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Aims and Scope

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

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Editorial Board

Journal of Neurocritical Care

Contents

Journal of Neurocritical Care

Vol. 14, No. 2, December 2021

REVIEW ARTICLE

63 Brain injury in extracorporeal cardiopulmonary resuscitation: translational to clinical research
Christopher Wilcox, Chun Woo Choi, Sung-Min Cho

78 Basic considerations on magnesium in the management of neurocritical patients
Ivan David Lozada-Martinez, Teddy Javier Padilla-Durán, Jhon Jairo González-Monterroza, Daniel Alfonso Aguilar-Espinosa, Kelly Nathalia Molina-Perea, William Camargo-Martinez, Luz Llamas-Medrano, Mariana Hurtado-Pinillos, Alejandra Guerrero-Mejía, Tariq Janjua, Luis Rafael Moscote-Salazar

ORIGINAL ARTICLE

88 Neuroleptic malignant syndrome cases in a Moroccan intensive care unit: a retrospective analysis and literature review
Soumaya Touzani, Mohammed Hamdouni, Nawfal Houari, Youssef Yaakoubi Khbiza, Abderrahim Elbouazzaoui, Brahim Boukatta, Nabil Kanjaa

CASE REPORT

98 Bilateral posterior cerebral artery stroke following transtentorial herniation caused by a subependymal giant cell astrocytoma in a patient with tuberous sclerosis: a case report
Joong-Goo Kim, Jay Chol Choi, Hong Jun Kim, Jong Kook Rhim, Tae Jun Jung, Chang-Lim Hyun, Jin Deok Joo

103 Successful treatment with rituximab in a patient with lupus cerebritis and posterior reversible encephalopathy syndrome: a case report
Saemi Choi, Young Seo Kim

109 Which one to do first?: a case report of simultaneous acute ischemic stroke and myocardial infarction
Kijeong Lee, Woohyun Park, Kwon-Duk Seo, Hyeongsoo Kim

113 Supranuclear oculomotor palsy in cerebral venous sinus thrombosis: a case report
Kumar Bismaya, Sabyasachi Pattanayak, Abhishek Dixit, Abhishek Pathak, Rameshwar Nath Chaurasia, Varun Kumar Singh

117 Flaccid quadriparesis with raised creatine kinase in Guillain-Barré syndrome: a case report with review of literature
Bandari Mahesh, Abhishek Pathak, Rameshwar Nath Chaurasia, Anand Kumar, Varun Kumar Singh

IMAGES IN NEUROCRITICAL CARE

121 Posterior reversible encephalopathy syndrome as delayed neurological sequelae after carbon monoxide intoxication
Hyesun Lee, Jinseok Park

123 Serial brain magnetic resonance imaging in a patient with invasive streptococcal infection with ventriculitis and choroid plexitis
Jaewoon Chung, Ji Young Lee, Young Seo Kim

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Brain injury in extracorporeal cardiopulmonary resuscitation: translational to clinical research

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REVIEW ARTICLE

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The addition of extracorporeal membrane oxygenation (ECMO) to conventional cardiopulmonary resuscitation (CPR), termed extracorporeal cardiopulmonary resuscitation (ECPR), has significantly improved survival in selected patient populations. Despite this advancement, significant neurological impairment persists in approximately half of survivors. ECPR represents a potential advancement for patients who experience refractory cardiac arrest (CA) due to a reversible etiology and do not regain spontaneous circulation. Important risk factors for acute brain injury (ABI) in ECPR include lack of perfusion, reperfusion, and altered cerebral autoregulation. The initial hypoxic-ischemic injury caused by no-flow and low-flow states after CA and during CPR is compounded by reperfusion, hyperoxia during ECMO support, and nonpulsatile blood flow. Additionally, ECPR patients are at risk for Harlequin syndrome with peripheral cannulation, which can lead to preferential perfusion of cerebral vessels with deoxygenated blood. Lastly, the oxygenator membrane is prothrombotic and requires systemic anticoagulation. The two competing phenomena result in thrombus formation, hemolysis, and thrombocytopenia, increasing the risk of ischemic and hemorrhagic ABI. In addition to clinical studies, we assessed available ECPR animal models to identify the mechanisms underlying ABI at the cellular level. Standardized multimodal neurological monitoring may facilitate early detection of and intervention for ABI. With the increasing use of ECPR, it is critical to understand the pathophysiology of ABI, its prevention, and the management strategies for improving the outcomes of ECPR. Translational and clinical research focusing on acute ABI immediately after ECMO cannulation and its short- and long-term neurological outcomes are warranted.

Keywords: Extracorporeal membrane oxygenation; Acute brain injuries; Extracorporeal cardiopulmonary resuscitation

INTRODUCTION

The use of extracorporeal membrane oxygenation (ECMO) to treat patients with cardiac arrest (CA) was first described in 1957 when several patients with CA refractory to conventional cardiopulmonary resuscitation (CCPR) including open cardiac massage were placed on cardiopulmonary bypass (CPB), allowing time for an attempt at definitive management [1]. A percutaneous system for ECMO cannulation initiated at the bedside was successfully implanted in five patients in 1983 by Phillips et al. [2]. Percutane-

ous ECMO was successfully applied to CA patients refractory to CCPR, which was termed extracorporeal cardiopulmonary resuscitation (ECPR), in 1991 when a specialized team achieved the 6-month survival of 64% of adult patients (n = 11) who had refractory CA close to a cardiac operating room [3]. A similar survival pattern was reported for children in 1992 when 11 patients aged 8–22 months were treated with ECMO for CA refractory to CCPR [4].

With the development of more portable ECMO devices and percutaneous implantation, ECPR has become possible in medical intensive care units and emergency rooms, expanding its potential use in patients with out-of-hospital cardiac arrest (OHCA) [5,6]. Multiple animal models have demonstrated improved survival and end-organ protection with ECPR, compared with CCPR, after CA [7-9]

Since the mid-2000s, the number of ECMO-capable centers participating in the Extracorporeal Life Support Organization (ELSO) has tripled, increasing the feasibility of ECPR [10-12]. Two meta-analyses of observational studies comparing ECPR and CCPR for patients with CA occurring in and outside of the hospital demonstrated an improvement in both survival and neurologic outcomes with ECPR. Both analyses showed improved survival among patients with in-hospital cardiac arrest (IHCA) on discharge and at 1-year follow-up. Patients with OHCA showed no difference in survival or neurologic outcomes on discharge; however, after 3–6 months, improvements in survival and neurologic outcomes were observed [13,14]. ECPR continues to be an active area of innovation; several clinical trials of emergency medical response teams, including providers capable of ECMO cannulation in the field as an effort to improve the ECPR outcomes, have been conducted [15].

CA INCIDENCE AND SURVIVAL

In the United States, the estimated annual incidences of IHCA and OHCA are 300,000 and 350,000–400,000, respectively. Globally, measures of incidence are lacking and vary significantly due to regional differences, for example, between developed and developing nations and rural and urban areas, with variable recordings of CA and outcomes. Multiple regional efforts are underway to determine the incidence and standardize the reporting of CA to more accurately measure survival and other outcomes [16-26]. In the United States, up to 25% of cases survive up to hospital discharge after IHCA, with the majority having favorable neurologic recovery demonstrated by a cerebral performance score (CPC) of 1 or 2 [14,16,27]. However, a recent meta-analysis reported only a 13% 1-year survival after IHCA [28]. OHCA survival is difficult to estimate because several patients are deceased before transport to the hospital, limiting the accurate recording of OHCA numbers. A review of emergency medical services (EMS) records indicates that approximately 6%–10% of patients who visit the hospital survive up to discharge [16-21].

ECPR INDICATIONS AND ELIGIBILITY

Although the optimal application of ECPR has not been established, the published literature has similar inclusion and exclusion criteria with limited data. The implementation of ECPR requires the rapid assembly and coordination of a specialized team, including members capable of cannulating ECMO, a perfusionist or specialist to monitor the ECMO circuit and flows, and trained nursing support. Appropriate patient selection relies on timely assessments and effective communication from the resuscitation team, including appropriate identification of ECPR-eligible patients, as well as determining the timing for transition to ECMO cannulation and transport during cardiopulmonary resuscitation (CPR).

