dimer at admission shown to be an independent risk factor for poor outcome [41].

COAGULOPATHY IN SYSTEMIC DISEASE

Acute liver failure
Acute liver failure is associated with a deficiency of both procoagulant and anticoagulant proteins. While CCT may show an elevated PT/INR in this patient population, TEG has demonstrated that the vast majority of these patients have a normal ability to form clots and may even be hypercoagulable [42].

Thrombocytopenia
Thrombocytopenia may be seen in a variety of conditions encountered in the neurocritical care unit, including sepsis (which is the most common cause of thrombocytopenia in critically ill patients), hypersplenism, DIC, blood loss, mechanical fragmentation, medications, bone marrow suppression, and immune-mediated disorders [43]. In a case series by Chan et al. [44] of patients with thrombocytopenia undergoing neurosurgical procedures, a platelet count < 100,000/µL was associated with a significant increase in the rate of postoperative hematoma formation when compared with patients with a platelet count > 100,000/µL. Current guidelines recommend a transfusion threshold of < 100,000/µL for patients with intracranial bleeding or those undergoing a neurosurgical procedure.

Disseminated intravascular coagulopathy
DIC is associated with multiple disease entities encountered in critically ill patients, most commonly due to sepsis, although trauma and malignancy are also common causes encountered in the neurocritical care unit [45]. It is characterized by widespread microvascular thrombosis due to TF expression, leading to massive fibrin deposition, consumption of platelets and coagulation factors, hyperfibrinolysis, hemorrhage, and organ failure [46]. The man-
agement of DIC is that of the underlying condition and CCT-guided transfusion if a patient is actively bleeding or at high risk of bleeding.

Uremia
Uremia is associated with an increased risk of hemorrhage secondary to platelet dysfunction. A rising prevalence of chronic kidney disease and the use of replacement therapy has led to this being encountered with increasing frequency in the neurocritical care unit as a cause of, or contributing to, intracranial bleeding [47,48]. Desmopressin (DDAVP) is the agent most commonly used in the treatment of uremic bleeding and has been shown to reduce bleeding time and normalize hemostasis in patients with uremic platelets undergoing surgery [49,50]. Its actions are mediated by an increase in endothelial release of von Willebrand factor and platelet membrane glycoprotein expression, which in turn promotes platelet adhesion to the endothelium [51,52]. It has been shown to restore platelet function within 30 minutes of administration, though its effects are short-lived at around 3 hours [53]. DDAVP is dosed at 0.4 µg/kg administered intravenously for this indication and is well tolerated with few reported side effects [3,12,54].

**REVERSAL OF ANTITHROMBOTIC THERAPY**

There has been a significant, continued increase in the use of antithrombotic agents among patients admitted to the neurocritical care unit, due to an aging population and increased diagnosis of ischemic events that warrant such therapies. The introduction of novel agents poses a diagnostic and therapeutic dilemma for the neurointensivist when managing the patient with intracranial hemorrhage. Antithrombotic agents may be roughly divided into APT and anticoagulant therapy.

**Antiplatelet therapy**
The main classes of antiplatelet drugs commonly used in practice include cyclooxygenase-1 (COX-1) inhibitors (e.g., acetylsalicylic acid; ASA or aspirin), phosphodiesterase inhibitors (e.g., dipyridamole and cilostazol), P2Y12 receptor inhibitors (e.g., clopidogrel, prasugrel, and ticagrelor) and glycoprotein IIb/IIIa inhibitors (e.g., abciximab, epifibatide, and tirofiban). Aspirin use confers an absolute risk increase of 0.1% per year of ICH compared to control [55]. Clopidogrel carried a similar rate of ICH incidence when compared to aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial [56]. Prasugrel, when compared to clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, demonstrated a higher risk of life-threatening bleeding overall although the rate of ICH was similar between the two groups [57]. Ticagrelor was associated with an increased rate of intracranial hemorrhage when compared to clopidogrel in the Platelet Inhibition and Patient Outcomes (PLATO) trial, although this difference was nonsignificant [58]. Single APT use is associated with a low risk of major bleeding, although this risk increases significantly when combination APT are implemented, similar to the risk of anticoagulants [12,59]. In a study of a large cohort of patients from the Get With The Guidelines-Stroke (GWTG-Stroke) database with ICH, the use of combination APT, but not single APT, was associated with a higher risk for in-hospital mortality when compared with patients not taking APT [60].

Reversal of APT in the bleeding patient may be achieved through the administration of platelet transfusion. Routine platelet transfusion for ICH based on reported use of APT alone was associated with an increased rate of poor functional outcome in the Platelet Transfusion in Spontaneous Intracerebral Hemorrhage (PATCH) trial [61]. It is important to note that this trial did not utilize qualitative platelet function testing and excluded surgical patients, so platelet transfusion may be appropriate for patients who require neurosurgical intervention. In a study by Choi et al. [62] of 107 patients presenting with traumatic intracranial hemorrhage and reported APT use, a significant percentage of patients had subtherapeutic ASA/P2Y12 assays that would be unlikely to benefit from platelet transfusion. Among patients that did receive platelet transfusions, the amount transfused did not adequately reverse its effect in almost half of this patient cohort [62]. There may, therefore, be a role for targeted platelet transfusions based on quantitative assessment of platelet function before and after transfusion. This was illustrated in a retrospective study by Naidech et al. [63] on a series of patients with ICH and abnormal platelet function activity. Early (< 12 hours from symptom onset) platelet transfusion improved platelet activity assay results and was associated with smaller final hemorrhage size and more independence at 3 months (modified Rankin Score < 4) [63]. Similarly, in a TBI population, TEG-directed platelet transfusion was associated with a decreased mortality compared to a historical cohort in a retrospective study by Furay et al. [64].

DDAVP use has also been demonstrated to improve platelet function in patients on COX-1 and ADP receptor inhibitors in several tests of platelet function compared to those who had not received reversal agents [3,50,51,65-68]. Clinically, it has been shown to reduce blood loss and improve hemostasis in patients with aspirin exposure undergoing cardiac surgery [49,69,70]. In two small studies of patients with intracranial hemorrhage and either reduced platelet activity on PFA-100 and/or known aspirin
use, DDAVP administration was associated with restoration of platelet function on repeat testing \[53,71\]. Given its low cost and relatively good safety profile, its administration should be considered in patients with intracranial hemorrhage who were exposed to antiplatelet agents \[3\].

**Anticoagulation therapy**

The main classes of anticoagulant drugs include vitamin K-dependent coagulation factor antagonists (VKA, e.g., warfarin), factor Xa inhibitors (e.g., fondaparinux, rivaroxaban, apixaban), direct thrombin inhibitors (DTI, e.g., argatroban, bivalirudin, dabigatran), and heparinoids (i.e., unfractionated, or UFH, and low-molecular-weight heparin [LMWH]). In the neurocritical care unit, common indications for these medications include stroke prevention in atrial fibrillation and treatment of venous thromboembolism. Reversal strategies for anticoagulation-associated intracranial hemorrhage are summarized in Table 2.

**Vitamin K antagonists**

VKA inhibit vitamin K-dependent factors in the coagulation cascade: factors II, VII, IX, and X. VKA activity can be assessed by PT/INR. The risk of bleeding while taking a VKA increases with the duration of therapy and higher INR levels. For each increment in INR elevation above the therapeutic range, the risk of bleeding on a VKA doubles \[72\].

Vitamin K replacement is essential to replenish the vitamin K-dependent factors and reverse VKA activity. It should be given promptly and IV administration mitigates variability in oral vitamin K absorption. Although the risk profile is low, it may take 24 hours or more to become effective \[3\].

Fresh frozen plasma (FFP) has been conventionally used to reverse VKA in conjunction with vitamin K. Although it is relatively inexpensive and widely available, its use is complicated by delays in administration, potential transfusion related reactions, and large volumes which may be required for full INR reversal. This had led to the more widespread use of prothrombin complex concentrate (PCC). PCC is derived from plasma and contains factors II, VII, IX, and X in variable proportions in different preparations. It is rapidly administered in a small volume. PCC has been demonstrated to reverse INR to < 1.4 and maintain INR reversal for > 48 hours in the majority of patients on VKA therapy \[73\]. In the INR Normalization in Coumadin Associated Intracerebral Haemorrhage (INCH) trial, a randomized trial comparing FFP and PCC for VKA reversal in intracranial hemorrhage, PCC provided more rapid INR reversal with an effective reduction in hematoma expansion \[74\]. The trial was stopped early due to safety concerns with FFP therapy. Both the AHA/ASA as well as the NCS/SCCM guidelines currently recommend consideration of PCC over FFP for VKA reversal in ICH \[3,9\].

**Factor Xa inhibitors**

Xa inhibitors prevent the conversion of prothrombin to thrombin. Detection of novel agents using calibrated chromogenic assays are expensive and not readily available, and the utility of existing anti-Xa assays have not been validated to identify the presence of the oral factor Xa inhibitors. There is data to support the use of TEG to detect coagulopathies induced by these agents, which may inform reversal strategies in these patients \[75\].

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Half-life</th>
<th>Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Reduction in vitamin K-dependent clotting factors (II, VII, IX, X)</td>
<td>20–60 hr</td>
<td>Vitamin K 10 mg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCC 25–50 U/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFP 10–15 mL/kg if PCC not available</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>13 hr</td>
<td>Idarucizumab 5 mg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22–35 hr if CrCl &lt;30</td>
<td>PCC if idarucizumab not available</td>
</tr>
<tr>
<td>Rivaroxaban, apixaban, edoxaban</td>
<td>Xa inhibitor</td>
<td>Rivaroxaban 7–9 hr Apixaban 9–14 hr</td>
<td>PCC 50 U/kg</td>
</tr>
<tr>
<td>Heparin</td>
<td>Indirectly inhibits Xa and IIa via antithrombin</td>
<td>60–90 min</td>
<td>Protamine 1 mg per 100 U heparin given within past 2–3 hr</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Same as heparin but mainly Xa</td>
<td>4 hr</td>
<td>Protamine reverses approximately 60% of effect &lt;8 hr: 1 mg per 1 mg enoxaparin 8–12 hr: 0.5 mg per 1 mg enoxaparin</td>
</tr>
</tbody>
</table>

Adapted from Frontera et al. \[3\], with permission of Springer Nature.

IV, intravenous; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; CrCl, creatinine clearance.
PCC is commonly used for Xa inhibitor reversal. PCC has been demonstrated to effectively reverse rivaroxaban in healthy volunteers [76]. In the setting of intracranial bleeding, it is recommended to administer 50 units/kg if the medication was ingested within 3 to 5 half lives or if the time of last exposure is unknown. In patients with a known ingestion within 2 hours, activated charcoal may also be utilized if this is deemed safe from an airway protection standpoint. Hemodialysis is not effective in removing Xa inhibitors [3].

Andexanet alpha is a recombinant inactive form of factor Xa. It binds to Xa inhibitors with high affinity and sequesters the medication, resulting in reduced anti Xa activity. In the Andexanet Alpha, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors-4 (ANNEXA-4) study of 352 patients with major bleeding, andexanet alpha reduced anti Xa levels by 92% in rivaroxaban/apixaban treated patients and 75% in enoxaparin [77]. Andexanet alpha is approved by the U.S. Food and Drug Administration for the reversal of rivaroxaban and apixaban, but widespread use is limited due to the cost of the medication.

Direct thrombin inhibitors
DTI directly inhibit the activity of factor IIa, which is the key factor in converting fibrinogen to fibrin. DTI have an additional unique indication in the treatment of heparin induced thrombocytopenia. Intravenous formulations are short acting and generally do not require reversal agents. However, the reversal of oral dabigatran was challenging before idarucizumab became available. Idarucizumab is a monoclonal antibody which binds to dabigatran with considerably higher affinity than factor IIa. In the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study of 503 patients with life-threatening bleeding (Group A) or need for emergent surgical procedure (Group B), idarucizumab reversed thrombin time to normal in 100% of patients and this effect remained relatively stable 24 hours after treatment. Normal intraoperative hemostasis was achieved in 92% of the patients in Group B [78]. The rate of thrombotic events in this study was similar to those reported after major surgical procedures or hospitalization for uncontrolled bleeding, and may be attributable to the low rate of reinitiation of anticoagulation [79,80]. Idarucizumab is administered in 2 doses of 2.5 g given within 15 minutes. Activated charcoal is an additional option for dabigatran, similar to Xa inhibitors, and is recommended for consideration in the AHA/ASA as well as the NCS/SCCM guidelines [3,9].

If idarucizumab is not available, hemodialysis and PCC are alternative options. Dabigatran is renally excreted and is effectively removed by hemodialysis. However, there is a theoretical risk of worsening cerebral edema in patients with mass lesions. The recommended dosing for PCC is 50 units/kg, the same as for Xa inhibitors. Administration of PCC beyond 3 to 5 half lives of dabigatran exposure may be considered in patients with renal insufficiency [3,9].

Heparin and low-molecular-weight-heparin
UFH activates antithrombin III activity, which inhibits factors IIa, and Xa. Heparin activity can be assessed utilizing aPTT or point-of-care activated clotting time. Heparin activity may also be assessed with TEG; shortening of R time with heparinase implicates the presence of heparin in the sample as the cause of coagulopathy. Its effects may be reversed with protamine, which is a naturally occurring protein that binds to heparin and its dosing is outlined in Table 2.

LMWH has a similar mechanism of action but is longer acting and thought to have more predictable pharmacology in the setting of normal renal function. Assessment of LMWH activity requires the use of an anti-FXa assay. Protamine may be used to reverse LMWH activity, but this reversal is incomplete and estimated to be around 60% [3]. A novel approach to LMWH is andexanet alpha. Although this is a potential therapeutic intervention with a possibility of more complete LMWH reversal than with protamine, it is currently not approved for this indication and is still undergoing further study [77].

CONCLUSION
Coagulopathy is commonly encountered in the neurocritical care unit and poses a challenge to the clinician when managing the patient with intracranial hemorrhage. Utilization of viscoelastic testing has shown great promise in this arena, allowing one to risk stratify patients and guide transfusion requirements. As the widespread use of antithrombotic therapy continues to increase, further development of specific testing for individual medications and targeted reversal agents would improve the management of hemorrhagic complications.

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Conflict of interest
No potential conflict of interest relevant to this article.

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REFERENCES


Cerebrovascular complications during pregnancy and postpartum

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INTRODUCTION

Pregnancy-associated neurocritical complications involve various diseases. Myasthenia gravis can be worsened in approximately 30% to 40% of women during pregnancy or during the postpartum period [1]. The relapse rate of multiple sclerosis increases in the 3 months postpartum [2]. Approximately one-third of pregnant women with epilepsy can experience worsening of seizure control due to various factors such as psychological stress, sleep deprivation, altered drug disposition, poor drug compliance due to fear of teratogenicity, increased estrogen levels leading to decline in seizure threshold, and decreased serum levels of antiepileptic drugs [3-5]. Pregnancy-related cerebrovascular disorder is one of the major causes of maternal mortality. In the present review, we focus especially on cerebrovascular complications during pregnancy and postpartum. These complications are closely related to physiological changes during pregnancy. Thus, it is important to understand the changes in the hemodynamic, vascular structural, and coagulation systems that can occur during pregnancy.

WHAT HAPPENS DURING PREGNANCY?

Cardiac output and blood volume increase 30% to 50% until late in the second trimester due to maternal hypervolemia and the de-
During pregnancy and the early puerperium, venous congestion, aortocaval compression by gravid uterus, and vascular damage related to vaginal or cesarean section delivery can induce hypercoagulability [13-15]. Biochemical changes, such as increased procoagulants (Factors VII, VIII, and X) and decreased coagulation inhibitors (antithrombin III and protein S) in late pregnancy, also result in a hypercoagulable state (Fig. 1) [15-17].

RISK FACTORS FOR THROMBOEMBOLISM DURING PREGNANCY AND POSTPARTUM

The strongest risk factors for venous thromboembolism (VTE) is a history of thrombosis, and pregnancy-related hypertension for both ischemic and hemorrhagic stroke during pregnancy and puerperium [16,17]. According to population-based studies, advanced maternal age (>35 years), obesity (body mass index > 30 kg/m²), multiple births, and multiple gestation are characteristics that can increase the risk for thromboembolism [16,18]. In terms of medical conditions and pregnancy complications, heart disease, systemic lupus erythematosus, immobilization, smoking, inflammatory bowel disease, cesarean delivery, preterm delivery (<36 weeks), transfusion, preeclampsia and eclampsia can amplify the maternal thromboembolic risk [16,19,20]. The inherited thrombophilias associated with thromboembolism in pregnancy is a genetic tendency of VTE in particular. Factor V Leiden mutation and prothrombin 20210A mutation are more common inherited thrombophilias in Caucasian populations [21]. However, Kim et al. [22] reported that a Factor V Leiden mutation and a prothrombin 20210A mutation was not found in 228 Korean patients with VTE. Another study also reported no Factor V Leiden mutation in Korean patients with deep vein thrombosis (DVT). As such, these inherited thrombophilias appear to be extremely rare in Asian populations, including Koreans with DVT [23]. On the other hand, deficiencies in antithrombin, protein S and protein C, and antiphospholipid syndrome, are relatively common in Korean populations, and are stronger risk factors [22,24-27].

Pregnancy-related hypertensive disorder is one of the leading causes of neurocritical illness in the perinatal or postnatal periods [28,29]. In particular, preeclampsia, eclampsia and HELLP syndrome (hemolysis with a microangiopathic blood smear, elevated liver enzymes and low platelets) represent the most important spectrum of pregnancy-related hypertensive disorders in the latter half of pregnancy or postpartum, which lead to increased risk for thromboembolic and hemorrhagic complications [28]. In 2019, the American College of Obstetricians and Gynecologists listed diagnostic criteria for preeclampsia (Table 1) [30]. Eclampsia (convulsive manifestation of preeclampsia) and HELLP syndrome are more severe forms of preeclampsia [30].

VENOUS THROMBOEMBOLIC COMPLICATIONS DURING PREGNANCY AND POSTPARTUM

Thromboembolism in pregnancy occurs in approximately 0.5 to 2.0 per 1,000 deliveries [15,31,32]. The risk for developing throm-

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**Fig. 1.** Changes in the coagulation system during the third trimester of pregnancy and early puerperium. vWF, von Willebrand factor; d/t, due to.
boembolism increases by a factor of 4 to 5 during pregnancy, and by up to 20 to 80 during the 3 months following delivery [33]. In particular, 2 weeks after delivery is the most critical period [34], accounting for approximately 10% of maternal mortality, resulting in 1.1 to 1.5 deaths per 10,000 deliveries [16].

Of pregnancy-related thromboembolisms, approximately 80% occur in the venous system, of which arterial thromboembolism accounts for 20% [35]. There are various mechanisms of VTE. The most common complication of VTE is DVT, which occurs in 80% of patients with VTE. Pulmonary thromboembolism (PTE) is the second most common cause [35]. It is difficult to diagnose DVT or PTE in pregnant women because approximately 50% of patients exhibit no specific symptoms, and common lower extremity symptoms in DVT, or tachycardia, tachypnea or dyspnea in PTE can occur in women who are pregnant.

Cerebral venous thrombosis (CVT) accounts for 2% to 37% of pregnancy-associated strokes [36,37]. Clinical presentations of CVT are characterized by headache, papilledema, visual loss, motor deficits, seizures, focal neurological deficits, and altered mentality depending on the involved cerebral vein and sinus (Fig. 2) [34,38]. Compared with CVT unrelated to pregnancy and puerperium, pregnancy-related CVT has an acute onset with a progressive course and, more often, concomitant extraneurological thromboembolism. Nevertheless, CVT during pregnancy and puerperium can be diagnosed earlier and its symptoms tend to subside or become stable faster, thereby resulting in better outcomes with lower mortality [34].

### Table 1. Diagnostic criteria for preeclampsia [30]

<table>
<thead>
<tr>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg on two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive woman</td>
</tr>
</tbody>
</table>

And the new onset of one or more of the following:

<table>
<thead>
<tr>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg/day urine collection or Protein/creatinine ratio ≥0.3 or Dipstick test ≥2+ if other quantitative measurements are unavailable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt;100,000/μL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine &gt;1.1 mg/dL or Doubling of the serum creatinine in the absence of other renal disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum transaminase &gt;2 times of upper limit of normal concentrations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral symptom</td>
</tr>
<tr>
<td>New onset and persistent headache or visual symptoms (blurred vision, flashing lights, or sparks)</td>
</tr>
</tbody>
</table>

Adapted from American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Obstetrics [30], with permission of Wolters Kluwer Health, Inc.

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**TREATMENT OF VTE DURING PREGNANCY AND POSTPARTUM**

Treatment of VTE during pregnancy is highly unique in many ways. Warfarin is a commonly used anticoagulant able to cross the placenta and may be teratogenic in the first trimester. In the third trimester, warfarin can increase the risk for bleeding in fetal intracranial bleeding [39,40]. Thus, its use during pregnancy should be avoided [41]. Direct oral anticoagulants are not recommended during pregnancy because their efficacy and safety have not been established, and should also not be used in women who are breastfeeding during puerperium [42]. The treatment of choice for VTE in pregnant women is subcutaneously administered low-molecular weight heparin (LMWH), which does not cross the placental barrier [43,44]. There is no fetal risk for bleeding or teratogenicity. Although intravenous (IV) unfractionated heparin can be considered as an alternative, subcutaneous LMWH is preferred over IV unfractionated heparin due to its higher bioavailability and a longer plasma half-life. Additionally, the use of LMWH is easier and appears to be more efficacious, with fewer bleeding complications [16,41].

The proportion of patients who present with intracranial hemorrhages, such as venous hemorrhage, hemorhagic infarction or, rarely, subarachnoid hemorrhage (SAH), represent approximately one-third of patients with CVT [45]. The presence of intracranial hemorrhage, however, is not a contraindication to anticoagulants in the management of CVT.

Reasonable initial dosing of subcutaneous LMWH is 1 mg/kg of enoxaparin every 12 hours, 100 units/kg of dalteparin every 12 hours, or 200 units/kg of dalteparin once daily. LMWH should be

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Hong JH. • Cerebrovascular complications during pregnancy
discontinued 24 hours before induction of labor or cesarean section and resumed 4 to 6 hours after vaginal delivery, or 6 to 12 hours after cesarean delivery \[46\]. Treatment should be continued for at least 6 weeks after delivery. Although warfarin metabolites are detected in breast milk, their low activity makes it safe to use warfarin during lactation \[47\]. There are also no contraindications to breastfeeding while undergoing unfractionated heparin or LMWH therapy.

Fig. 2. Cerebral venous thrombosis. (A) Diffusion-weighted magnetic resonance (MR) imaging (MRI) revealing acute cerebral infarctions (arrows) at both frontal lobes. (B, C) T1-weighted MRI revealing hyperintense signal of the thrombus at the superior sagittal sinus and right transverse sinus (filled arrows). (D) Gradient echo sequences demonstrating hypointense thrombus (filled arrow) in the superior sagittal sinus. (E) There is no superior sagittal sinus (arrowheads) detectable on coronal MR venography. (F) Sagittal MR venography demonstrates absent flow due to occlusion of the superior sagittal sinus and right transverse sinus (arrowheads). Filled arrowheads indicate straight sinus in (E) and left transverse sinus in (F).

ARTERIAL THROMBOEMBOLIC COMPLICATIONS DURING PREGNANCY AND POSTPARTUM

Arterial thromboembolism is a less common complication but is, however, more critical and disabling. The incidence of pregnancy-associated stroke is 25 to 34 per 100,000 deliveries, a figure that has been rising steadily \[36,48\]. In comparison, the incidence of stroke unrelated to pregnancy in women 15 to 45 years of age is approximately 11 per 100,000 deliveries \[49\].

The risk for arterial ischemic stroke is higher during puerperium than during pregnancy. A previous study by Kittner et al. \[50\] reported that the risk for ischemic stroke increased in the puerperium period but not during pregnancy. Hemorrhagic stroke occurred more frequently during the second or early third trimesters, and in the early postpartum period. More specifically, the risk for aneurysmal SAH peaks at 30 to 34 weeks of pregnancy; however, intracerebral hemorrhage occurs more during puerperium than in pregnancy \[50\]. Approximately 50% of all aneurysmal ruptures in women < 40 years of age are pregnancy-related. Arteriovenous malformations (AVMs), however, are more controversial. One study reported that cerebral hemorrhage due to AVMs associated with pregnancy occurred evenly throughout the entire gestation and postpartum periods \[51,52\].

Although there are many causes of stroke during pregnancy or...
puerperium, most are similar, with common etiologies such as ischemic or hemorrhagic stroke; however, pregnancy-specific causes include preeclampsia/eclampsia. Amniotic fluid embolism, AVMs, cerebral artery aneurysm, posterior reversible encephalopathy syndrome (PRES), and postpartum angiopathy (PPA) are also well-known causes [53-56].

PRES AND PPA DURING PREGNANCY AND POSTPARTUM

PRES is a clinical and radiographic syndrome and is classically characterized by vasogenic edema in the bilateral parietooccipital lobes (Fig. 3). Symmetrical hyperintense signals on T2 and fluid-attenuated inversion recovery magnetic resonance imaging, with increased value on the apparent diffusion coefficient map, can also be evident in atypical areas such as the basal ganglia, frontal lobes, cerebellum, and brainstem [57,58]. Approximately 20% of CVT can be accompanied by hemorrhagic stroke [53,59]. The mechanism is not completely understood; however, a breakdown of the blood-brain barrier and cerebral auto-regulation attributed to hyperperfusion results in extravasation of fluid containing blood by-products into the brain parenchyma, which in turn causes vasogenic edema. Endothelial dysfunction also plays a key role in the mechanism, and is especially associated with preeclampsia (Fig. 4). The levels of serological markers of endothelial dysfunction are increased during pregnancy with preeclampsia [60,61]. With regard to anatomical distribution, sympathetic innervation in the posterior circulation is relatively scant compared with the anterior circulation [62]. Sympathetic innervation of the intracranial arterioles has a protective role in rapid and dynamic fluctuations in blood flow. The posterior circulation, therefore, is vulnerable to breakthrough of the blood-brain barrier and failure of cerebral autoregulation.

PPA, one of the spectrums of reversible cerebral vasoconstriction syndrome, is a noninflammatory vasoconstrictive condition [63]. Two-thirds of PPA cases occur in the first week after delivery [64]. Patients with PPA exhibit reversible segmental constrictions and dilatations of large- or medium-size cerebral arteries (Fig. 5), and approximately 40% of PPA can be accompanied by intracranial hemorrhage [54]. PPA and PRES share many clinic-radiological features and pathophysiological mechanisms, and are considered to be overlapping conditions (Fig. 4) [65,66]. More than 85% of PRES exhibits multifocal vasoconstriction of the cerebral arteries and reversible cerebral edema occurs in approximately one-third of PPA cases. Both can present with thunderclap headache, seizure, and focal neurological deficits such as visual symptoms. Usually, however, they have a self-limited benign course, and radiological

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**Fig. 3.** Posterior reversible encephalopathy syndrome. (A) Axial fluid-attenuated inversion recovery magnetic resonance image revealing abnormal signal intensity in both parieto-occipital lobes. (B) Apparent diffusion coefficient map reveals increased values in the areas of fluid-attenuated inversion recovery abnormality, indicative of cortical vasogenic edema.
abnormalities are resolved within several days to weeks [67]. Steroid is not a recommended therapy for pregnancy-associated PRES [48,63]. Although there is no supportive therapeutic evidence, short-term steroids, oral calcium channel blockers, and/or IV magnesium are administrated by some physicians for PPA [54]. As such, it remains controversial whether these treatments are effective in altering the natural disease course. However, 10% can be exacerbated by severe vasoconstriction and cerebral edema, leading to fulminant neurological deficits or death.