For eligibility, there is a paucity of data to support age cutoffs in selecting ECMO candidates. Age of < 70 years is recommended by the ELSO based on retrospective data and < 75 years by some experienced regional centers with OHCA ECPR protocols [29-33]. Patients should have a minimum no-flow time, defined as the time between CA and the initiation of CPR. The goal is to have a no-flow time of < 5 minutes, which may depend on the presence of a witnessed CA and bystander CPR before the arrival of EMS for OHCA. The target time from CA to the initiation of ECMO (low-flow time) was < 60 minutes [30].

An initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) is suggestive of a primary reversible cardiac etiology for CA, and OHCA patients can be considered for early transportation to an ECPR-capable center if VT/VF is refractory after three shocks [30,31,33]. This strategy allows early identification and transport of patients to an ECPR-capable facility with continued CPR and pre-notification to the cardiac catheterization laboratory to prepare for immediate ECMO cannulation and cardiac catheterization. For patients with IHCA, ECMO cannulation can be considered after CA refractory to 10–20 minutes of CCPR if there is a suspected reversible etiology or after three shocks for VT/VF. Markers of perfusion that may aid in patient selection include those with end-tidal CO_2 of > 10 mmHg measured during CPR by capnography, PaO_2 of > 55 mmHg (O_2 saturation > 85%), and lactate of < 18 mmol/L. However, they are often not available before cannulation, and there are limited data on their association with outcomes [15,31,34,35]. The exclusion criteria

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included significant comorbidities such as terminal disease, advanced cancer, advanced neurological disease, and low-performance status before CA [30,31].

The optimal timing for the transition from CCPR to ECPR has not yet been established. Careful consideration and further research are necessary to determine the ideal ECPR eligibility and timing to improve outcomes and minimize unnecessary ECMO cannulation. A retrospective analysis of OHCA demonstrated benefits related to survival and neurologic outcomes measured by CPC at 3 months beginning after CPR for 21 minutes with propensity-matched patients having improved outcomes if they were treated with ECPR, compared with CCPR, if the duration was >21 minutes and no survival benefit if initiated earlier [36]. As the use of ECPR increases, early detection of acute brain injury (ABI) and the improvement of neurological outcomes are crucial in improving overall outcomes in this population. Fig. 1 outlines the proposed mechanisms of ABI in patients after ECPR.

SOCIETY GUIDELINES ON ECPR

In 2020, the American Heart Association stated that there was insufficient evidence in support of the routine use of ECPR, but the therapy may be considered in select patients with suspected reversible etiology of CA [37]. In 2021, the European Resuscitation Council weakly recommended the consideration of ECPR for cases of refractory CA because of the low level of evidence [38]. None of the organizations provided specific indications for ECPR. The ELSO recently published a consensus statement for ECPR. Although ELSO did not provide specific guidelines or inclusion criteria due to the lack of strong evidence, they highlighted the importance of appropriately trained healthcare providers, teamwork, and planning. The ELSO recommended regional inclusion criteria, including resource availability and capability, to maximize favorable neurologic outcomes. They provided sample inclusion criteria, which included age of <70 years, witnessed CA, arrest to CPR (no-flow time) of <5 minutes, initial rhythm

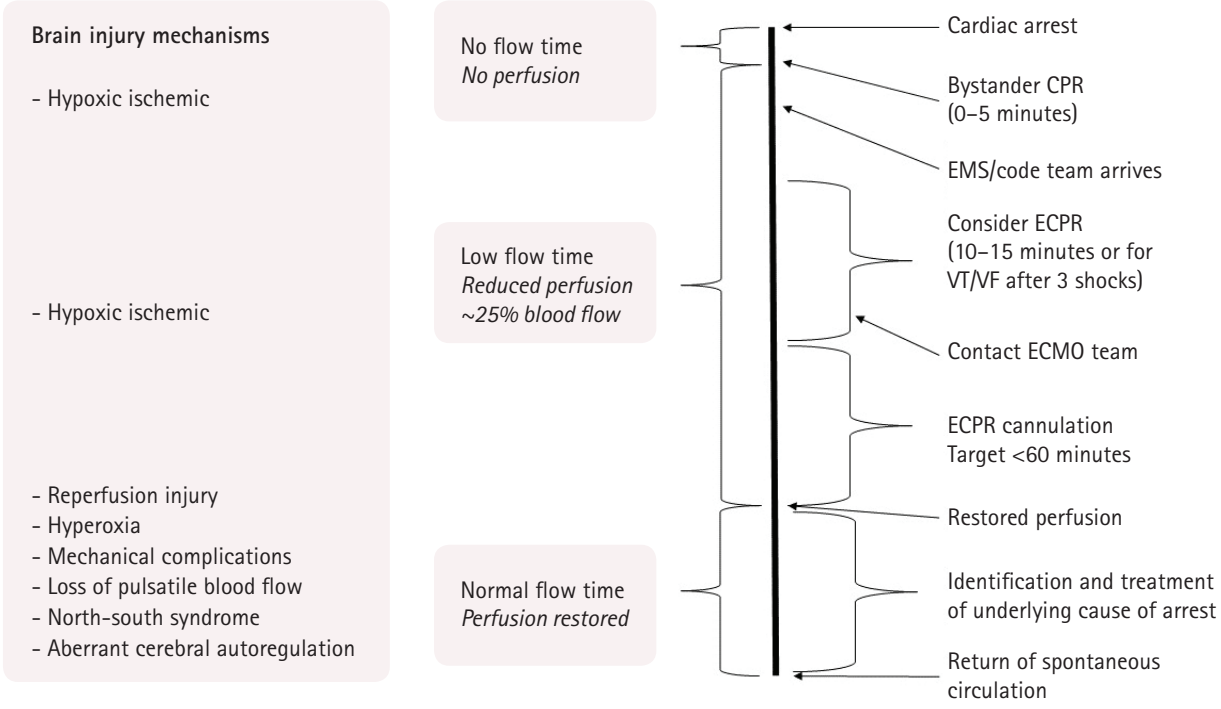

Fig. 1. Extracorporeal cardiopulmonary resuscitation (ECPR) model with associated risk factors for brain injury. This figure represents the model for the proposed timing for ECPR. ECPR should be considered if return of spontaneous circulation (ROSC) is not obtained within 10–15 minutes or after 3 shocks for ventricular tachycardia (VT)/ventricular fibrillation (VF). The cannulation goal is <60 minutes. Perfusion is restored after cannulation; however, ROSC may not be achieved until the underlying cause is addressed. The left column shows proposals of brain injury mechanisms during different stages of resuscitation. Flow time refers to duration in minutes. Bystander cardiopulmonary resuscitation (CPR) refers to life support measures initiated by on-scene persons before the arrival of emergency medical services (EMS) or health care agents before the arrival of the code team. ECMO, extracorporeal membrane oxygenation.

VT/VF, pulseless electrical activity for IHCA, end-tidal CO_2 of >10 mmHg during CPR, absence of life-limiting comorbidity, and absence of known aortic valve incompetence [12,30]. The current guidelines do not provide standard neurological definitions and monitoring and management recommendations.

SURVIVAL AND OUTCOMES AFTER ECPR

Survival of up to 30% of appropriately selected patients after CA refractory to CCPR treated with ECPR has been reported [12,39]. However, there is significant variability in survival based on the location of CA, with one study reporting 50% survival if CA occurred in or near a cardiac catheterization lab and 15% for other locations [11]. A recent randomized controlled trial, the Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomized controlled trial, compared ECPR and CCPR for OHCA with VF or VT rhythms persisting after three defibrillations. The trial was discontinued early with a significant survival benefit of ECPR over CCPR (43% vs. 7%) [30]. The ARREST trial demonstrated that a streamlined systematic approach in a high-volume ECMO center with experienced staff could dramatically improve the ECPR outcomes; however, the results of this study lack generalizability and should be validated in other centers with larger samples [40].

Among survivors of CA, long-term neurological sequelae, such as cognitive impairment and difficulties in performing activities of daily life, are common. The prevalence of hypoxic-ischemic brain injuries (HIBIs) in OHCA is higher with CCPR than with ECPR among survivors (50% vs. 23%) [41,42]. Although several of these survivors continue to improve toward near or complete functional independence in the long term, they still have a poor quality of life [43-45]. Despite the survival benefits and possibly improved neurological outcomes with ECPR, compared with CCPR, there are sparse data on the long-term function and quality of life of ECPR survivors [13,14,40]. As the data on ABI after ECPR accumulate, it is important to study the long-term neurological outcomes in this population.