TREATMENT OF STROKE DURING PREGNANCY AND POSTPARTUM

The treatment of stroke during pregnancy and postpartum is guided by etiology and subtype. The safety of reperfusion strategies for pregnant women who experience acute ischemic stroke remains uncertain. IV alteplase does not cross the placenta because of its large molecular weight, but is listed as a pregnancy category C drug [68]. The major concern for administration of IV alteplase is the risk for maternal and fetal bleeding. Previous stroke guidelines have listed pregnancy as a relative exclusion criterion [69]. A recent study using the American Heart Association’s Get With the Guidelines-Stroke Registry showed that 40 pregnant or postpartum

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**Fig. 4.** The overlapping mechanism of postpartum angiopathy (PPA) and posterior reversible encephalopathy syndrome (PRES) during pregnancy and postpartum. BBB, blood-brain barrier.

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**Fig. 5.** Postpartum angiopathy. (A) Multiple acute cerebral infarctions in both cerebral hemispheres and right cerebellum. (B) Multifocal mild to moderate stenosis at both middle cerebral artery M2 segments, right anterior cerebral artery proximal A2 segment, right posterior cerebral artery (PCA) P1 segment, and left PCA P2 segment.

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women receiving emergent reperfusion therapy for acute ischemia exhibited a trend toward increased symptomatic intracranial hemorrhage compared with nonpregnant young women undergoing reperfusion therapy. However, they had more severe stroke severity, which is one of the major risk factors for symptomatic intracranial hemorrhage. Nevertheless, there were no significant differences in functional outcomes at discharge, life-threatening hemorrhage, and in-hospital mortality between pregnant or postpartum and nonpregnant women with ischemic stroke who received reperfusion therapy [70]. The updated 2018 American Heart Association/American Stroke Association guidelines reported that IV alteplase administration may be considered in the management of acute ischemic stroke for pregnant women when the anticipated benefit of IV alteplase outweighs the potential risk(s) for bleeding [71]. Recently, direct endovascular thrombectomy without IV alteplase has been attempted as an alternative treatment for pregnant women with a potentially high risk for bleeding on IV alteplase.

For antiplatelet therapy, the administration of aspirin can be considered in patients who experience acute ischemic stroke and have contraindications to anticoagulants [72]. Although ischemic stroke occurs less frequently during the first trimester of pregnancy, data regarding the safety of daily aspirin use during this period are limited. Aspirin can cross the placenta and increase the risk for birth defects. Therefore, daily use of aspirin is not recommended during the first trimester of pregnancy. In terms of the dose issue, high-dose aspirin is not recommended due to the risk for congenital malformation and bleeding in the brains of premature infants [72]. Previous studies using low-dose aspirin in the second and third trimester; however, demonstrated no differences in congenital defects, developmental delay, or bleeding problems [73,74]. Based on this evidence, low-dose aspirin (60 to 150 mg/day) can be used for ischemic stroke during the second and third trimesters of pregnancy [72]. There is a lack of evidence supporting the daily use of other antiplatelet medications, including clopidogrel (pregnancy category B) and dipyridamole (pregnancy category D) during pregnancy. Antithrombotic drugs should be discontinued before a planned delivery. Specific days depend on type: aspirin should be stopped 7 days before delivery, and LMWH should be discontinued 24 hours before delivery.

Early surgical clipping or endovascular coiling leads to better outcomes in pregnant women with SAH due to ruptured aneurysms [75,78]. Vaginal delivery can be safe after successful aneurysm obliteration. AVMs in pregnant women are also managed as they would in non-pregnant women. If an AVM bleeds during pregnancy, treatment depending on grade should be considered during the pregnancy [7]. Pregnant women should be always protected with shielding of the abdomen during radiological procedures and evaluations.

**BLOOD PRESSURE MANAGEMENT DURING PREGNANCY**

The National Institute for Health and Clinical Excellence recommends that management of hypertensive disorders during pregnancy should be initiated at blood pressures ≥ 150/100 mm Hg, and should be also used to maintain systolic blood pressure < 150 mm Hg and diastolic blood pressure of 80 to 100 mm Hg [76]. However, all antihypertensive drugs can cross the placenta, and there are no comparative data regarding efficacy and fetal safety from large randomized trials. Labetalol, nifedipine, and methyldopa are recommended as primary options, and angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, renin inhibitor, and mineralocorticoid receptor antagonist should be avoided due to increased risk for fetopathy [77]. If IV administration is required in the acute period of severe hypertension or pregnancy-related hemorrhagic stroke, hydralazine, labetalol, or nicardipine can be used primarily. Hydralazine (5 mg IV administration for 1 to 2 minutes) is a drug widely used in the acute stage of severe pre-eclampsia and, if the reduction in blood pressure is insufficient, 5 to 10 mg IV administration can be further injected further up to 30 mg, with the drug effect lasting 2 to 4 hours. The initial dose of IV labetalol is 20 mg, and 20 to 80 mg IV can be administered repeatedly every 30 minutes up to 300 mg in total. Blood pressure drops within 5 to 10 minutes and lasts 3 to 6 hours. Nicardipine can be administered intravenously in emergency cases. If the initial dose of 5 mg/hr is not effective, it can be increased to a maximum of 15 mg/hr [78].

**OTHER NEUROCRITICAL CARE DURING PREGNANCY**

In pregnant women with increased intracranial pressure due to various neurological complications, hypertonic saline is preferred over mannitol for osmotherapy. Mannitol can lead to fetal hypoxia and acid-base imbalances [17]. In terms of eclamptic seizure management, IV magnesium sulfate has been shown to be superior to commonly used anticonvulsants [79]. Typical dosing is 4 to 6 g over a period of 20 to 30 minutes, followed by continuous infusion of 2 g/hr. If seizures occur during treatment, additional 2 g boluses of IV magnesium sulfate may be administered.

**CONCLUSION**

Cerebrovascular complications during pregnancy and puerperium
such as CVT, ischemic and hemorrhagic stroke, PRES and postpartum angiopathy present a challenge to neurointensivists because pregnancy is a very unique condition. Neurointensivists should understand the maternal changes in the hemodynamic, vascular structural, and coagulation systems that can occur during pregnancy and postpartum and also consider potential risk on the fetus. Knowledge of pregnancy-related cerebrovascular complications will provide optimal management for both fetus and mother.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article.

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Author contributions
Conceptualization: JHH. Data curation & Formal analysis: JHH. Visualization & Writing—original draft: JHH. Writing—review editing: JHH.

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Primary neurocritical care involving therapeutic hypothermia for acute ischemic stroke patients with malignant infarct cores

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Background: Acute ischemic stroke patients with malignant infarct cores were primarily treated with neurocritical care based on reperfusion and hypothermia. We evaluated the predictors for malignant progression and functional outcomes.

Methods: From January 2010 to March 2015 ischemic stroke patients with large vessel occlusion of the anterior circulation with infarct volume >82 mL on baseline diffusion weighted image (DWI) within 6 hours from onset, with National Institutes of Health Stroke Scale ≥15 were included. All patients were managed with intent for reperfusion and neurocritical care. Malignant progression was defined as clinical signs of progressive herniation. Predictive factors for malignant progression and outcomes of decompressive hemicraniectomy (DHC) were evaluated.

Results: In total, 49 patients were included in the study. Among them, 33 (67.3%) could be managed with neurocritical care and malignant progression was observed in the remainder. Decompressive surgery was performed in nine patients (18.4%). Factors predictive of malignant progression were initial DWI volumes (odds ratio [OR], 1.01; 95% confidence interval [CI], 1.00 to 1.02; \( P = 0.046 \)) and parenchymal hematoma (OR, 6.77; 95% CI, 1.50 to 30.53; \( P = 0.013 \)) on computed tomography taken at Day 1. Infarct volume of >210 mL predicted malignant progression with 56.3% sensitivity and 90.9% specificity. Among the malignant progressors, 77.7% resulted in grave outcomes even with DHC, while all patients who declined surgery died.

Conclusion: Acute ischemic stroke patients with malignant cores between 82 to 209 mL can be primarily treated with neurocritical care based on reperfusion and hypothermia with feasible results. In patients undergoing surgical decompression due to malignant progression, the functional outcomes were not satisfactory.

Keywords: Infarction, middle cerebral artery; Brain edema; Thrombectomy; Hypothermia, induced; Critical care; Decompressive craniectomy
field of acute stroke. In terms of reperfusion, intravenous (IV) thrombolysis has been approved for the time window of up to 4.5 hours [2], and endovascular treatment (EVT) has become the standard of care [3]. Neurocritical care for patients with massive ischemic stroke has also improved, especially in terms of neuroprotection and the antiswelling effect of therapeutic hypothermia [4]. While the therapeutic benefits of hypothermia on functional outcomes need to be further validated in prospective trials [5], there is evidence that it can reduce cerebral edema, reduce hemorrhagic transformation and improve outcomes, especially in those with complete reperfusion [4,6]. These developments have possibly increased the number of patients eligible for reperfusion therapies, while potentially reducing the number of patients that show malignant progression [7].

Furthermore, in acute stroke populations eligible for reperfusion, DHC trials could not be applied, as randomization usually occurred at least 12 hours after symptoms onset [8], and usually did not include patients in the acute period who underwent IV thrombolysis [9]. Accordingly, there are currently few indicators for the optimal management of acute stroke patients with large vessel occlusion presenting with malignant infarct cores.

For such patients, our institution pursues rapid reperfusion, combined with primary neurocritical care based on therapeutic hypothermia. The impact of malignant progression and its predictive factors have not been studied in this population. Furthermore, the outcomes of emergent DHC in patients primarily managed with neurocritical care have not been reported. Therefore, the aim of our study was to address these points.

METHODS

Patient enrollment
This was a retrospective single center study from January 2010 to March 2015. In this period, 315 patients underwent our institutional stroke endovascular reperfusion critical pathway. Of these patients, those with acute ischemic stroke involving the MCA territory with infarct volume $>$ 82 mL on baseline diffusion weighted image (DWI) who presented within 6 hours from onset [10], with National Institutes of Health Stroke Scale (NIHSS) $\geq$ 15 (according to previous literature that malignant cerebral edema is seldom encountered in patients with NIHSS under 15) [11] were included. Infarct size was measured in baseline DWI using nordicICE semiautomated software (NordicNeuroLab, Bergen, Norway). Patients with significant contralateral infarction or space occupying infarct hemorrhage were excluded.

The data collection protocol was approved by the Institutional Review Board of each participating hospital and implemented in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The need for written informed consent was waived given the retrospective nature of the study.

Reperfusion treatment
IV thrombolysis and endovascular reperfusion treatment were performed on patients based on the decision of the attending stroke neurologist. All patients underwent cerebral angiography for the initial intent of mechanical thrombectomy. In patients with very large DWI infarct volumes, aggressive reperfusion was avoided after performing digital subtraction angiography. However, as most of the patients were managed before the success of major EVT trials, and there is still disagreement about the upper infarct volume limit for EVT, reperfusion was sometimes performed for very large infarcts.

Primary neurocritical care
All patients were managed with intent for primary neurocritical care. This was performed based on a stepwise protocol, and the treatment degree was individualized on a patient by patient basis [12]. In brief, the treatment starts with general management including head elevation, easy venous drainage, and avoidance of fever, hypoxia, hypercapnia, or hyponatremia. Early rapid sequence intubation was performed on patients with altered mental status, or those in which therapeutic hypothermia was performed. In patients who underwent hypothermia, cooling was performed with adequate sedation and neuromuscular blockade. Patients underwent 48 hours of cooling (target temperature 34.5°C) and 48 hours of rewarming. Osmotherapy was performed with mannitol or hypertonic saline as required.

Malignant progression and DHC
Late DHC was usually performed based on clinical signs. Throughout neurocritical care, clinical signs of progressive herniation such as significant decrease in mentality, unilateral pupillary abnormality, impairment of eye movements, respiratory pattern abnormalities, and flexor or extensor motor posturing [13] were screened. Patients that showed these clinical signs, with computed tomography (CT) evidence of impending or imminent herniation, were termed as malignant progressors. DHC was performed on these patients as soon as possible after clinical decision and consent. There were no age limitations for decompressive surgery if family agreement was obtained. Previous IV thrombolysis was not a contraindication for decompression in this study. It was not performed on patients with bilateral fixed pupils [1].

Statistical analysis
First, the patients were dichotomized to malignant progressors and
nonprogressors. Factors predictive of malignant progression were evaluated through univariate and multivariate analysis. Second, the impact of initial DWI volume on prediction of malignant change was evaluated through receiver operating characteristic analysis. The functional outcomes of DHC performed on malignant progression were evaluated. A grave outcome was defined as a modified Rankin Scale (mRS) of 5–6. Third, factors predictive of grave outcomes in the patients that were managed with primary neurocritical care were evaluated through univariate and multivariate analysis. The data are presented as the mean ± standard deviation or as the median (interquartile range). A P < 0.05 was considered statistically significant. For multivariate analysis, variables with P values < 0.100 were included for logistic regression analysis by the forward conditional method. Statistical analyses were performed using IBM SPSS Statistics software version 25 (IBM Corp., Armonk, NY, USA).