RANDOMIZED CLINICAL TRIALS

The ARREST trial was a phase 2 open-label randomized clinical trial (RCT) of ECPR compared with CCPR in OHCA patients who presented initially with VF or VT. Participants were eligible if their dysrhythmia was refractory to three defibrillation shocks and were randomized to continue CCPR or ECPR. The trial was discontinued early after the pre-specified analysis showed clear superiority in the ECPR arm. The survival rate was 43% at discharge, and all patients were alive at 6 months with favorable CPC scores, with medians of 2.5 at discharge and 1.2 at 6 months, respectively, in the patients receiving ECPR. In contrast, patients in the CCPR group had a 0% survival within 6 months [40]. Another RCT, the Prague OHCA study (NCT 01511666), compared the standard care of CPR in the field with immediate transport using CPR assisted with a mechanical device for chest compressions followed by ECPR upon arrival at the hospital if return of spontaneous circulation (ROSC) was not obtained. Survival at 180 days was not significantly different (CCPR, 22% vs. ECPR, 31.5%); however, neurologic recovery at 30 days was significantly improved in the ECPR group (22.7% vs. 34.7%) as was survival in the group with prolonged CA (>45 minutes) receiving CPR [46]. Despite these encouraging outcomes, these findings need to be replicated with multicenter RCTs to validate the findings and possibly generalize to different populations. Other ongoing RCTs evaluating ECPR at the time of this article include the APACAR2 trial (NCT02527031), the Extracorporeal Cardiopulmonary Resuscitation for Refractory Out-of-Hospital Cardiac Arrest (ERO-CA): Results of a Randomized Feasibility Trial of Expedited Out-of-Hospital Transport (NCT03065647), and the Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION) trial (NCT03101787) [47].

ABI IN ECPR: MECHANISTIC CONSIDERATION

Hypoxic-ischemic injury and reperfusion injury

HIBIs from the cessation of blood flow after CA is a leading cause of morbidity and mortality in CA survivors and has been reported in 23% of patients treated with ECPR [42,48,49]. This primary injury is followed by secondary ABI after ROSC because adequate blood supply is restored, leading to the formation of reactive oxygen species (ROS), alteration in microvasculature blood flow, and reperfusion injury [48,50-52]. These insults may be compounded by prolonged resuscitation and immediate restoration of oxygenated cerebral blood flow during ECPR.

The abatement of these injuries with targeted temperature management (TTM) by induction of mild hypothermia (32°C–34°C) in survivors of CA has been shown in multiple RCTs to improve survival and neurologic outcomes [53,54]. The ECMO circuit allows for rapid cooling for TTM, and the feasibility of cooling within minutes has been demonstrated in an adult swine model [55,56]. Survival benefits were demonstrated for TTM after ECPR; however, this was a single-center observational study, and other studies have found no benefit. Overall, there are no

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high-quality data on the impact of TTM on ECPR outcomes [53,54,57]. An additional consideration for TTM in this population is that ECMO-associated coagulopathy may be exacerbated by lower temperature targets and the need for systemic anticoagulation.

Retrospective studies of increased mean arterial pressure (MAP; > 80 mmHg) after CA have demonstrated improved survival and neurologic outcomes after CA. However, clear benefits have not been found in RCTs, and the most recent American Heart Association guidelines state that targeting MAP of > 80 mmHg may be beneficial, but data are lacking [37,58,59]. In the setting of ECPR, the addition of anticoagulation to prevent circuit clotting increases the risk of hemorrhage, especially in patients with a significant burden of HIBIs with fresh cerebral infarcts. Therefore, optimal blood pressure management is unknown and MAP of > 65 mmHg may be recommended to ensure adequate cerebral perfusion without a significantly increased risk of intracerebral hemorrhage and minimize the increased afterload created by ECMO flow against native heart blood flow.

Hyperoxia and ROS

Oxygen therapy plays a paramount role in the success of CPR after CA. However, excessive oxygenation or hyperoxia (commonly defined as mild PaO_2 > 100 or 120 mmHg and severe PaO_2 > 300 mmHg) after ROSC can lead to ABI. The detrimental effect of hyperoxia on ABI has been demonstrated in several different diseases, including traumatic brain injury, ischemic and hemorrhagic stroke, aneurysmal subarachnoid hemorrhage, and HIBIs. The underlying mechanism of ABI is an insult by ROS to the lipid membrane, deoxyribonucleic acid, and proteins.

Additionally, in CA, prolonged periods of ischemia deplete cells of adenosine triphosphate (ATP), preventing the recycling of reducing agents that neutralize ROS [60]. A decrease in the production of ATP also disrupts Na^+/K^+ ATPase, which is responsible for maintaining membrane potential in neurons and leads to a Ca^{2+} influx that causes the release of cytochrome c, leading to neuronal cell death via apoptosis. During ECPR, ECMO provides immediate cerebral blood flow restoration, which may exacerbate reperfusion injury in patients who are vulnerable to HIBIs with a global cerebral ischemic insult. Furthermore, ECMO decannulation is known to induce a systemic inflammatory response syndrome response, leading to further production of ROS and compounding the potential for secondary ABI [61].

Animal CA and ECMO models on "hyperoxia"

Established canine models of VF-induced CA lasting for 10 minutes followed by ROSC, were divided into normoxia (PaO_2, 80–120 mmHg) and hyperoxia (PaO_2 > 120 mmHg) groups. ROS formation increased in a dose-dependent manner with an increase in the PaO_2 level. This correlated with increased disruption of the mitochondrial pyruvate dehydrogenase complex, an enzyme that produces reducing agents to nullify ROS in hyperoxia compared with normoxia groups. Postmortem examination demonstrated that the cerebral cortex and hippocampal neurons had increased disruption of pyruvate dehydrogenase complex and cell death specifically in neuronal Purkinje cells. Although both normoxia and hyperoxia increased inflammatory activation of microglial cells and macrophages, Purkinje cell loss was greater in the hyperoxia group [62]. Similar results were observed in a rat model of global cerebral ischemia, where normoxia was compared with hyperoxia after 10 minutes of bilateral carotid occlusion. At 7 and 30 days postintervention, more hippocampal neurons remained normal on histological examination in normoxic rats and hyperoxic rats [63].

In an ECMO model of global hypoxia, adult New Zealand White rabbits were cannulated with veno-venous (VV)- and veno-arterial (VA)-ECMO and subsequently hypoventilated to a PaO_2 of 27 mmHg and a pH of < 7.0 and injected with bacterial endotoxin. The ECMO circuit was utilized to reoxygenate after the hypoxic event with 100% sweep oxygen compared with the control, which was reoxygenated through ventilation. Both VV and VA-ECMO groups demonstrated significantly increased concentrations of malondialdehyde, a byproduct of lipid damage by ROS and a marker of oxidative injury, both in the lung tissue and plasma compared with the control. This suggests that reperfusion via the ECMO circuit after a global hypoxic event increases ROS and lipid membrane peroxidation, which can lead to alveolar damage [64,65]. Table 1 summarizes the established animal models of ECPR.

Clinical research on "hyperoxia" in ECPR

Recently, the Conservative Oxygen Therapy during Mechanical Ventilation in the intensive care unit (ICU-ROX) study aimed to determine the benefits of conservative oxygen treatment and compare them with usual oxygen treatment for any mechanically ventilated patient in need of > 24 hours of mechanical ventilation in the ICU [66]. The study compared the goal-directed oxygen treatment (FiO_2 decreased to 0.21 as soon as possible with an upper limit alarm set for SpO_2 ≥ 97%) to the usual oxygen treatment (standard care with no specific measures limiting FiO_2 or SpO_2) and found no difference in the number of ventilator-free days. However, in the subgroup analysis of patients with suspected HIBIs, mortality differed significantly between the goal-directed (conservative) oxygen group and the usual (standard) oxygen