### RESULTS

#### Overall outcomes

A total of 49 patients were included for analysis in this study. IV thrombolysis was performed in 37 patients (75.5%) and EVT was performed in 39 patients (79.6%). Any form of reperfusion was performed in 45 patients (91.8%), while both IV thrombolysis and EVT was performed in 31 patients (63.3%). Therapeutic hypothermia was performed in 27 patients (55.1%). Among the 49 patients, 33 (67.3%) could be managed with primary neurocritical care, without malignant progression. In the nonprogressors, 3-month functional outcomes of mRS 0–3 were achieved in 27.3%, while grave outcomes were recorded in 42.4%. However, among the malignant progressors, 87.5% resulted in grave outcomes (Table 1).

### Table 1. Factors predictive of malignant progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonprogressor (n=33)</th>
<th>Malignant progressor (n=16)</th>
<th>Univariate P value</th>
<th>OR (95% CI)</th>
<th>Multivariate P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.5±13.3</td>
<td>65.1±17.9</td>
<td>0.335</td>
<td></td>
<td></td>
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<tr>
<td>Male sex</td>
<td>16 (48.5)</td>
<td>8 (50.0)</td>
<td>0.921</td>
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<td></td>
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<tr>
<td>HTN</td>
<td>20 (60.6)</td>
<td>13 (81.3)</td>
<td>0.148</td>
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<td></td>
</tr>
<tr>
<td>DM</td>
<td>7 (21.2)</td>
<td>7 (43.8)</td>
<td>0.101</td>
<td></td>
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<tr>
<td>Dyslipidemia</td>
<td>16 (48.5)</td>
<td>11 (68.8)</td>
<td>0.362</td>
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<td></td>
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<tr>
<td>Smoking</td>
<td>5 (15.2)</td>
<td>5 (31.3)</td>
<td>0.190</td>
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<td></td>
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<td>Atrial fibrillation</td>
<td>20 (60.6)</td>
<td>6 (37.5)</td>
<td>0.201</td>
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<td></td>
</tr>
<tr>
<td>Initial NIHSS</td>
<td>18.0 (15.0–19.5)</td>
<td>17.5 (16.0–20.5)</td>
<td>0.200</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infarct burden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI volume</td>
<td>149±44</td>
<td>236±114</td>
<td>0.009</td>
<td>1.01 (1.00–1.02)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Therapeutic management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>26 (78.8)</td>
<td>11 (68.8)</td>
<td>0.444</td>
<td></td>
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<tr>
<td>EVT</td>
<td>23 (69.7)</td>
<td>16 (100.0)</td>
<td>0.014</td>
<td></td>
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<td>Mannitol</td>
<td>20 (60.6)</td>
<td>15 (93.8)</td>
<td>0.016</td>
<td></td>
<td></td>
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<tr>
<td>Hypertonic saline</td>
<td>2 (6.1)</td>
<td>3 (18.8)</td>
<td>0.169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>21 (63.6)</td>
<td>14 (87.5)</td>
<td>0.083</td>
<td></td>
<td></td>
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<td>Hypothermia</td>
<td>18 (54.5)</td>
<td>9 (56.3)</td>
<td>0.910</td>
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<tr>
<td><strong>Hemorrhagic change on D1 CT</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (33.3)</td>
<td>1 (6.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI1</td>
<td>6 (18.2)</td>
<td>2 (12.5)</td>
<td></td>
<td></td>
<td></td>
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<td>HI2</td>
<td>9 (27.3)</td>
<td>1 (6.3)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PH1</td>
<td>4 (12.1)</td>
<td>3 (18.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH2</td>
<td>3 (9.1)</td>
<td>9 (56.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH1-2</td>
<td>7 (21.2)</td>
<td>12 (75.0)</td>
<td>&lt;0.001</td>
<td>6.77 (1.50–30.53)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Functional outcome</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>6 (18.2)</td>
<td>0</td>
<td>0.069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–3</td>
<td>9 (27.3)</td>
<td>1 (6.3)</td>
<td>0.087</td>
<td></td>
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<tr>
<td>mRS 5–6</td>
<td>14 (42.4)</td>
<td>14 (87.5)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±SD, number (%), or median (interquartile range). Variables with P values <0.100 in univariate analysis were included for multivariate analysis. Variables included in multivariate analysis but not included in the final model are marked with a hyphen. OR, odds ratio; HTN, hypertension; DM, diabetes mellitus; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; EVT, endovascular therapy; CT, computed tomography; HI, hemorrhagic infarct; PH, parenchymal hematoma; mRS, modified Rankin Scale.

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Prediction of malignant changes

in the analysis to detect potential factors predictive of malignant progression, initial DWI lesion volume (odds ratio [OR], 1.01; 95% confidence interval [CI], 1.00 to 1.02; \( P = 0.046 \)) and parenchymal hematoma, postprocedure or at Day 1, by CT (OR, 6.77; 95% CI, 1.50 to 30.53; \( P = 0.013 \)) showed significant association, highlighting the impact of initial infarct volume on malignant progression (Table 1). EVT, or IV osmotherapy with mannitol, was associated with malignant progression in the univariate analysis, but this association was not apparent in the multivariate analysis.

When the predictive ability of initial DWI for malignant progression was assessed, it could predict malignant course with an area under the curve of 0.735 (range, 0.569 to 0.901) (Fig. 1). Infarct volume of >210 mL predicted malignant progression with 56.3% sensitivity and 90.9% specificity. When the included patients were divided into subgroups according to initial infarct volume, the percentage of malignant progressors increased sharply when the infarct volume increased to >210 mL, with 42.9% progressors in the 201 to 299 mL group, while all patients with >300 mL of infarct core showed malignant progression (Fig. 1).

Impact of decompressive surgery

among the 16 malignant progressors, nine underwent DHC and seven refused surgery. In the nonprogressors, grave outcomes were encountered in 42.4% of patients. However, of the malignant progressors, 87.6% resulted in grave outcomes (\( P = 0.031 \)) (Fig. 2). Even with DHC, 77.7% resulted in grave outcomes, while all patients that declined surgery died.

Outcomes in the nonprogression group

When the factors predictive of grave outcomes in the nonprogressors were delineated, age (OR, 1.08; 95% CI, 1.01 to 1.16; \( P = 0.024 \)) and initial DWI volume (OR, 1.03; 95% CI, 1.00 to 1.05; \( P = 0.049 \)) were shown to be significant predictive factors (Table 2). Performing EVT was associated with mRS 0–4 in the univariate analysis, but this association was insignificant in the multivariate analysis. There was a tendency for therapeutic hypothermia, resulting in more frequent mRS 0–4 (\( P = 0.062 \)).

DISCUSSION

The results of this study show that primary neurocritical care with reperfusion and therapeutic hypothermia is feasible for acute ischemic stroke with malignant infarct cores. Factors predictive of malignant transformation are presenting infarct volume and occurrence of parenchymal hematoma. An infarct volume >210 mL was associated with increased ratios for malignant course. For those patients in which malignant progression occurred, decom-
pressive surgery did not seem to offer much benefit for improved functional outcomes, most likely due to the large infarct burden.

The primary finding of this study shows that in this population, malignant progression was a major determinant of functional outcomes. As previously reported, initial infarct volume [14] and parenchymal hematoma type hemorrhages [15] were strong predictors of malignant change also in this population. In contrast, endovascular reperfusion or thrombolysis was not significantly associated, showing that potential reperfusion injuries are mostly influenced by the burden of initial infarct volume.

In the malignant progressors, however, DHC did not result in the robust functional improvements seen in the DHC trials1 that

**Table 2.** Factors predictive of outcomes in the nonprogressors

<table>
<thead>
<tr>
<th>Variable</th>
<th>mRS 0–4 (n=19)</th>
<th>mRS 5–6 (n=14)</th>
<th>Univariate P value</th>
<th>OR (95% CI)</th>
<th>Multivariate P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65±14</td>
<td>76±8</td>
<td>0.014</td>
<td>1.08 (1.01–1.16)</td>
<td>0.024</td>
</tr>
<tr>
<td>Male sex</td>
<td>12 (63.2)</td>
<td>4 (28.6)</td>
<td>0.049</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HTN</td>
<td>11 (57.9)</td>
<td>9 (64.3)</td>
<td>0.710</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DM</td>
<td>2 (10.5)</td>
<td>5 (35.7)</td>
<td>0.080</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10 (52.6)</td>
<td>6 (42.9)</td>
<td>0.530</td>
<td>–</td>
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<tr>
<td>Smoking</td>
<td>4 (21.1)</td>
<td>1 (7.1)</td>
<td>0.271</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (47.4)</td>
<td>11 (78.6)</td>
<td>0.070</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Infarct burden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI volume</td>
<td>133±31</td>
<td>170±51</td>
<td>0.026</td>
<td>1.03 (1.00–1.05)</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Therapeutic management</strong></td>
<td></td>
<td></td>
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<tr>
<td>Thrombolysis</td>
<td>15 (78.9)</td>
<td>11 (78.6)</td>
<td>0.979</td>
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<td>–</td>
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<tr>
<td>EVT</td>
<td>16 (84.2)</td>
<td>7 (50.0)</td>
<td>0.035</td>
<td>–</td>
<td>–</td>
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<td>Mannitol</td>
<td>10 (52.6)</td>
<td>10 (71.4)</td>
<td>0.275</td>
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<td>–</td>
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<tr>
<td>Hypertonic saline</td>
<td>1 (5.3)</td>
<td>1 (7.1)</td>
<td>0.823</td>
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<td>–</td>
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<tr>
<td>Mechanical ventilation</td>
<td>13 (68.4)</td>
<td>8 (57.1)</td>
<td>0.506</td>
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<td>–</td>
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<tr>
<td>Hypothermia</td>
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<td>5 (35.7)</td>
<td>0.062</td>
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<td>–</td>
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<tr>
<td>Hemorrhagic change on second CT</td>
<td></td>
<td></td>
<td>0.337</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>None</td>
<td>6 (31.6)</td>
<td>5 (35.7)</td>
<td></td>
<td>–</td>
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</tr>
<tr>
<td>HI1</td>
<td>2 (10.5)</td>
<td>4 (28.6)</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HI2</td>
<td>5 (26.3)</td>
<td>4 (28.6)</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PH1</td>
<td>4 (21.1)</td>
<td>0</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PH2</td>
<td>2 (10.5)</td>
<td>1 (7.1)</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PH1–2</td>
<td>6 (31.6)</td>
<td>1 (7.1)</td>
<td>0.090</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or number (%). Variables with P values <0.100 in univariate analysis were included for multivariate analysis. Variables included in multivariate analysis but not included in the final model are marked with a hyphen.

mRS, modified Rankin Scale; OR, odds ratio; HTN, hypertension; DM, diabetes mellitus; DWI, diffusion-weighted imaging; EVT, endovascular therapy; CT, computed tomography; HI, hemorrhagic infarct; PH, parenchymal hematoma.

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Fig. 2. Functional outcomes of nonprogressors and malignant progressors. DHC, decompressive hemicraniectomy; mRS, modified Rankin Scale.

![Graph showing functional outcomes](https://doi.org/10.18700/jnc.190076)
showed 78% survival and 43% with mRS ≤ 3. This finding may be explained in two ways. First, due to the large infarct volumes (despite earlier presentations), the patients included in this study may have shown more fulminant course than those included in the decompressive craniectomy trials. This is evidenced by the concept of late window paradox [16], in which a larger core at presentation can suggest rapid growth with poor collaterals [17] or complex type occlusions [18]. Second, the patients that would have obtained functional benefit with decompressive craniectomy could have been tolerably managed with primary neurocritical care. As a result, only the patients with fulminant infarcts may have been selected for DHC and such bias could have caused the dismal outcomes in the decompressive surgery group. If this is the case, the effectiveness of reperfusion and neurocritical care on patient outcomes may diminish the potential benefits of decompressive surgery in actual clinical practice.

The findings of our study also potentially extend the volume threshold for reperfusion therapy. As compared to patients with initial infarct volume in the 82 to 144 mL range, patients with infarct volumes in the 145 to 209 mL range did not show an increased chance of malignant progression. This is in contrast to the selection criteria of infarct volumes > 145 mL that was used for the decompressive surgery trials [8]. Furthermore, when considering that the patients analyzed in this study presented earlier with evolving infarcts, the same 145 mL cut-off would include patients with potentially more malignant profiles. Thus, we can postulate that a large number of patients considered for decompressive surgery previously would have been manageable with a combination of reperfusion treatment and neurocritical care. The upper infarct volume limit of EVT has not been clearly defined and numerous studies have tried to extend the limit, which was previously taken to be an Alberta Stroke Program Early CT Score (ASPECTS) score of 6 [19]. In such studies, EVT was shown to reduce infarct growth, reduce the need for hemicraniectomy and improve outcomes in patients with ASPECTS of 5 to 7 [20]. Another study suggested a final infarct volume threshold of 133 mL as a cut-off for unfavorable outcomes after EVT [21]. Our study data further suggest that through the use of reperfusion therapy combined with primary neurocritical care, initial infarct volumes between 145 to 209 mL can be potentially manageable. Such findings warrant future prospective trials.

Our study has some limitations. First, it is limited by the retrospective nature of the study and number of patients. However, malignant cerebral edema is a rare disease with an incidence of 10 to 20 per 100,000 per year [22], and acute ischemic stroke with malignant core occurs even less often. Thus we believe that our study findings well describe the clinical characteristics and outcomes in this special population, that will gain more clinical attention, as indications for EVT expand. In this context, future studies are needed to validate these findings. Second, the study included patient data from 2010 to 2014. During this period, financial reimbursement for stent retrievers was not permitted and second generation direct aspiration devices were not yet introduced [23]. Thus, outcomes of EVT were somewhat below current standards and this should be taken into account when interpreting the results of this study.