Table 1. Comparison of animal models for CA, ECMO, and ECPR

Study	Species	CA induction	CA duration	n	ECMO duration	Comparison	Main finding
Pediatric model							
Itoh et al. (2016) [67]	Piglet	Electrical current	NR	14	180 min	Pulsatile vs. nonpulsatile flow	Pulsatile ECMO produces significantly more hemodynamic energy and improves systemic microcirculation compared with nonpulsatile.
Ostadal et al. (2018) [68]	Female swine	NA - CS		16	90–120 min of CS	Pulsatile vs. nonpulsatile flow	Pulsatile ECMO, compared with continuous-flow ECMO, preserved LV function and coronary flow in a model of cardiogenic shock.
Liu et al. (2019) [8]	Male swine	Electric current	8 min	20	6 hr	CCPR vs. ECPR survival and hemodynamics	ECPR improves hemodynamics and cardiac function, reduces reperfusion injury and oxidative damage, and inhibits myocyte apoptosis.
Short et al. (1993) [69]	Lamb	NA		14	1 hr	Cerebral autoregulation in sham vs. VA-ECMO	Cerebral autoregulation is lost in lower cerebral perfusion pressures measured via oxygen consumption on VA-ECMO.
Adult model							
Wang et al. (2015) [70]	Female swine	NA		10	24 hr	Pulsatile vs. nonpulsatile flow	Pulsatile ECMO provides superior end-organ protection with improved renal function and systemic vascular tone.
Vereczki et al. (2006) [62]	Female beagle	Electric current	10 min	12	NA	Hyperoxia vs. normoxia post-CA	Hyperoxia was associated with oxidative stress and hippocampal neuronal cell death.
Trittenwein et al. (1999) [64]	Rabbit	NA		31	5 hr of hyperoxygenation	Lipid peroxidation in control VV-ECMO vs. VA-ECMO	Hyperoxia enhances oxidative damage to lipids in endotoxin primed animals.
Yuan et al. (2018) [9]	Male swine	Electric current	12 min	16	6 hr	Survival and AKI in CPR vs. ECPR	ECPR improves survival and renal function in a swine model of CA.
Passmore et al. (2017) [71]	Ovine	NA		27	24 hr	Hemostasis in sham vs. VV-ECMO vs. VV-ECMO+S-ALI	Introduction of ECMO alters hemostasis via decreases in vWF, fibrinogen, platelet aggregation. These effects are worse with S-ALI.
Wollborn et al. (2019) [7]	Sprague-Dawley rodents	Cessation of MV	6 min	33	150 min	Renal damage in CCPR+PDE4i vs. ECPR+PDE4i	PDE4i reduces ECMO-induced vascular permeability and improves microcirculation.
Luo et al. (2018) [72]	Male swine	Ligation of LAD	<40 min	24	6 hr	ECPR low flow vs. normal flow	In an ECPR model, a low-flow ECMO strategy in the first 6 hours was associated with lower cerebral blood flow and lactate clearance.
Weiser et al. (2017) [55]	Swine	Electrical current	14 min	8	60 min	Feasibility of rapid cerebral cooling with ECPR	Rapid cooling within minutes is feasible after CA.

CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; NR, not reported; NA, not applicable; CS, cardiogenic shock; LV, left ventricle; CCPR, conventional cardiopulmonary resuscitation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation; AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; S-ALI, simulated acute lung injury; vWF, Von-Willebrand factor; MV, mechanical ventilation; PDE4i, phosphodiesterase 4 inhibitor; LAD, left anterior descending artery.

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group (43% vs. 59%; reparatory rate, 0.73; 95% confidence interval, 0.54–0.99), highlighting the potential benefits of avoiding hyperoxia in patients at risk of brain ischemia. However, the effect of hyperoxia on ECPR patients remains unclear. In pediatric studies that have examined this specific question, moderate hyperoxia during the first 48 hours was an independent risk factor for increased mortality [73]. In a prior analysis of the ELSO registry from 2010 through 2015, hyperoxia, defined as a PaO_2 > 100 mmHg at 24 hours, was associated with increased mortality in patients treated with VA-ECMO [74]. A second prospective single-center analysis identified that hyperoxia (PO_2 > 300 mmHg) during the first hour after resuscitation was associated with a worse neurologic outcome at discharge [75]. A recent analysis of 10,342 VA-ECMO patients from the ELSO showed that all subtypes of ABI were more common in patients with hyperoxia, as measured by 24-hour ABG [76]. However, data on this for ECPR patients are limited.

Animal models of nonpulsatile blood flow and cerebral autoregulation in ECMO

The loss of pulsatile blood flow occurs as a consequence of continuous flow ECMO systems and has been linked to endothelial dysfunction, increased sympathetic tone, decreased local oxygen consumption, and increased systemic vascular resistance [77-79]. An adolescent swine cardiogenic shock model was placed on VA-ECMO with a pulsatile (utilizing an electrocardiogram synchronized system) or nonpulsatile circuit, and cardiogenic shock was induced via balloon occlusion of the left main coronary artery [70,80]. ECMO flow was increased in a stepwise manner with intravascular measurement catheters showing significantly higher cardiac output, coronary artery blood flow, and MAP in patients with pulsatile blood flow than in those with nonpulsatile flow [68].

In a cerebral autoregulation model, newborn lambs were separated into the VA-ECMO group (n = 7) or controls with right carotid artery and jugular vein ligation (n = 7) and had an intracranial catheter inserted to manipulate cerebral perfusion pressure (CPP). Cerebral blood flow was maintained at lower CPPs in the control group, suggesting a loss of protective antiregulatory mechanisms in animals treated with VA-ECMO [69].

Loss of pulsatile flow and autoregulation in cardiac surgery

Pulsatile and nonpulsatile CPB flows were compared in 32 adult patients undergoing open-heart surgery with CPB. Cerebral blood flow velocity was measured using stereotactic transcranial Doppler (TCD) monitoring of the middle cerebral artery. Normal vasodilatory and constrictive responses to CO_2 in the nonpulsatile group were blunted compared to the pulsatile flow, suggesting a loss of cerebral autoregulation in response to changes in CO_2 with the loss of pulsatile blood flow [81]. In patients placed on CPB for surgery, the microcirculation of sublingual tissue was compared with pulsatile and nonpulsatile flow using a previously established noninvasive spectral imaging technique [82].

At the microcirculation level, disrupted perfusion and leukocyte activation in sublingual tissue were observed in the nonpulsatile group, compared with the pulsatile group. This effect was statistically significant, and it increased in magnitude with CPB time and was associated with lower lactate in the pulsatile flow group, suggesting an aberrant antiregulatory response with the loss of pulsatile flow [78]. In patients with implanted left ventricular assist devices, pulsatile flow devices (vs. nonpulsatile devices) showed significant reductions for stroke (9.9% vs. 19.4%) and disabling ischemic stroke (3.9% vs. 5.9%) two years post-implantation [83]. Non-pulsatile blood flow may impair cerebral autoregulation, reducing the normal protective response of cerebral vessels to changes in CPP and CO_2 and further increasing the risk of ABI after CA; the feasibility and benefit of pulsatile flow during VA-ECMO and ECPR have yet to be established, but it warrants consideration as a mechanism for reducing ABI.

Animal model of impaired coagulation in ECMO

One animal model examined coagulopathy in adult sheep exposed to smoke-induced lung injury by comparing animals placed on VV-ECMO to controls (mechanical ventilation only). During 24 hours of ECMO flow, there was an increase in collagen-induced platelet aggregation, increased platelet aggregation time, and decreased clot firmness as measured by thromboelastography. Additionally, fibrinogen, factor VIII, and von Willebrand factor were all reduced in animals treated with VV-ECMO and were synergistically worse when combined with smoke-induced lung injury than in controls. This model suggests that abnormal platelet aggregation and decreased clot effectiveness in ECMO may predispose patients to coagulopathy, increasing the risk of thrombosis and bleeding [71].

Ischemic stroke and intracranial hemorrhage in VA-ECMO

In addition to HIBIs, acute ischemic stroke (AIS) and intracranial hemorrhage (ICH) are major complications that increase mortality in patients supported with ECMO [76,84,85]. In patients treated with VA-ECMO, the prevalence of AIS is 3.3% and may be as high as 16% on autopsy [86,87]. The risk factors for AIS include circuit clots (oxygenator clot), left ventricle (LV) thrombus, and insertion of ECMO catheters [86,88-90]. The prevalence of

ICH with VA-ECMO is reported to be between 2% and 18% and as high as 24% on autopsy [86,87]. Thrombocytopenia and heparin use pre-dispose to ICH and rapid hematoma expansion, which may be exacerbated by impaired coagulation function in ECMO patients [71,91,92].

Cerebral microbleeds (CMBs) were detected in 60% of patients treated with ECMO at autopsy and in 50% of survivors from a retrospective analysis, both of which are much higher than the rates in the general population [93,94]. Several other case series and retrospective observational studies also reported CMBs in patients treated with ECMO with unknown clinical significance or long-term outcomes [95-97]. CMBs may indicate ongoing cerebral small vessel disease in patients treated with ECMO, but their significance and etiology remain to be elucidated.

Harlequin syndrome

Harlequin syndrome, also described as the North-south syndrome, dual circulation, and differential hypoxia, is a phenomenon that occurs in peripherally cannulated VA-ECMO patients with respiratory failure and cardiac failure, such that they are unable to adequately oxygenate blood. The ECMO venous catheter drains oxygen from the inferior vena cava and returns oxygenated blood from the ECMO circuit to the aorta, which meets with the blood ejected from the LV that is recovering. This blood preferentially circulates towards the lower extremities and returns via the inferior vena cava, where it is recirculated through the ECMO circuit. Deoxygenated blood, due to pulmonary dysfunction, ejected from the LV may preferentially perfuse the aortic arch in an antegrade fashion, thereby perfusing the head vessels with deoxygenated blood as it competes with the oxygenated retrograde arterial blood flow from the femoral artery cannula. This mismatch of upper body hypoxia coupled with lower body normoxia, hence differential hypoxia, is called Harlequin syndrome [98-100]. Hypoperfusion and ischemia of the brain and heart are associated with HIBIs. The prevalence is reported to be approximately 9%; therefore, it is critical to monitor arterial blood gas values from the patient's right radial artery, the most distal arterial access from the femoral artery cannula, to gain insights into the oxygenation status of the upper torso [101].

NEUROLOGIC MONITORING FOR ABI IN ECPR

Accurate estimation of the prevalence of ABI associated with ECPR is difficult due to limitations in neurological examination with the use of sedatives as well as safety concerns in performing neuroimaging studies during ECMO support. Magnetic resonance imaging is currently precluded because of the ECMO circuit [102]. Even if head computed tomography (HCT) is performed, the utility of HCT in detecting early ischemia and lesions in the posterior circulation territory is limited. Other noninvasive neurological monitoring methods include TCD, somatosensory evoked potentials, cerebral near-infrared spectroscopy (cNIRS), and electroencephalography (EEG), which may systematically assess the occurrence of ABI [103-105]. Another useful tool for noninvasive monitoring is optic nerve sheath diameter measurement with ultrasound, which may provide information on intracranial pressure [102]. A standard neurological monitoring protocol can increase sensitivity in the detection of ABI [103]. TCD may have a role in detecting ECMO circuit clots, such as arterial-sided oxygenator clots, which may be associated with ischemic stroke [89]. In addition, TCD can be used to detect ongoing cerebral microembolic signals while on ECMO, but further study is necessary to establish a firm relationship between AIS and TCD microembolic signals [106]. cNIRS may be a useful real-time bedside neuromonitoring tool to detect ABI in ECMO patients when an acute drop in regional oxygenation saturation occurs [107]. It is recommended to monitor patients after CA with continuous EEG (cEEG) [108]. Similarly, ECPR patients should be monitored with cEEG, as patients are at a high risk of seizures. Furthermore, EEG features such as absent EEG reactivity and discontinuous background may be associated with poor outcomes in comatose ECMO patients [109,110]. Therefore, cEEG monitoring is recommended for ECMO patients with disorders of consciousness off sedation and somatosensory evoked potentials for patients with motor Glasgow Coma Scale scores of < 4 [103,104]. Optic nerve sheath diameter can be abnormal due to ABI but is less useful in the prevention of injury [111]. Each of these neurological monitoring tools has limitations. Therefore, a standardized multimodal neuromonitoring approach, as well as clinical neurological assessment with neurological consultation, may facilitate early detection of ABI associated with ECPR. However, the effectiveness of this approach in improving outcomes by primary and secondary prevention or providing reliable neurological prognostic information is yet to be established [103]. Fig. 2 summarizes the neurological complications, monitoring, and prognostication of ECPR.

BIOMARKERS IN ECPR

Several biomarkers have been identified and associated with ABI in patients treated with ECMO. These include markers of neuronal injury (neuron-specific enolase [NSE] and intercellular adhe-

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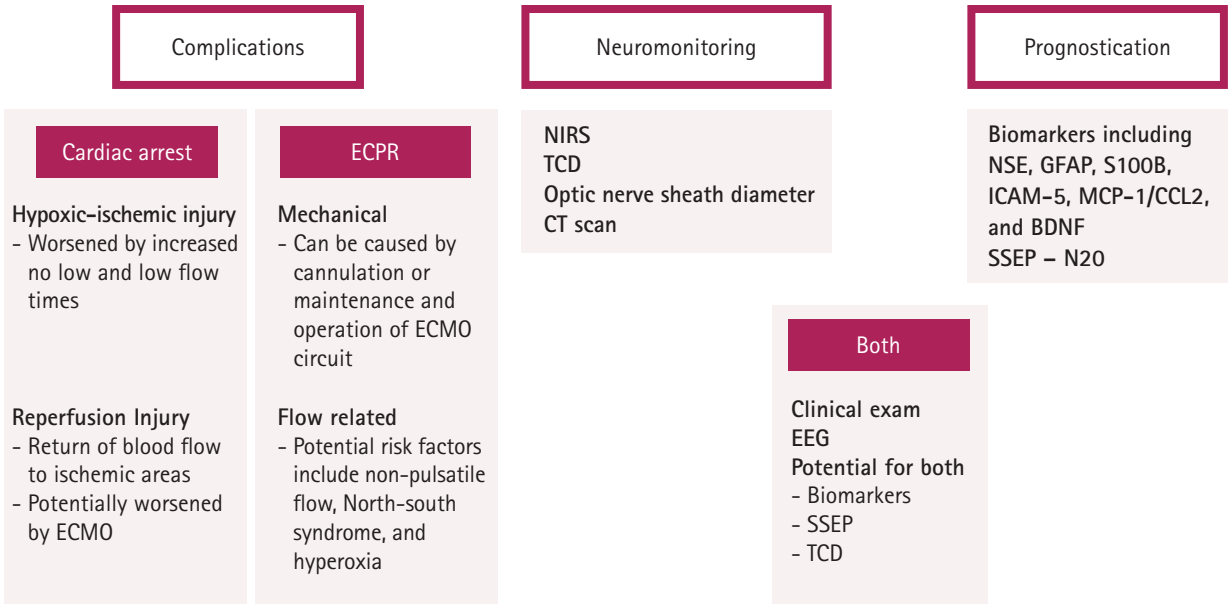

Fig. 2. Components of neurologic complications, monitoring, and prognostication in extracorporeal cardiopulmonary resuscitation (ECPR). NIRS, near-infrared spectroscopy; TCD, transcranial Doppler; CT, computed tomography; NSE, neuron-specific enolase; GFAP, glial fibrillary acidic protein; S100B, calcium-binding protein B; ICAM-5, intercellular adhesion molecule 5; MCP-1/CCL2, monocyte chemoattractant protein 1/chemokine (C-C motif) ligand-2; BDNF, brain-derived neurotrophic factor; SSEP, somatosensory evoked potential; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalography.

sion molecule 5), glial cell injury (glial fibrillary acidic protein [GFAP], calcium-binding protein B [S100B], and brain-derived neurotrophic factor), and neuronal inflammation (monocyte chemoattractant protein 1/chemokine [C-C motif] ligand 2 [MCP-1/CCL2]) [102]. In patients treated with ECPR, higher NSE has been shown to correlate with increased mortality and ABI; however, hemolysis is common in ECMO and may result in false positives in NSE measurement [112,113]. In patients with ABI associated with ECMO treatment, S100B was found to be significantly elevated, and in a separate case series of infants, it was significantly elevated 72 hours before ICH [114,115]. There is evidence that GFAP is associated with ICH, brain death, cerebral edema, and mortality and is elevated in children 1–2 days before the detection of ABI on imaging [116]. S100B and GFAP in combination may be representative predictive biomarkers for children as the levels were elevated 1–3 days before the detection of ABI [115,116]. A marker of axonal injury in neurons, tau, measurable via serum assay may be significantly better than NSE for neuro prognostication after CA; however, there is a lack of data on the use of ECMO and EPCR [117]. Similarly, after CA, another marker of axonal injury, the neurofilament light chain, is associated with HIBIs in children and poor long-term neurologic outcomes in adults [118,119]. Post-CA biomarkers have been shown to peak at different periods but they are not sensitive or specific enough to be independent prognostic markers [120]. For ECPR, biomarkers may aid in prognostication as part of the multimodal evaluation, including imaging and clinical assessments, to increase sensitivity.