In conclusion, acute ischemic stroke patients with malignant cores between 82 to 209 mL can be treated with primary neurocritical care based on reperfusion and therapeutic hypothermia, with feasible results. In patients undergoing emergent surgical decompression due to malignant course, the functional outcomes were not satisfactory.

**ARTICLE INFORMATION**

**Conflict of interest**
No potential conflict of interest relevant to this article.

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**REFERENCES**


Clinical and neuroimaging determinants of minimally conscious and persistent vegetative states after acute stroke

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Background: Patients with persistent vegetative state (PVS) show no evidence of awareness of self or their environment, and those with minimally conscious state (MCS) have severely impaired consciousness with minimal but definite behavioral evidence of self or environmental awareness after stroke. Neuroimaging and clinical characteristics separating these two close consciousness states after stroke were insufficiently studied.

Methods: We conducted a hospital-based cohort study of all patients with stroke (2011 to 2017) who underwent 3T magnetic resonance imaging and consciousness assessment after 3 months of inclusion. Univariate and multivariate regression analyses were used to estimate the relative risk of neuroimaging markers for differentiation of PVS and MCS.

Results: Of 3,600 eligible subjects, 323 patients (0.09%) had PVS and 93 (0.02%) had MCS (mean age, 62.25 ± 13.4 years). Higher stroke volume was strongly associated with PVS compared to MCS (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.98 to 1.00; \( P = 0.001 \)). On univariate analysis, cingulate gyrus (OR, 2.7; 95% CI, 1.62 to 4.36; \( P = 0.001 \)) and corpus callosum (OR, 2.1; 95% CI, 1.28 to 3.44; \( P = 0.003 \)) involvement was significantly associated with PVS. However, on multivariate analysis, only cingulate gyrus involvement was independently associated with PVS (OR, 2.2; 95% CI, 1.33 to 3.72; \( P = 0.002 \)).

Conclusion: Our results indicate that PVS and MCS are different consciousness states according to clinical and neuroimaging findings. To predict outcome, cognitive performance of these patients should be well questioned after stroke.

Keywords: Minimally conscious state; Persistent vegetative state; Ischemic stroke; Hemorrhagic stroke; Cognition disorders; Outcome

INTRODUCTION

Consciousness is the state of full awareness of the self and one's relationship to the environment. Clinically, the level of consciousness of a patient is defined operationally at the bedside by the responses of the patient to the examiner. Consciousness has two major components: arousal and awareness [1,2]. The content of consciousness represents the sum of all functions mediated at a cerebral cortical level, including both cognitive and affective responses. Very few surviving patients with severe forebrain damage after stroke remain in an eyes-closed coma for more than 10 to 14 days; then, a vegetative state (also called coma vigil or...
apallic state) usually replaces coma by that time [3]. The American Neurological Association advises that persistent vegetative state (PVS) can be considered only in patients in that state for 1 month [4]. The minimally conscious state (MCS) is a concept that was defined by the Aspen Workgroup [5], which identifies a condition of severely impaired consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated.

However, the neuroimaging markers of PVS and MCS and their relative contributions after acute stroke have not been precisely defined. A large body of evidence suggests that several brain magnetic resonance imaging (MRI) markers may be linked to the incidence of PVS and MCS: stroke subtype (ischemic or hemorrhagic), stroke volume and gross location (with a detrimental effect of hemispheric stroke), strategic locations, multiple lesions, and recurrent stroke [6-10]. Surprisingly, the contribution of previous cognitive disorders to consciousness disorders has not been confirmed by systematic studies of stroke cohorts despite having been largely emphasized on poststroke cognitive disorders [11]. Most of the abovementioned studies presented some limitations. First, the studies focused on neurocognitive disorders rather than the more frequent consciousness disorders. Second, most studies separately examined the association between PVS and MCS and various determinants without evaluating their relative contributions. Lastly, most studies were based on a mass-effect approach (i.e., global tissue damage), which precluded any conclusions on the contribution of precise stroke locations and patterns (e.g., strategic regions). Hence, we aimed to find neuroimaging determinants of poststroke PVS and MCS based on clinical and neuroimaging findings in a large, prospective cohort of patients with stroke. To improve the determination of clinical-neuroimaging relationship, we used an optimized clinical questionnaire (OCQ) and combined both quantitative measures related to structure loss and qualitative measures related to the presence of strategic lesions.

**METHODS**

Between September 2011 and November 2017, 3,600 patients in our comprehensive stroke center had been prospectively included. Details of the stroke registry protocol have been previously reported [12]. All patients were enrolled within 48 hours of stroke onset. Briefly, all consenting Turkish-speaking patients aged between 40 and 80 years who were hospitalized for acute (< 30 days) cerebral infarct or hemorrhage with initial positive imaging and had a reliable informant and conditions affecting cognition were included. Clinical evaluation was performed in the neurointensive care unit by physicians and nurses. Baseline examinations, including questionnaire administration, blood chemistry, and extracranial and intracranial ultrasonography, were performed in all patients to confirm the referral diagnosis and screen for risk factors. The baseline examinations and definitions of vascular disease and risk factors are described briefly below.

Prospectively recorded variables included age, sex, previous stroke, risk factors, blood pressure and modified Rankin Scale (mRS) score [13], National Institutes of Health Stroke Scale (NIHSS) [14], and Glasgow Coma Scale (GCS) [15] scores at the time of admission, etiological subtypes in patients with ischemic stroke (IS) according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [16] classification, topography of infarcts and hemorrhage on MRI studies, in-hospital recurrent stroke, neurologic and systemic complications, and treatment modalities including osmotherapy, decompression surgery, thrombolysis, and thrombectomy. The study was performed in accordance with institutional guidelines and approved by the Ethics Committee of the Ege University Medical Center Institutional Review Board, and a written informed consent was obtained from all the relatives or parents of the participants. Ege University Medical Ethical Committee was approved this study following the principles outlined in the Helsinki Declaration before starting the study (2010).

**Assessment of consciousness state**

Clinical consciousness examination of each patient was performed at stroke onset in the neurointensive care and stroke unit. A consciousness assessment was performed every hour after entry into the neurointensive care and stroke unit. Consciousness state of the patients were determined by two trained neurologists and followed continuously in the neurointensive care unit. The kappa value between the two neurologists who performed the final consciousness assessment was 0.98. Coma was considered if there is a state of unresponsiveness in which the patient lies with eyes closed, cannot be aroused to respond appropriately to stimuli even with vigorous stimulation, and does not have localized responses or discrete defensive movements. PVS denotes the recovery of crude cycling of arousal states heralded by the appearance of “eyes-open” periods in an unresponsive patient. PVS was presumed if the patient remained in that state for at least 30 days according to the criteria of the Multisociety Task Force on PVS [17,18]. MCS was considered if the patient had a condition of severely impaired consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated. The differential diagnosis of PVS and MCS was made according to criteria of the Aspen Working Group [5]. An OCQ of the Aspen Working Group Criteria was administered, and evidence of limited but clearly discernible self or environmental
awareness was obtained according to one or more of the following behaviors: (1) following simple command; (2) gestural or verbal “yes/no” responses (independent of accuracy); (3) intelligible verbalization; (4) purposeful behavior; and (5) affective behavior.

### Lesion location

MRI was performed within the first week of admission by 3T scanners (Siemens Sonata, Siemens Medical Solutions, Erlangen, Germany). MRI scanners consisted of axial T1- and T2-weighted spin-echo, T2-weighted fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). Sagittal and axial FLAIR or DWIs were used to assess lesion size and site. Two neuroradiologists who evaluated the images were blinded to the clinical picture (interobserver agreement, 0.97). The presence, type, and number of strategic lesions and volume for consciousness impairment were determined using the 3-dimensional-T1 BRAVO sequence and the STandards for Reporting Vascular changes on nEUroimaging (STRIVE) criteria. Senior investigators manually segmented the lesions on native 3D-T1 MRI data sets using MRIcon (a cross-platform NIfTI format image viewer). Normalized lesion masks were used to compute the stroke volume that considered all strokes. Strategic sites include foci within the following regions: left and right middle frontal gyrus, left and right middle and superior temporal gyrus, left and right parietal cortex (angular and supramarginal gyrus), putamen, pallidum, cingulate gyrus and corpus callosum, left arcuate fasciculus, anterior and middle parts of the left and right thalamus, ventral and dorsal midbrain, and dorsal pons. The white matter hyperintensities (WMHs) burden was assessed using the Fazekas scale score on the basis of FLAIR sequence. Brain microbleeds were defined as small (<10 mm in diameter) areas of signal void according to the brain observer microbleed scale criteria. T2 sequence was used to assess the presence of dilated perivascular spaces.

### Stroke mechanisms

After analyzing DWI, angiographic, and clinical data, stroke mechanisms were categorized according to previous descriptions. Large-artery disease (LAD) was presumed in patients with symptomatic carotid artery stenosis > 50%. Small-artery disease or local branch occlusion was defined in patients with infarcts < 15 mm in diameter localized in the deep regions of the brain or in the brainstem without LAD and cardiac embolism (CE). CE was considered in patients with a source of CE. Strokes of other determined or undetermined causes were also recorded. The presence, type, and volume of cerebral hemorrhage were noted.

### Concomitant risk factors

Among cognitive risk factors, minor or major neurocognitive disorder was recorded. Previous cognitive status of every patient were asked from their practitioner or from the National Health Data System. Vascular risk factors including hypertension, current cigarette smoking, and serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, glucose, and glycated hemoglobin levels in hemolysates were determined. Apolipoprotein E (ApoE) genotype was determined by polymerase chain reaction, and patients were classified by presence or absence of at least 1 ApoE epsilon 4 allele.

### Statistical analyses

Proportions, odds ratios (ORs), and means of baseline, clinical, and neuroimaging characteristics were compared between patients with PVS and those with MCS using the chi-square test, logistic regression, and analysis of variance, respectively. Univariate associations between PVS and MCS according to age, sex, vascular risk factors, previous stroke and recurrence, history of neurocognitive disorder, stroke subtypes, strategic locations, white matter lesions, microbleeds, and dilated perivascular spaces were analyzed using logistic regression to estimate unadjusted ORs. Association between PVS and MCS was determined to estimate models using multivariate logistic regression analysis with backward stepwise selection, which is based on the probability of the likelihood-ratio statistic according to the maximum partial likelihood estimates by including clinical and neuroimaging findings. The selection process of the final model was performed in three steps by entering all variable(s) in binary logistic regression analysis. In the last model of variables, changes in –2 log-likelihood and model log likelihood and significance of the change were obtained. Probability values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

### RESULTS

Data were available for 323 patients with PVS and MCS (mean age, 62.25 ± 13.4 years; male, 41%). Characteristics of patients with PVS (n = 230) and MCS (n = 93) are presented in Table 1. Of 230 patients with PVS, 83% had coma state at stroke onset, and the rest showed transition from severe consciousness disturbances to coma, while 70 patients (75%) with MCS had coma, 15 (16%) had transition from vegetative state to MCS in 3 months, and eight (9%) had progressive deterioration to MCS after stroke. Almost all patients had an mRS score ≥ 4 (median, 5 [4 to 5]), NIHSS score ≥ 12 (median, 24 [12 to 32]), and GCS score ≤ 7.
Most patients (n = 285, 88%) presented with IS, 38 (12%) had hemorrhage, and 24 (7.4%) had recurrent stroke between inclusion and 3-month follow-up. Fifty patients (15.5%) (28 [9%] with minor and 22 [7%] with major neurocognitive disorder) had prestroke neurocognitive disorders, but there was no statistically significant difference between the two groups.

Univariate analysis of lesion location showed that the cingulate gyrus (OR, 2.14; 95% confidence interval [CI], 1.30 to 3.51; P = 0.003) and corpus callosum (OR, 1.68; 95% CI, 1.30 to 2.75; P = 0.004) were more frequently involved in patients with PVS. There were more patients with multiple lesions in those with PVS (102 [44%]) compared with those with MCS (32 [34%]), but it did not reach a significant level in the analysis. Isolated thalamic and midbrain lesions were found in two patients with MCS, while others had additional supratentorial lesions (Table 2). On the standardized OCQ, the factors related strongly to MCS including following simple command, gestural

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with PVS (n=230)</th>
<th>Patients with MCS (n=93)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63±13</td>
<td>62±14</td>
<td>0.540</td>
</tr>
<tr>
<td>Male sex</td>
<td>123 (54)</td>
<td>44 (47)</td>
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</tr>
<tr>
<td>Vascular risk factor</td>
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<tr>
<td>Previous stroke</td>
<td>30 (13)</td>
<td>16 (17)</td>
<td>0.210</td>
</tr>
<tr>
<td>History of MND</td>
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<td>Hypertension</td>
<td>116 (50)</td>
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<td>Diabetes mellitus</td>
<td>34 (15)</td>
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<td>47 (20)</td>
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<td>Atrial fibrillation</td>
<td>51 (22)</td>
<td>18 (19)</td>
<td>0.330</td>
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<td>110 (48)</td>
<td>47 (51)</td>
<td>0.380</td>
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<tr>
<td>ApoE ε4 allele</td>
<td>45 (20)</td>
<td>26 (28)</td>
<td>0.070</td>
</tr>
<tr>
<td>WMH burden (Fazekas scale 1–3)</td>
<td>128 (56)</td>
<td>43 (46)</td>
<td>0.080</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>23 (10)</td>
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<td>0.220</td>
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<td>Stroke volume (cm³)</td>
<td>165±57</td>
<td>136±59</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of dilated perivascular spaces</td>
<td>45 (20)</td>
<td>7 (8)</td>
<td>0.004</td>
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<td>Stroke pathogenesis</td>
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<td>Large-artery disease</td>
<td>95 (41)</td>
<td>42 (45)</td>
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<td>Cardioembolic stroke</td>
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<td>0.490</td>
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<td>13 (6)</td>
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<td>2 (2)</td>
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<td>8 (9)</td>
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<tr>
<td>NIHSS at stroke onset</td>
<td>24 (10–32)</td>
<td>24 (17–29)</td>
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<tr>
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<td>5 (4–5)</td>
<td>5 (4–5)</td>
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<tr>
<td>Glasgow coma score (eye-opening, motor, and verbal)</td>
<td>5 (3–7)</td>
<td>6 (3–7)</td>
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</tr>
<tr>
<td>One pupil fixed and dilated</td>
<td>87 (38)</td>
<td>25 (27)</td>
<td>0.070</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>Thrombolysis</td>
<td>78 (34)</td>
<td>35 (38)</td>
<td>0.310</td>
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<tr>
<td>Thrombectomy</td>
<td>16 (7)</td>
<td>5 (5)</td>
<td>0.400</td>
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<td>Decompression surgery</td>
<td>57 (25)</td>
<td>21 (23)</td>
<td>0.390</td>
</tr>
<tr>
<td>Osmotherapy</td>
<td>158 (69)</td>
<td>71 (76)</td>
<td>0.110</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>110 (48)</td>
<td>36 (39)</td>
<td>0.090</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD, number (%), or median (interquartile range). PVS, persistent vegetative state; MCS, minimally conscious state; MND, major or minor neurocognitive disorder; ApoE, apolipoprotein E; WMH, white matter hyperintensity; NIHSS, National Institutes of Health Stroke Scale.
or verbal "yes/no" response, intelligible verbalization, and purposeful and affective behaviors ($P = 0.001$, respectively). Few patients with PVS ($< 1\%$) showed limited visual fixation or tracking and inappropriate attempt to reach objects.