CONCLUSIONS

ECPR represents advancement in CPR, allowing a bridge to therapy in appropriately selected patients after refractory CA. Currently, ECPR is most successful at centers with experienced staff or communities with an appropriately trained and experienced ECMO team. Although ECPR may improve survival, ABI remains the leading cause of morbidity and mortality among patients treated with ECPR. A standardized neuromonitoring protocol may improve ABI detection. A better understanding of the role of early hyperoxia, TTM, cerebral blood flow, and reperfusion injury is important for improving neurological outcomes of ECPR survivors. Furthermore, cerebral microcirculation and autoregulation with non-physiological blood flow in ECMO may play a critical role in cerebral small vessel disease. "Bench-to-Bedside" translational and clinical research on "ABI in ECMO" is necessary as the use of ECPR is increasing, as well as its associated increase in survival.

ARTICLE INFORMATION

Ethics statement
Not applicable.

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

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Basic considerations on magnesium in the management of neurocritical patients

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Magnesium is an essential chemical element in human life. In the brain, it is physiologically responsible for a large number of processes involved in intracellular homeostasis, blood-brain barrier integrity, protein synthesis, neuronal proliferation, aging, and apoptosis. Considering that neurocritical care is a relatively new discipline in certain regions of the world and is an independent protective factor of neurological diseases in critical care, it is essential to disseminate basic concepts and utilities of tools that can positively impact the neurological disease burden. Magnesium and its use in neurocritical care are poorly understood. Therefore, this study aimed to review basic concepts regarding the physiology of magnesium in neurological dynamics, its role in the pathophysiology of neurological disorders, and the outcome of its use in the management of neurocritical illnesses.

Keywords: Magnesium; Magnesium deficiency; Physiology; Nervous system diseases; Neurocritical care

INTRODUCTION

Magnesium (Mg) is a chemical element that is essential for human life. In the brain, it is physiologically responsible for many processes involved in intracellular homeostasis, blood-brain barrier integrity, protein synthesis, neuronal proliferation, aging, and apoptosis [1]. This element is also a special target of research and clinical monitoring [2] as it is associated with memory and learning [3], headache and migraine [4], cerebral edema [4], stroke [5], and traumatic brain injury [6], among many other neurological disorders [1-4]; therefore, knowledge regarding Mg in neurocritical care is crucial. However, there is a paucity of literature on the role of this cation in physiological and pathophysiological mechanisms that occur in neuronal dynamics. Although the num-

ber of studies is few, the results obtained are interesting.

Considering that neurocritical care is a relatively new discipline in certain regions of the world [7,8] and that it is an independent protective factor for neurological diseases in critical care [9,10], the dissemination of basic concepts and utilities of tools that can positively impact the burden of neurological diseases that occur mainly in low- and middle-income countries is essential [11], especially due to cerebrovascular disease and neurotrauma [11]. In the published literature, most of the studies that have evaluated the usefulness of Mg in neurocritical care have focused on the management of subarachnoid hemorrhage [12-17], neurocritical complications during pregnancy and puerperium [18,19], and traumatic brain injury [20-22], and its use in other conditions of great interest, such as seizures and epilepsy is unknown, neuromuscular disorders, metabolic encephalopathies and delirium, neuroendocrine diseases, neurogenetic diseases, neuropsychiatric disorders [3], and non-neurological complications in neurocritical patients, which implies a wide knowledge gap between Mg and neurocritical care.

Understanding neurological physiology from the most basic aspects (at the molecular level) and seeking solutions in translational metabolomics research [2] will help in improving outcomes in the management of neurocritical pathologies to improve the quality of care of these patients, providing patient and family satisfaction, and reducing costs in acute care, as well as in neurorehabilitation and disability. In this order of ideas, the objective of this manuscript is to review basic concepts on the physiology of Mg in neurological dynamics, its role in the pathophysiology of neurological disorders, and the results of its use in the management of neurocritical diseases.

BASIC ASPECTS OF MAGNESIUM PHYSIOLOGY IN THE CENTRAL NERVOUS SYSTEM

Role of magnesium in cell dynamics

Mg has been described as an indispensable chemical element in the maintenance of cellular dynamics as it is associated with several enzymatic reactions that regulate cellular metabolism and protein synthesis [23]. This mineral is absorbed in the gastrointestinal tract and kidneys and its serum level, together with that of calcium (Ca), is increased by parathormone [3]. Its free concentrations do not correlate with the total body concentration, as approximately 1% of this mineral is found in the extracellular fluid [24]. Among its different forms, ionized Mg is the most biologically active [24].

Mg facilitates organic activities in the neuromuscular system, such as neuronal and muscular excitability, contractibility, and rhythm in the cardiovascular system, and vasodilatation in the circulatory system [25-27]. More specifically, in the brain, it is responsible for intracellular transmission, myelination, synapse formation and maintenance, and regulation of cholinergic, dopaminergic, and serotonergic transmission (through the decrease of acetylcholine release at the neuromuscular junction; blockade of N-methyl-D-aspartate (NMDA) receptors, inhibiting the excitatory function of glutamate, and stimulation of GABA receptors generating neuronal hyperpolarization, and exerting an inhibitory effect in the process) [28-31]. It is also involved in the release of calcitonin gene-related peptide (neuropeptide). It decreases the release of substance P, induces the secretion of inflammatory mediators, such as tumor necrosis factor α and interleukin 1, and intervenes in the mitigation of neuroinflammatory processes [32,33].

Therefore, it is directly involved in the maintenance of neurological integrity, neuroprotection against apoptosis in situations of hypoxia-ischemia, prevention of synapse loss in neurodegeneration, promotion of neurogenetic activities, proliferation of neural stem cells, and neuromaturation [1-4,32]. Likewise, it plays a fundamental role in neuroplasticity, and precisely because of this, research on this element and its impact on the acute management and neurorehabilitation of neurological disorders is important [34]. However, it is first necessary to know the neurometabolic processes that enable the establishment of hypotheses with biological plausibility and the prediction outcomes in biological and human models.

Magnesium and the blood-brain barrier

The blood-brain barrier is a highly selective semi-permeable border of endothelial cells that prevents solutes in the circulating blood from crossing non-selectively into the extracellular fluid of the central nervous system, where neurons reside [35]. In the brain, there are two main associated fluid compartments: the extracellular fluid, which surrounds neurons and glial cells, and the cerebrospinal fluid, which is located in the subarachnoid space and ventricles of the brain [36]. The passage of Mg through this barrier is made possible by a complex system of genes and proteins [1].

Animal studies have shown that Mg can cross the blood-brain barrier and is transported across the barrier with a net flow from the blood to the parenchyma [37-39]. The active transport of Mg from the blood to the extracellular fluid of the brain is evidenced by its higher concentration in the extracellular cortical fluid than in the plasma dialysate or cisternal cerebrospinal fluid [38,39]. Another interesting finding is that Mg administration could atten-

uate cell death secondary to alterations in the cytoskeleton and, therefore, reduce apoptosis due to p53 expression after brain trauma [1].

Concerning the association between Mg and brain edema, it has been proposed that Mg supplementation decreases regional brain tissue water content, attenuates brain edema formation after trauma, protects the blood spinal cord blood, improves clinical recovery, and preserves normal spinal cord ultrastructure in the case of experimental spinal cord injury in rats [1,40-42]. This has been demonstrated in experimental studies focused on the treatment of cerebral edema that sought to demonstrate the benefits of Mg administered in combination with various pharmacological drugs in animal models and its possible role in the resolution of cerebral edema [43]. They revealed that increased aquaporin-4 (AQP-4), which is a bidirectional transmembrane water channel believed to play a role in brain injury by contributing to increased brain water content, could result in cerebral edema [40,41].

In this order of ideas, and given that Mg supplementation causes the downregulation of AQP-4 [40,41], Mg is able to exert beneficial effects in neurocritical conditions (Fig. 1). Furthermore, it also exerts neuroprotective effects in anoxic insults by enhancing the recovery of synaptic transmission and blocking the loss of protein kinase C [42], restricting the opening of paracellular pathways through Ca antagonism, alleviating oxidative stress, and preventing hypertensive encephalopathy by reducing the cerebral perfusion pressure [1].