In the multiple stepwise linear regression analysis, three factors that were independently associated with the PVS compared to MCS were selected: cingulate gyrus involvement, stroke volume, and presence of dilated perivascular spaces (Table 3). Among the strategic regions, cingulate gyrus damage was strongly related to PVS compared to MCS ($OR, 2.2; 95\% CI, 1.33 to 3.72; P = 0.002$). Assessments of a possible threshold effect of WMH burden, number of microbleeds, stroke recurrence, multiple infarcts, and treatment strategies did not affect the main findings, while there was an independent effect of presence of dilated perivascular spaces on consciousness state ($OR, 3.2; 95\% CI, 1.34 to 7.68; P = 0.004$). Stroke volume also played an important role, which accounted for severe loss of consciousness in patients with PVS compared to MCS ($OR, 0.99; 95\% CI, 0.98 to 1.00; P = 0.001$).

**DISCUSSION**

The major finding of this prospective, hospital-based study of poststroke patients is that, of the different MRI markers, (1) stroke volume and (2) the presence of a lesion within strategic regions (cingulate gyrus and corpus callosum) were the main determinants of PVS compared with MCS. Differentiating the PVS from MCS is often one of the most challenging tasks in the stroke unit. These two clinical entities are close consciousness states, but there is a critical level of awareness manifested by purposeful and affective behaviors that differentiates both clinical pictures [22]. For the explanation of this critical level, we observed that lesion volume and some regional involvement are critical. Most studies measuring volumetric indices in PVS/MCS were based on traumatic [23] or anoxic brain injury [24], while

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with PVS (n=230)</th>
<th>Patients with MCS (n=93)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimized clinical questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following simple command</td>
<td>1 (0.4)</td>
<td>25 (27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gestural or verbal &quot;yes/no&quot; response</td>
<td>0</td>
<td>29 (31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intelligible verbalization</td>
<td>0</td>
<td>34 (37)</td>
<td>0.001</td>
</tr>
<tr>
<td>Purposeful behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to linguistic content of questions</td>
<td>0</td>
<td>38 (41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Touching or holding objects</td>
<td>1 (0.4)</td>
<td>55 (59)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sustained visual fixation or tracking</td>
<td>3 (1)</td>
<td>52 (56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Reaching for objects in appropriate direction</td>
<td>2 (0.9)</td>
<td>72 (77)</td>
<td>0.001</td>
</tr>
<tr>
<td>Affective behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate smiling or crying</td>
<td>9 (4)</td>
<td>59 (63)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2: Clinical and lesion characteristics of patients with minimally conscious state and persistent vegetative state at 3 months poststroke

Values are presented as number (%).
PVS, persistent vegetative state; MCS, minimally conscious state.

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Poststroke pathologic studies showed severe tissue damage with diffuse axonal loss in patients with PVS and only focal brain damage in some patients with MCS [25]. Our and previous findings suggest that significant variations may exist in the underlying mechanisms of cognitive disabilities and residual brain function accompanying MCS.

There are no clear neuroimaging criteria in determining when PVS becomes permanent and MCS appears after severe stroke. One reason for the inability to predict permanence early in the course of PVS is that patients usually have severely damaged cerebral hemispheres combined with a relatively intact brainstem [26]. Our patients with PVS presented likely similar pattern of regional involvement, recurrent stroke, multiple lesions, presence and extent of WMH, and microbleeds compared with those with MCS. The common denominator of PVS may be damage to the corticostriato-pallidal-thalamocortical loops that are critical for the function of the frontal lobes [27]. As we noted in our patients with PVS and MCS, severe damage affected the ventral striatum, ventral pallidum, and mediodorsal nucleus of the thalamus most likely with bilateral damage at any level of this system and interrupted pathways connecting the two hemispheres. At least partial cognitive function can be recovered following restricted bilateral injuries to the paramedian thalamus and mesencephalon [28,29]. In our study, we observed that patients with isolated lesions restricted to the bilateral paramedian thalamus and mesencephalon recovered to the state of MCS after being in an eyes-closed coma, in 3 months.

The study had some limitations. First, the follow-up period was relatively short. Our findings indicate that like PVS, MCS presented in one of seven patients as a transitional state arising during recovery from coma after acute stroke or after worsening of progressive stroke in one of 10 patients. A few studies have examined differences in outcome between PVS and MCS [30]. Studies examined either traumatic or nontraumatic injuries, and patients with MCS had significantly better outcomes compared with patients with PVS at 1 year [31]. Long-term outcome and transition between them after stroke warrant further investigation that are beyond the scope of the present study. Second, the

| Characteristic | Univariate analysis | | Multivariate analysis | |
|----------------|---------------------| |----------------------| |
| | Crude OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
| **Clinical characteristic** | | | |
| Ischemic stroke | 1.6 (0.70–3.62) | 0.270 | - | - |
| Previous stroke | 1.3 (0.52–3.05) | 0.610 | - | - |
| Recurrent strokes after inclusion | 1.4 (0.72–2.68) | 0.330 | - | - |
| History of MND | 2.0 (0.94–4.36) | 0.070 | - | - |
| NIHSS at stroke onset | 0.92 (0.87–0.98) | 0.006 | - | - |
| **Neuroimaging characteristic** | | | |
| Stroke volume (cm^3) | 0.99 (0.98–1.00) | 0.003 | 0.99 (0.98–1.00) | 0.001 |
| Right hemisphere lesion | 0.6 (0.38–1.04) | 0.070 | - | - |
| Left hemisphere lesion | 1.3 (0.79–2.09) | 0.300 | - | - |
| Bilateral hemispheric lesions | 1.3 (0.71–2.24) | 0.430 | - | - |
| Multiple lesions | 1.5 (0.92–2.51) | 0.100 | - | - |
| **Strategic regions** | | | |
| Cingulate gyrus | 2.7 (1.62–4.36) | 0.001 | 2.2 (1.33–3.72) | 0.002 |
| Corpus callosum | 2.1 (1.28–3.44) | 0.003 | - | - |
| **Infratentorial herniation sign** | | | |
| WMH burden (Fazekas scale) | | | |
| 1 | 3.0 (1.38–6.67) | 0.060 | - | - |
| 2 | 3.7 (1.60–8.78) | 0.020 | - | - |
| 3 | 1.1 (0.37–3.17) | 0.880 | - | - |
| Presence of microbleeds | 1.6 (0.63–4.10) | 0.320 | - | - |
| Presence of dilated perivascular spaces | 2.9 (1.29–6.90) | 0.010 | 3.2 (1.34–7.68) | 0.004 |

OR, odds ratio; CI, confidence interval; MND, major or minor neurocognitive disorder; NIHSS, National Institutes of Health Stroke Scale; WMH, white matter hyperintensity.
cross-sectional design prevented us from investigating the relationship between neuroimaging markers and long-term outcome of consciousness states. However, in patients with stroke who remained in PVS at 3 months, neuroimaging findings showed that structural injuries within the corpus callosum and cingulate gyrus significantly predicted loss of self or environmental awareness as in previous studies [32,33]. Patients with isolated rostrocaudal midbrain and dorsolateral thalamic lesions showed transition from coma to MCS with signs of awareness, but those with additional supratentorial lesions did not recover and continued to live with PVS. The pathophysiological role of these structures on awareness have not been fully elucidated; interruption of the brainstem-hemispheric awareness network is probably one of the main contributors. Moreover, recent studies with functional MRI reported that patients with MCS showed more widespread activations with cortico-cortical functional connectivity compared with patients with PVS [34].

Our study had several strengths. First, the large sample size allowed us to define different aspects of two different consciousness levels and feed many factors into the regression model. Our study provides an original and reliable approach using OCQ in a large population with severe stroke and radiological examination to assess involved brain structures and relationship of poststroke consciousness states. Second, we analyzed most of the likely radiological determinants of poststroke consciousness states and delineated higher frequency of multiple lesions, WMH burden, and bilateral hemispheric lesions either in the anterior and posterior circulation, but these factors were not statistically different in both groups. Third, the present study clearly showed significant difference of awareness between PVS and MCS using OCQ to explore gestural or verbal responses, intelligible verbalization, and purposeful and affective behaviors. Fourth, we found higher frequency of involvement of strategic regions (i.e., left and right middle frontal gyri, left and right middle and superior temporal gyrus, left and right parietal cortex [angular and supramarginal gyri], putamen, pallidum, cingulate gyrus and corpus callosum, anterior and middle parts of the left and right thalami, ventral and dorsal midbrain, and dorsal pons) in both groups and cingulate gyrus and corpus callosum involvement, which might be an independent risk factor for PVS [35,36]. A large body of evidence suggests that lesions in strategic areas have a key role in the development of consciousness disorders regardless of their volume but the associations between strategic sites and consciousness states warrant further investigation that are beyond the scope of our study. Fifth, we preferred to study both cerebral infarcts, hemorrhage, and all causes of stroke (large and small infarcts and all hemorrhages) so that our study cohort was representative of clinical populations. Furthermore, this design has the advantage of reducing multiple linearity and confirming stroke-related factors for all subtypes. Sixth, in our large cohort, we found a higher rate of previous neurocognitive disorder especially in patients with PVS and MCS, which might increase the risk of cognitive and awareness impairment [37,38]. Lastly, the present study was characterized by older age and higher stroke severity compared with population-based stroke studies [39]. The absence of patients with mRS score < 5 is explained by the fact that patients with severe consciousness impairment were followed and their consciousness states were assessed in the stroke unit for 3 months. Furthermore, the present study was designed to focus on consciousness state of patients with mRS score 5.

Finally, PVS and MCS are different consciousness states especially in terms of awareness function according to clinical and radiological findings. Cognitive capacities and performance of these patients should be well questioned after stroke to improve the determination of outcome of consciousness states. Further long-term clinical trials are warranted to determine the consciousness prognosis and late recovery of patients with PVS and MCS after stroke.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article.

Author contributions
Conceptualization: EK and FEB. Data curation & Formal analysis: All authors. Visualization & Writing–original draft: All authors. Writing–review editing & Supervision: EK and CEE.

References


Recurrent aseptic meningitis as an initial clinical presentation of primary Sjögren’s syndrome

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INTRODUCTION

Sjögren’s syndrome (SjS) is a chronic autoimmune disease that may be primary or secondary to other connective tissue disorders, particularly rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis. SjS is clinically characterized by sicca symptoms, which develop due to a mononuclear infiltration and secondary chronic dysfunction of the lacrimal and salivary glands. Systemic, extra-glandular manifestations are found in many patients with primary SjS and may occur in almost any organ, including the nervous system. The central nervous system (CNS) involvement includes diffuse abnormalities (cognitive impairment, psychiatric changes, and aseptic meningitis), and focal or multifocal involvement of the brain and spinal cord (seizures, cerebellar syndrome, myelopathy, and optic neuropathy) [1-4]. However, recurrent aseptic meningitis is an uncommon neurological manifestation of primary SjS; only few cases have been published in the medical literature, and none have been reported in Korean literature [4,5]. Herein, we report the case of a 54-year-old woman with recurrent aseptic meningitis associated with primary SjS.

Background: The neurological manifestations of Sjögren’s syndrome (SjS) are nonspecific and may precede the onset of sicca symptoms. Hence, the diagnosis of SjS is often delayed. Recurrent aseptic meningitis is an uncommon neurological manifestation of primary SjS; only few cases have been reported in the medical literature.

Case Report: A 54-year-old woman was admitted for recurrent aseptic meningitis. The patient had a history of two episodes of aseptic meningitis, which had occurred 12 and 7 years before this presentation. The patient had overt sicca symptoms for 5 years. SjS was diagnosed based on the results of serum autoantibody tests, Schirmer’s test, and salivary scintigraphy. We concluded that recurrent aseptic meningitis occurred as an initial presentation of primary SjS.

Conclusion: This case suggest that SjS should be included in the differential diagnosis of recurrent aseptic meningitis.

Keywords: Sjogren’s syndrome; Meningitis, aseptic; Autoimmune diseases
CASE REPORT

A 54-year-old woman was admitted owing to headache, nausea, and fever following mild flu-like symptoms for 7 days. On admission, her body temperature was 38.2°C, blood pressure was 110/60 mm Hg, and pulse rate was 80/min. The physical examination revealed mild nuchal rigidity. The remainder of the examination was normal. The patient had a history of two episodes of aseptic meningitis, which had occurred 12 and 7 years before this presentation (Table 1). For the previous two episodes of aseptic meningitis, the patient was treated only with supportive care (intravenous hydration and nonsteroidal anti-inflammatory drugs for pain control) and was discharged within 2 weeks. Her medical history was otherwise unremarkable. The laboratory blood tests revealed a mild normochromic anemia (hemoglobin level, 10.2 g/dL), and an elevated erythrocyte sedimentation rate (120 mm/hr). The analysis of the cerebrospinal fluid (CSF), obtained by lumbar puncture, revealed a crystal-clear appearance, mildly elevated opening pressure of 170 mm H₂O, moderate pleocytosis (170/mm³, 51% lymphocytes), and normal protein (49.43 mg/dL) and glucose levels (52 mg/dL).

The patient was initially suspected to have recurrent benign lymphocytic meningitis associated with herpes simplex virus (HSV) type 2 and was started on a treatment with intravenous acyclovir at a dose of 30 mg/kg daily. The tests for an infectious etiology, polymerase chain reaction for HSV type 1 and 2 and varicella-zoster virus, were negative, and cultures for bacteria, mycobacterium, and fungi were also negative. Cerebral magnetic resonance imaging did not reveal any abnormalities (Fig. 1). Five days after admission, the patient recovered to normal condition without fever, headache, or nuchal rigidity. Acyclovir was stopped after 7 days of administration due to no evidence of HSV infection. The patient was discharged to her home 8 days after admission in a stable condition.

For evaluation of the relapsing meningitis, an investigation for systemic autoimmune diseases was conducted. Anti-Ro/SS-A, anti-La/SS-B, as well as anti-nuclear antibodies resulted positive in the serum. Rheumatoid factor, anti-Smith, and anti-double-stranded DNA (dsDNA) antibody tests were negative. Through a more detailed medical history taking, it was determined that the patient has been using artificial tears for ocular dryness for 5 years. She also complained that it was difficult to swallow without water when eating dry food in the last 5 years. She had chronic fatigue, but denied Raynaud’s phenomenon, arthralgia, myalgia, and photosensitivity. At this point, primary SjS was suspected, and more specific investigations were performed for diagnostic confirmation. Schirmer’s test showed a decreased tear secretion rate in the left eye (5 mm of filter paper moistened for 5 minutes). In addition, scintigraphy of the salivary glands showed nearly non-functioning parotid glands and submandibular gland (Fig. 2). Therefore, the patient was diagnosed with SjS and recurrent aseptic meningitis. We consulted a rheumatologist, and oral pilocarpine medication was started for the sicca symptoms. The patient is followed up in the rheumatology outpatient clinic.

**DISCUSSION**

This case report describes a patient with recurrent aseptic meningitis, which preceded the diagnosis of SjS. Our patient was di-

### Table 1. Laboratory and radiologic findings in the three episodes of aseptic meningitis

<table>
<thead>
<tr>
<th>Episode</th>
<th>First presentation 2007</th>
<th>Second presentation 2012</th>
<th>Third presentation 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure (mm H₂O)</td>
<td>Not recorded</td>
<td>180</td>
<td>170</td>
</tr>
<tr>
<td>White blood cells (f/mm³)</td>
<td>709</td>
<td>194</td>
<td>196</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>83</td>
<td>96</td>
<td>51</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>9</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>65.86</td>
<td>34.46</td>
<td>49.43</td>
</tr>
<tr>
<td>Glucose CSF/blood (mg/dL)</td>
<td>52/113</td>
<td>55/91</td>
<td>52/108</td>
</tr>
<tr>
<td>Adenosine deaminase (IU/L)</td>
<td>3.2</td>
<td>3.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Bacterial culture</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Mycobacterium culture</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HSV PCR type 1/type 2</td>
<td>Negative/not performed</td>
<td>Negative/not performed</td>
<td>Negative/negative</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Anti-nuclear antibody</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction.
Fig. 1. Brain magnetic resonance images with gadolinium enhancement. (A) Axial T2-weighted images show no abnormal signal intensity in the brain. (B) Axial T1-weighted images after administration of gadolinium show no abnormal parenchymal and meningeal enhancement.

diagnosed with SjS according to the 2016 criteria proposed by the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR), which is the most recently used standard for classification in clinical and scientific research [6]. The patient had ocular and oral symptoms for 5 years, positive anti-Ro/SS-A antibodies, and abnormal Schirmer’s test. In addition, the diagnosis of SjS was excluded in the item of the 2016 ACR-EULAR criteria; however, the abnormal scintigraphy supported this diagnosis.

Recurrent meningitis is rarely seen; however, when it occurs, a detailed investigation for determining the pathogenesis underlying the recurrent episodes must be pursued. Causes of recurrent meningitis fall into five main categories: infections, malignant neoplasms, benign tumors, drugs, and autoimmune diseases [7]. Recurrent aseptic meningoencephalitis as a neurological manifestation of primary SjS was first reported by Alexander and Alexander [4] in 1983. The exact pathogenesis of aseptic meningitis in SjS is still not fully understood. Hypersensitivity to some agents, such as viruses, drugs, or others, and the presence of oligoclonal bands, elevated immunoglobulin G levels, and CSF antibodies that cross-react with the meningeal cells is hypothesized to cause CNS lymphocyte infiltration and autoantibody production [5].

In our case, the diagnosis of SjS was delayed because the neurological manifestation preceded the overt sicca symptoms, which is the reason that investigations for SjS were not performed during the two prior episodes of meningitis. Because CNS involvement frequently predates the onset of sicca symptoms in SjS and often transpires as recurrent, multifocal episodes separated by long disease-free intervals, the diagnosis can often be very challenging [1]. According to previous studies, neurological manifestations may
Fig. 2. Scintigraphy of the salivary glands. Salivary gland scintigraphy revealed a remarkably low accumulation level and a poor response to secretion stimulation. ANT, anterior; RT, right; LAT, lateral; LT, left; WASH, washout.

precede the typical sicca symptoms in 25% to 92% of the cases \cite{8,9}. In a study of 82 patients with primary SjS with neurologic manifestations, 66 (81%) patients were diagnosed after the onset of neurologic symptoms, with a mean delay of 4.6 years \cite{1}. To reflect these points, the most recent 2016 ACR-EULAR classification for primary SjS excludes the subjective ocular and oral symptoms \cite{6}.

The early and accurate diagnosis of SjS can help prevent or ensure adequate treatment of the many complications associated with the disease. It is well known that there is an increased risk of lymphoproliferative disease development as a severe complication of primary SjS. The risk of B-cell non-Hodgkin lymphoma occurrence in the setting of SjS has been previously estimated to be 7- to 19-fold higher than that in the general population \cite{10}.

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At present, there is no treatment modality that can cure primary SjS. Hence, symptomatic treatment for the sicca symptoms is commonly used. However, in case of significant systemic involvement, including neurological manifestation, immunomodulatory or immunosuppressive therapy can be applied, despite the limited evidence in small, uncontrolled case series [11,12].

Our case report has some limitations. It is our presumptive diagnosis that primary SjS was the cause of recurrent aseptic meningitis. Particularly, two episodes of meningitis before the onset of sicca symptoms cannot be attributed to SjS. However, other known causes for recurrent meningitis, such as other autoimmune diseases, drugs, benign tumors, and malignancies, could be excluded when considering our patient’s clinical history, laboratory findings, and clinical course.

In conclusion, this case highlights that SjS should be considered in the differential diagnosis of recurrent aseptic meningitis. In addition, the diagnostic approach should include both a detailed medical history taking and serological examinations, including immunological screening.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article.

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REFERENCES

Status epilepticus due to cerebral air embolism after the Valsalva maneuver

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INTRODUCTION

Cerebral air embolism is a rare but potentially severe complication of iatrogenic procedures or destructive lung disease, possibly resulting in neurological disorders such as encephalopathy, stroke, or seizure. Due to a low overall incidence, cerebral air embolism may go undiagnosed. We report the case of a patient with cerebral air embolism presenting with status epilepticus after the Valsalva maneuver during a pulmonary function test.

CASE REPORT

A 56-year-old man with a medical history of right upper lobectomy due to lung cancer presented to the emergency room with changes in mental status after the Valsalva maneuver, followed by status epilepticus during admission. Brain and chest computed tomography showed cerebral air embolism and accidental pneumothorax in the right major fissure. After antiepileptic drug infusion and oxygen therapy, he recovered completely.

Background: Cerebral air embolism is uncommon but potentially causes catastrophic events such as cardiac damage or even death. However, due to a low overall incidence, it may go undiagnosed.

Case Report: A 56-year-old man with a medical history of right upper lobectomy due to lung cancer showed changes in mental status after the Valsalva maneuver, followed by status epilepticus during admission. Brain and chest computed tomography showed cerebral air embolism and accidental pneumothorax in the right major fissure. After antiepileptic drug infusion and oxygen therapy, he recovered completely.

Conclusion: Since cerebral air embolism may result in fatal outcomes, it should be suspected in patients with sudden neurological deterioration after routine medical procedures.

Keywords: Status epilepticus; Embolism, air; Pneumothorax; Valsalva maneuver
bral subarachnoid space and deep cerebral white matter, suggesting air embolism (Fig. 1A). In addition, chest CT revealed localized pneumothorax in the right major fissure (Fig. 2).

With the intravenous administration of fluid and applied O2 therapy for 8 hours, the patient was able to make eye contact. However, about 11 hours after the event, three attacks of generalized tonic-clonic seizures with right gaze deviation occurred for 40 minutes. The patient did not regain consciousness between the seizures. Suspecting status epilepticus with acute kidney injury, antiepileptic drug with levetiracetam 1,500 mg intravenous was loaded, followed by postictal confusion over 8 hours. Within the 8 hours, he showed tactile and visual extinction, left-sided weakness, and bilaterally positive Babinski signs.

Five days after the seizure, brain magnetic resonance imaging re-

Fig. 1. (A) Brain computed tomography 30 minutes after symptom onset; multiple air bubbles observed prominently in the right parenchymal and subarachnoid vessels (arrowheads). (B, C) Brain magnetic resonance imaging after 5 days after symptom onset; diffuse leptomeningeal enhancement of the right frontal, bilateral parietooccipital, and bilateral cerebellum with diffuse enhancement in the perivascular space of deep white matter (arrows).

Fig. 2. (A, B) Chest computed tomography; localized pneumothorax in the right major fissure.
vealed newly appearing diffuse leptomeningeal enhancement of the right frontal, bilateral parietooccipital, and bilateral cerebellum with diffuse enhancement in the perivascular space of bilateral deep white matter (Fig. 1B, 1C). Magnetic resonance angiography revealed mild atherosclerotic changes in the bilateral proximal and cavernous internal carotid arteries and focal stenosis at left M1. Furthermore, a transesophageal echocardiogram revealed patent foramen ovale (PFO) Grade I. Five days after supportive therapies such as mechanical ventilation and oxygen therapy, the patient was discharged from the hospital without any neurological deficits. After discharge, he took levetiracetam 500 mg twice a day daily.

DISCUSSION

Cerebral air embolism is a rare but life-threatening event, which may cause sudden-onset respiratory distress or neurological events such as seizure and comatose mental status [1,2]. It often occurs with lung trauma or during vascular interventions or surgical procedures such as central venous catheter removal, cardiac surgeries, and endoscopic operations [3,4].

Diagnosis of cerebral air embolism should be based on the patient's medical history and clinical suspicion. Brain CT may be a valuable tool if the air is visible within the cerebral parenchyma or subarachnoid space early in the disease course. However, there is no established imaging technique for the definite diagnosis of cerebral air embolism [5].

In our case, status epilepticus was caused by acute cerebral damage after cerebral air embolism. Anticonvulsant medication may be required for the control of seizures. Otherwise, prophylactic use of lidocaine not only controls seizures but also reduces infarct size and prevents cardiac arrhythmias associated with air embolism [6].

There are two mechanisms behind cerebral air embolism. One is the retrograde venous cerebral embolism via the venous system [1]. In our case, during the Valsalva maneuver, the increased intra-thoracic pressure and tension pneumothorax may have provided a pressure gradient for the air to enter the pulmonary veins, resulting in air embolus. The other is the paradoxical embolism in the presence of right-to-left shunting such as PFO and pulmonary arteriovenous fistula [5,7-10]. The conditions that elevate the pulmonary artery pressure enable the air bubbles to move from right to left. The presence of intracardiac shunt (PFO G1) in this patient may explain the cause of air embolism.

The initial treatment consists of immediate volume expansion, administration of 100% oxygen by face mask, and hyperbaric oxygen therapy [1,5]. Hyperbaric oxygen therapy is the adjunct therapy for cerebral air embolism by removing the volume of air embolus and improving the tissue oxygenation. The side effects of hyperbaric oxygen therapy are rare but can occur by oxygen toxicity on the cardiovascular and neurological systems. Hyperoxic convulsions are exceptionally rare and due to the reperfusion phenomenon.

Iatrogenic gas embolism is a serious disease, with a crude mortality rate of 25/119 (21%) at 1 year [11]. Therefore, cerebral air embolism should be treated as soon as possible, and immediate therapy has been reported to decrease the mortality rate to 7% [12].

To the best of our knowledge, this is the first case of status epilepticus caused by cerebral air embolism after the Valsalva maneuver. In addition, this report emphasizes the need for awareness of suspected cerebral air embolism following routine medical procedures to avoid poor prognosis.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article.

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Primary central nervous system lymphoma with intramedullary spinal cord involvement mimicking inflammatory demyelinating disease

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Background: Spinal cord involvement of primary central nervous system lymphoma (PCNSL) is rare in a young immunocompetent patient and can be misdiagnosed as an inflammatory demyelinating disease (IDD) of the central nervous system.

Case report: We report a case of PCNSL mimicking IDD in a previously healthy 46-year-old man with weakness in both hands for 1 week. Magnetic resonance imaging (MRI) of the cervical spinal cord revealed contrast-enhancing intraparenchymal and leptomeningeal lesions in the cervical spinal cord and medulla oblongata. Cerebrospinal fluid analysis revealed pleocytosis (37/mm³). The patient’s symptoms and lesions improved with corticosteroid treatment. However, he developed semicomatose mentality 5 months later. Brain MRI, ventricular biopsy, and 18F-fluordeoxyglucose positron emission tomography/computed tomography confirmed PCNSL. The patient deceased 3 months later, despite high-dose methotrexate chemotherapy.

Conclusion: Persistent gadolinium-enhancing MRI lesions along the ventricular regions and spinal leptomeninges could differentiate PCNSL involving the spinal cord from IDD in the early stages of the disease.

Keywords: Primary central nervous system lymphoma; Neuromyelitis optica; Multiple sclerosis; Spinal cord; Magnetic resonance imaging

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an uncommon form of extranodal non-Hodgkin lymphoma in the central nervous system (CNS), including the brain, eyes, and cerebrospinal fluid (CSF), with no evidence of systemic spread at
Primary CNS lymphoma and inflammatory CNS disease

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the time of diagnosis [1]. PCNSL develops in immunocompromised patients and is relatively rare in immunocompetent people [2]. PCNSL mainly develops in the elderly (aged 60 years and above) [3]. In addition, involvement of the intramedullary spinal cord in PCNSL is uncommon and accounts for less than 1% of PCNSL cases [4-6]. Therefore, PCNSL involving the intramedullary spinal cord in a younger immunocompetent patient can be misdiagnosed as an inflammatory demyelinating disease (IDD) of the CNS, such as multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) [7,8]. Early diagnosis and treatment are important, as two-thirds of the immunocompetent PCNSL patients achieve complete response after treatment with methotrexate [2].

Here, we report a young immunocompetent PCNSL patient with intramedullary spinal cord involvement misdiagnosed with IDD in the early stage of the disease. We discuss the clinical and radiologic features differentiating PCNSL from IDD of the CNS.

CASE REPORT

A 46-year-old man with mild hypertension presented with asymmetric motor weakness (Medical Research Council scale scores: 4+/5 and 4+/5 in the right and left sides, respectively) in both hands for 1 week. Noncontrast magnetic resonance imaging (MRI) of the brain and cervical spinal cord showed faint T2-hyperintensity in the medulla oblongata and cervical spinal cord (Fig. 1), which were overlooked. Three weeks after onset of symptoms, the patient visited our neurology clinic for the etiological diagnosis. Gadolinium (Gd)-enhanced cervical spinal cord MRI showed prominent lesions in the intramedullary cervical spinal cord and medulla oblongata and contrast enhancement along the ventricular region and spinal leptomeninges (Fig. 2). CSF examination revealed lymphocyte-predominant pleocytosis (37/mm³), with an elevated protein level (132 mg/dL), but CSF cytomorphologic examination was negative for malignancy, and other neuroimmunological tests including antibody to aquaporin 4 (AQP4), were negative. In addition, serologic tests including the thyroid function test, tumor marker tests, viral tests (human immunodeficiency virus, human T-lymphotropic virus type 1, hepatitis C, herpes simplex virus, cytomegalovirus), CSF-Venereal Disease Research Laboratory test, fluorescent treponemal antibody absorption test, and tests for parasitic infection, were negative. The patient was treated with intravenous methylprednisolone for 5 days, followed by an oral taper of prednisone for 3 months under the presumptive diagnosis of IDD. At the end of the corticosteroid treatment course, the patient showed notable

Fig. 1. Initial magnetic resonance imaging (MRI) of the brain and spinal cord 1 week after onset of symptoms. (A) Sagittal and (B, C) axial T2-weighted images show faint hyperintense multifocal lesions in the medulla oblongata (arrows) and cervical spinal cord (arrowhead). (D, E) High signal intensity in the medulla oblongata on T2-weighted images are not clearly detected on fluid-attenuated inversion recovery. No supratentorial or periventricular white matter lesion was seen on brain MRI (images not shown).
improvement in neurological function. A follow-up cervical MRI revealed significant decrease in parenchymal lesions, except for persistent leptomeningeal enhancement (Fig. 3). Repeat CSF cytomorphicologic examination to exclude hematologic malignancy was negative. Five months after completion of the corticosteroid treatment, the patient presented with acute deterioration in mental status. Computed tomography (CT) of the brain revealed a subependymal high-attenuation lesion in all ventricles, with obstructive hydrocephalus and periventricular edema (Fig. 4), and the patient underwent emergency ventriculoperitoneal shunting. Brain MRI showed lesions in the hypothalamus and bilateral periventricular white matter, with subependymal contrast enhancement (Fig. 5). Neuronavigation-guided stereotactic ventricular biopsy confirmed diffuse large B-cell lymphoma (DLBCL), which was positive for B-cell markers, including CD20 and CD79a, but negative for the representative T-cell marker CD3 (Fig. 6). 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT of the whole body to detect the presence of non-CNS lymphoma showed abnormal FDG uptake in the right lateral ventricle of the brain with no evidence of systemic involvement (Fig. 7). The patient was treated with high-dose methotrexate (HD-MTX) for three cycles after the final diagnosis of PCNSL. The follow-up brain MRI showed complete resolution of the subependymal nodular enhancing lesions along the ventricles and hypothalamus (Fig. 8). However, the patient died from hospital-acquired, multidrug-resistant Klebsiella pneumoniae bacteremia 3 months after the PCNSL diagnosis, despite complete remission of PCNSL after HD-MTX treatment.

The study protocol was approved by the Institutional Review Board at Chonnam National University Hospital (CNUH-EXP-2018-018).

DISCUSSION

The patient was diagnosed with IDD of the CNS before confirmation of DLBCL on brain biopsy. PCNSL rarely mimics IDD, including MS, NMOSD, and acute transverse myelitis (TM) [6-8]. Both conditions can present with acute neurological signs of localized contrast-enhancing lesions in the CNS, with no detectable cause in a routine blood or CSF analysis [9]. Furthermore, both conditions tend to improve after corticosteroid administration [6,7]. In this case, PCNSL was overlooked.
Fig. 3. Follow-up cervical spinal cord magnetic resonance imaging 6 months after the onset of symptoms. T2-weighted images (A, C) show marked decrease in multifocal lesions with no parenchymal enhancement (B, D). Gadolinium-enhanced T1-weighted sagittal images show persistent leptomeningeal enhancement (B, arrowheads).

Fig. 4. Brain computed tomography (CT) at the onset of the semicomatose status. Brain CT shows subependymal hyperdense lesions in all ventricles, including the right lateral ventricle, with hydrocephalus (A), and edema in the periventricular white matter and cerebral peduncle (B).
Fig. 5. Brain magnetic resonance imaging (MRI) after ventricular brain biopsy. (A, B) Axial T2-weighted images show hyperintensities in the hypothalamus and periventricular white matter. (C, D) Gadolinium-enhanced MRI shows multifocal subependymal nodular enhancing lesions.
Fig. 6. Pathologic findings. Hematoxylin and eosin staining (A) reveals large atypical lymphocytes mixed with small mature lymphocytes. Tumor cells were positive for CD20 (B, B-cell marker), with the Ki-67 labeling index approaching 80% (C), but negative for CD3 (D, T-cell marker) on immunohistochemical analysis (original magnification, ×200).

for 8 months after the onset of symptoms for the following reasons: (1) immunocompetence and young age of the patient; (2) focal neurologic symptoms and signs suggesting acute TM; (3) unremarkable serial CSF cytromorphologic tests, with no exposure to corticosteroids; (4) improvement in symptoms and MRI lesions after corticosteroid treatment; and (5) initial CNS lesions confined to the intramedullary cervical spinal cord and vicinity of the medulla oblongata, which is rare in PCNSL [4-6]. Therefore, therapy with HD-MTX for PCNSL was delayed in this case.

The survival time and clinical outcome in patients with PCNSL have significantly improved since the introduction of HD-MTX, which can penetrate the blood-brain barrier, as the first-line chemotherapy regimen [1,2,5]. In this case, PCNSL was only suspected after deterioration in mental status because of tumor infiltration in the supratentorial white matter and ventricles. Therefore, HD-MTX chemotherapy was administrated 8 months after the onset of initial neurologic symptoms, and delayed treatment for PCNSL may have caused the poor outcome. Treatment initiation in the early stages of PCNSL can improve the survival rate and clinical outcome before PCNSL spreads widely or infiltrates diffusely [1,2], while PCNSL in the late stages is often refractory to HD-MTX chemotherapy, or can recur or progress to systemic involvement [1,2,10]. Therefore, early brain biopsy should be performed to diagnose DLBCL pathologically in patients suspected with PCNSL [1,10], considering that precise diagnosis and early initiation of treatment are important for good prognosis in PCNSL. The patient’s prognosis would have been better with HD-MTX chemotherapy administration before PCNSL spread or infiltrated other CNS regions. HD-MTX chemotherapy was effective in our case, as observed on follow-up MRI. However, early brain biopsy is not suitable for PCNSL-suspected patients with lesions in the intramedullary spinal cord because of risk of permanent postoperative neurological deficit [5]. Whole-body 18F-FDG-PET/CT can be performed to detect sys-
Fig. 7. 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) of the brain. 18F-FDG-PET shows abnormal FDG uptake in the right lateral ventricle (A, white arrow) and inferior 4th ventricle (C, black arrow). PET and coregistered PET/magnetic resonance fusion imaging shows asymmetric, mild hypermetabolic lesions along the body, atrium, and posterior horn of the right lateral ventricle with a maximum standardized uptake volume (SUVmax) of 4.4 (A, B), and moderate hypermetabolic lesions along the inferior 4th ventricle with an SUVmax of 5.6 (C, D).

Systemic lymphoma before corticosteroid administration in a PCNSL-suspected patient who has difficulty undergoing brain biopsy, as systemic involvement of DLBCL is found in 7% of PCNSL-suspected patients at initial diagnosis [11]. However, studies on the usefulness of 18F-FDG-PET/CT in differentiation of PCNSL from IDD is lacking [12]. The key radiologic features that help distinguish PCNSL with spinal cord involvement from IDD are: (1) multifocal intramedullary lesions with brain lesions [5]; (2) involvement of the conus medullaris or cauda equine [5]; (3) persistent Gd-enhancing intramedullary lesions for over 8 weeks [5]; (4) persistent, contiguous Gd-enhancing MRI lesions along the ventricular regions and spinal leptomeninges [4];
Fig. 8. Brain magnetic resonance imaging (MRI) after high-dose methotrexate chemotherapy. (A, B) Axial T2-weighted images show complete resolution of the multifocal subependymal nodular lesions in the hypothalamus and ventricular regions. (C, D) Gadolinium-enhanced MRI shows diffuse pachymeningeal thickening with no leptomeningeal enhancement.
and (5) intraparenchymal tadpole-like enhancing lesions, which may be helpful in suspected PCNSL cases. In addition, CSF flow cytometry is superior to CSF cytomorphologic testing in PCNSL diagnosis [13,14].

This case highlights that PCNSL with involvement of the intramedullary spinal cord can be misdiagnosed as IDD. The characteristic radiologic features, including persistent Gd-enhancing MRI lesions along the ventricular regions and spinal leptomeninges, may be helpful in differentiating PCNSL from IDD in early stages of the disease.

**ARTICLE INFORMATION**

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**REFERENCES**

Cerebral air embolism treated using hyperbaric oxygen therapy

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A 59-year-old man underwent endoscopic balloon dilation for esophageal stricture. Upon the completion of the procedure, he was observed to be stuporous and quadriplegic. Computed tomography (CT) of the brain revealed multiple air emboli (Fig. 1A). Magnetic resonance imaging (MRI) performed 45 minutes after symptom onset revealed multiple lesions showing signal loss on susceptibility-weighted imaging, high signal intensity on diffusion-weighted imaging, and diffuse enhancement on T1-weighted contrast-enhanced imaging, which were compatible with air emboli, hyperacute infarcts, and a disrupted blood–brain barrier, respectively (Fig. 1B-1D). Hyperbaric oxygen therapy (HBOT) was administered 80 minutes after MRI (targeting 3.0 atmospheric pressure for 2 hours). Follow-up CT performed 80 minutes after HBOT revealed disappearance of the air emboli (Fig. 1E). Follow-up MRI performed 5 days after HBOT also revealed a decrease in the resolution of previously documented findings (Fig. 1F-1H). Most of his neurological symptoms improved, except mild left hemiparesis.

This case indicates that MRI is a useful modality in diagnosing cerebral air embolism by documenting air emboli, hyperacute infarcts, and disruption of the blood–brain barrier [1-3]. HBOT may accelerate the disappearance of air emboli and promote the early resolution of ischemic lesions and reversal of the disrupted blood–brain barrier [4].

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REFERENCES


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- Figures and tables used in the main body must be indicated as “Fig.” and “Table.” For example, “Magnetic resonance imaging of the brain revealed…” (Figs. 1–3).

How to Draw a Figure

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

**How to Write a Table**

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

**References**

- All references must be indicated in English.
- Every reference in the Reference section should be cited in the text. The number assigned to the reference citation is according to the first appearance in the manuscript. References in tables or figures are also numbered according to the appearance order. Reference number in the text, tables, and figures should in a bracket ([ ]).
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- The journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nmccatalog/journals).
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- **Book & book chapter**

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