MAGNESIUM ALTERATIONS AND MOLECULAR PATHOPHYSIOLOGICAL MECHANISMS

Hypomagnesemia

Hypomagnesemia is defined as a plasma Mg concentration of < 1.7 mg/dL [44,45]. The clinical manifestations of hypomagnesemia are nonspecific since hypomagnesemia is associated with hypocalcemia and hypokalemia in many cases [44-46]. The causes of hypomagnesemia can be classified according to their pathophysiology, as follows: (1) decreased intake; (2) redistribution secondary to an increase in the passage of Mg from the extracellular to the intracellular space (present in pathologies such as hyperparathyroidism, hyperthyroidism, etc.); (3) gastrointestinal losses (diarrhea, vomiting, or surgical resection of the intestine); and (4) renal losses [44-47]. However, given that serum Mg concentration is not usually requested as part of routine blood tests, it should be kept in mind and its measurement should be requested directly in clinical situations that could possibly be associated with alterations in its homeostasis [48].

Among the clinical manifestations of hypomagnesemia are cardiac arrhythmias, which are the most important, and neuromuscular alterations, such as convulsions, paresthesia, nystagmus, Chvostek's sign, and positive Trousseau's sign [44-48]. A curious fact is that between 40% and 60% of patients with hypokalemia also have hypomagnesemia. This is because there are

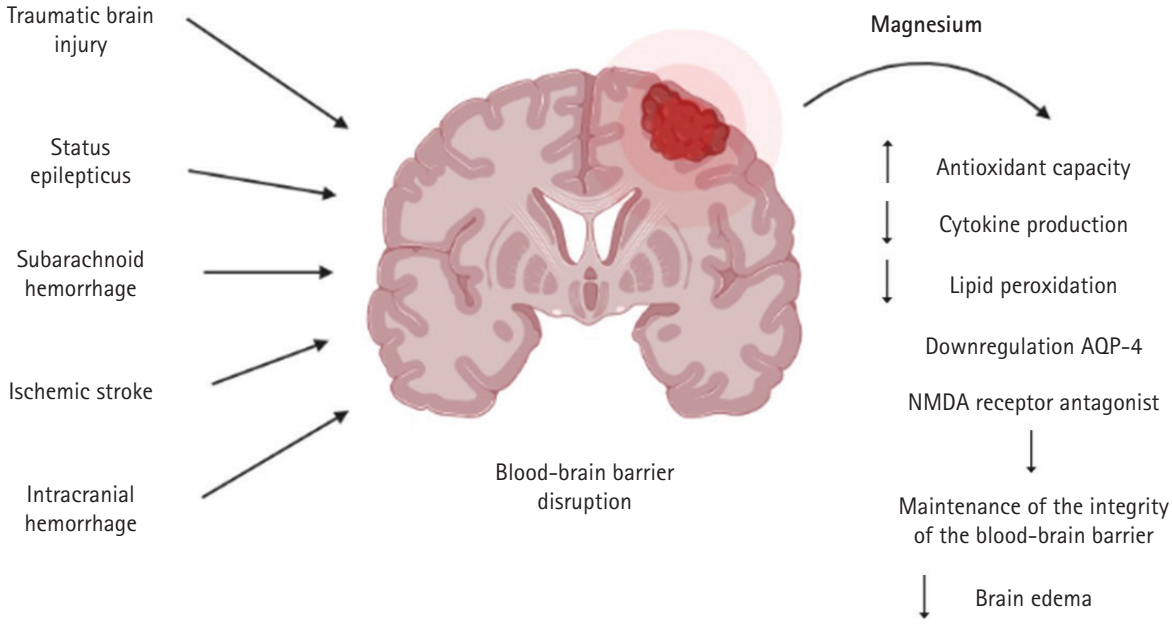

Fig. 1. Neuroprotective mechanisms of magnesium against blood-brain barrier disruption. NMDA, N-methyl-D-aspartate; AQP-4, aquaporin-4. Created by the authors using BioRender.

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different circumstances specific to the patient that cause the loss of both Mg and potassium, including gastrointestinal losses (diarrhea) and the chronic use of diuretics, such as furosemide [45,46].

As for treatment, it is known that in cases where plasma Mg deficiency is severe (< 1 mEq/L in serum), or symptomatic with clinical manifestations of neuromuscular, neurological, or cardiac arrhythmias, the Mg repletion should be achieved by prompt intravenous administration of 2 g of magnesium sulfate ($MgSO_4$) in 100 mL of D5W for 5 to 10 minutes, followed by a continuous infusion of 4 to 6 g/day for 3 to 5 days (only in the case where the renal function remains relatively normal and stable) while treating the underlying cause of the Mg deficiency to prevent future recurrence in the case where it is secondary to another pathology [44-48]. As for maintenance therapy, oral administration of Mg oxide (400 mg twice a day or three times a day) can be used as long as the risk factors for Mg deficiency are maintained [44-48].

Hypermagnesemia

Hypermagnesemia is defined as a serum Mg level of > 2.2 mg/dL. This entity is very rare; however, it can occur iatrogenically when intravenous $MgSO_4$ is being administered in patients with chronic renal disease or in those who chronically ingest Mg-containing laxatives [48,49].

The clinical manifestations of intoxication will depend on the level of Mg in plasma; as such, in the case of mild hypermagnesemia, it may even be asymptomatic. Therefore, its clinical manifestations may only appear with levels above 2.5 mmol/L [50,51]. The clinical manifestations of hypermagnesemia include oliguria (2.5%), loss of patellar reflex (1.6%), cardiac conduction disturbance, respiratory depression, and cardiorespiratory arrest [52]. However, certain studies suggest that hypermagnesemia is associated with an increased need for vasopressor drugs, increased risk of respiratory failure, and increased mortality [48-52].

Serious gastrointestinal manifestations may also arise as a cause of this pathology, such as the association of hypermagnesemia with the presence of toxic megacolon or ischemic colitis due to altered intestinal circulation, possibly leading to local ischemia due to decreased intestinal motility caused by fecal impaction and increased intraluminal pressure that could be aggravated if accompanied by prolonged hypotension [48-53]. The treatment of intoxication is based on adequate hydration, increasing renal excretion through the use of diuretics, and the administration of 1 g of the antidote (Ca chloride or Ca gluconate) [49-52].

MAGNESIUM AND NEUROLOGICAL DISORDERS

Status epilepticus

There is extensive experience regarding the use of $MgSO_4$ infusion in eclampsia seizures; however, there are few studies supporting the effectiveness of this drug in status epilepticus and super-refractory status epilepticus [54-56].

During these states, the NMDA receptor is overregulated, leading to glutamate hit-toxicity and seizure potentiation. Because this receptor plays a key role in drug resistance and the genesis of status epilepticus of status epilepticus and super-refractory status epilepticus, NMDA receptor antagonists have been studied as anticonvulsants of choice for these pathologies [54-56].

Previous studies have shown that the use of $MgSO_4$ as an NMDA receptor antagonist at a dose of 4 g, followed by a continuous infusion at a rate of 2–6 g/hr, safely increases plasma Mg levels by 3.5 mmol/L, with positive results for this group of patients [54-56].

Intracranial hemorrhage

Intracranial hemorrhage is considered the second most common type of stroke, with the lowest percentage improvement in mortality and morbidity among all strokes. It occurs in two stages: the first consists of the growth and stabilization of an initial hematoma that appears acutely, and the second consists of the expansion of the perihematoma edema and its irruption into the blood-brain barrier [5,57-59].

Mg has been reported to prevent hematoma formation in both stages due to three of its specific properties [57-59]: (1) Its vasodilator function is achieved thanks to its property as a Ca channel antagonist, which prevents the entry of Ca and its release by the sarcoplasmic reticulum. Its function as an angiotensin-converting enzyme inhibitor and its capacity to increase prostacyclin production also play a role. This vasodilator effect favors the lowering of blood pressure, which attenuates the volume of the hematoma and its progression to intracranial hemorrhage [57-59]. (2) Its ability to promote hemostasis: This cation acts as a substantial cofactor in hemostasis by increasing Ca^{2+} binding to factor IX, stabilizing its binding, and promoting the activation of factor IX by factor Xia. It promotes the interaction between tissue factor and the γ-carboxyglutamate-rich domain of factor X [57,58]. (3) Its ability to preserve the blood-brain barrier: Functioning as an NMDA receptor antagonist potentiates presynaptic adenosine and inhibits oxidized low-density lipoproteins. Further, it can relax vascular smooth muscles and improve cerebral blood flow. In this way, it acts in the second stage of hemorrhage formation, minimizing he-

matoma breakthrough to the blood-brain barrier [57,58].

Cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage

Cerebral vasospasm occurs in approximately 70% of patients with aneurysmal subarachnoid hemorrhage, which is the main cause of morbidity and mortality in these patients. This fact has led to research focused on the prevention of vasospasm as a measure to reduce irreversible sequelae in these patients [60-62]. It has been shown that $MgSO_4$ can decrease outcomes in patients with subarachnoid hemorrhage by attenuating vasospasm [1]. This is achieved by different mechanisms, including blockade of NMDA receptors, inhibition of excitatory amino acids, and antagonism of voltage-dependent Ca channels [60-62].

Recent studies have shown that $MgSO_4$ therapy is safe and reduces the incidence of ischemia following subarachnoid hemorrhage vasospasm. It consists of ingesting doses of 64 mmol/day, which would bring serum Mg to levels of 1–2 mmol/L, which do not represent a risk for the organism [4]. $MgSO_4$ therapy has shown greater effectiveness than other drugs, such as milrinone, by producing greater hypotension with a consequent requirement for dopamine and norepinephrine compared to Mg [60-62].

Ischemic stroke

In 2019, Larsson et al. [63] reported an inverse relationship between serum Mg levels and the risk of cardioembolic stroke, associating hypomagnesemia with a 70%–80% higher risk of suffering from this pathology. The mechanisms through which Mg contributes to reducing the risk of ischemic stroke are largely explained by its properties: its ability to improve endothelial function, reduce blood pressure, atherosclerotic plaque formation, oxidative stress, insulin resistance, and fasting glycemia. It is also believed to possess qualities that reduce platelet aggregation, decrease thromboxane A2 synthesis, and von Willebrand factor binding [63,64]. Mg's ability to affect the dynamics of autoregulation of the cerebral vasculature and its neuroprotective effect by inhibiting the action of NMDA receptors [64] has made this electrolyte one of interest to the stroke research community.

To date, few randomized clinical trials and prospective studies have evaluated the role of $MgSO_4$ in both ischemic and hemorrhagic stroke, mostly using mixed groups (ischemic and hemorrhagic stroke) (Table 1) [63,65-72]. In 2004, one of the first representative studies, a clinical trial with the objective of determining whether the administration of $MgSO_4$ in the prehospital phase of stroke was safe and favorable, was published; in this study, it was observed that neuroprotective activity was indeed observed [65]. However, the total number of patients was 20, and it was a mixed group (80% ischemic stroke and 20% hemorrhagic stroke) [65]. Almost a decade later, Saver et al. [66] conducted a trial with the purpose of evaluating the role of $MgSO_4$ administration time from symptom onset in patients with stroke and long-term functional outcomes. In this study, 1,700 patients who had an ischemic stroke (73.3%) were enrolled, and the average time of drug administration from symptom onset was 45 minutes; no significant benefits were obtained compared to placebo [66].

In particular, Pan et al. [68] carried out a study in which they evaluated the impact of the oral administration of Mg and potassium as supplements to table salt on the recovery of stroke patients, observing that out of three groups (salt [Na], salt+K, and salt +K+Mg), the group that received Mg supplementation had a more favorable recovery in the neurological evolution of stroke [68]. Unfortunately, other studies have reported non-significant results; however, like those described here, they have limitations and are heterogeneous. In spite of this divergence, the neuroprotective effect of $MgSO_4$ was remarkable. Similar results are evident in studies that used groups of patients with subarachnoid hemorrhage in both the prehospital and hospital phases [70,71].

In a systematic review conducted by Fang et al. [72] that included 40 prospective cohort studies, a 7% reduced risk of stroke was found in people with high Mg intake compared to those with low Mg intake. Recently, the most powerful claims have been in favor of the usefulness of $MgSO_4$ in improving the prognosis of stroke patients. However, it is necessary to continue to propose high-quality studies with a considerable sample size to obtain convincing results [73].

Traumatic brain injury

The neuroprotective role of Mg was evidenced in experimental studies by the inhibition of glutamate release, NMDA receptor activation, Ca channel opening, lipid peroxidation, free radical production, edema formation, and the opening of mitochondrial permeability transition pores responsible for apoptosis, such as p53 and Bax [74-77].

Hypomagnesemia in patients with severe traumatic brain injury is associated with an increase in negative outcomes, such as mortality and poor functional prognosis [74-77], and adequate control is part of the comprehensive management of patients with severe traumatic brain injury [75]. Lyons and Blackshaw [77] conducted a systematic review and meta-analysis in which they evaluated the impact of $MgSO_4$ in the management of adults with traumatic brain injury, where it was observed that the pooled results of six studies found all-cause mortality to not be significantly different in the treatment group (relative risk, 0.84; 95% confidence interval, 0.54–1.33; $p = 0.46$) with an I^2 value of $> 70\%$. With re-

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Table 1. Summary of the results of randomized and non-randomized studies that evaluated $MgSO_4$ in ischemic cerebrovascular disease and subarachnoid hemorrhage

Study	Objective	Design	Result	Conclusion
Saver et al. (2004) [65]	To demonstrate the safety of $MgSO_4$ in the prehospital setting and its potential neuroprotective effect in the management of stroke	Open-label, non-randomized trial	20 Patients, 80% of whom had ischemic stroke and 20% hemorrhagic stroke; the time from the arrival of the paramedic to the start of drug infusion was 26 minutes, and the patient transfer time was 37 minutes. - 4 Patients (20%), improved - 15 Patients (75%), no change - 1 Patient (5%), worsened	Feasibility and safety of $MgSO_4$ and a neuroprotective effect in the management of stroke were found.
Saver et al. (2015) [66]	To determine the beneficial effect on functional response of early administration of $MgSO_4$ in patients with stroke	Randomized double-blind clinical trial	1,700 Patients: 857 experimental, 843 control - Ischemic stroke, 73.3% - Hemorrhagic stroke, 22.8% The median time from onset of pathology to drug infusion was 45 minutes. The death rate 90 days later was 15.5%.	No benefit for stroke patients who received early pre-hospital $MgSO_4$
Shkirkova et al. (2017) [67]	Determine whether tubes with a fixed lumen size can initiate intravenous infusions to allow more rapid neuroprotective therapy with $MgSO_4$	Randomized double-blind clinical trial	1,700 Patients; mean time from last known sample to agent onset was 45 minutes. Paramedic arrival time was 23 minutes. Patients with the highest serum Mg levels had excellent functional outcomes at day 90.	Effectiveness in the technique was determined, achieving a decrease in the drug initiation time, with the advantage of doubling the serum Mg level and maintaining it during the first 24 hours.
Pan et al. (2017) [68]	To identify the beneficial effect of a salt diet supplemented with K and Mg on the recovery of stroke patients	Multicenter, double-blind, randomized, multicenter clinical trial	291 Patients, of which 40 patients (42.1%) of those on K and Mg salt showed improvement at 3 months. - 30 Patients (30.9%), K-salt - 26 Patients (26.3%), sodium salt	The neurological evolution of stroke patients, even with a moderate amount of oral K and Mg salt, was determined to be beneficial.
Larsson et al. (2019) [63]	To identify the association of serum calcium and Mg levels with stroke	Mendelian randomization analysis	None of the calcium-related single nucleotide polymorphisms had a significant association with ischemic stroke or any of its types. However, significant and favorable results were found with serum Mg.	It was found that the calcium concentrations determined were not associated with any type of ischemic stroke. However, high serum Mg concentrations were found to be associated with a lower risk of cardioembolic stroke.
Bechler et al. (2020) [69]	To identify the benefit of early initiation of high-dose intravenous $MgSO_4$ in patients with adverse cardiac effects who have suffered a stroke	Randomized phase-3 clinical trial	1,126 Patients, 71.8% of whom had ischemic stroke and 24.6% had hemorrhagic stroke. - Treatment with Mg, 565 (50.2%) - Cardiovascular adverse effect, 159 (14.1%); atrial fibrillation, 4.7%; bradycardia, 2.9%; cardiac arrest, 2.2%	No significant benefit was identified between patients receiving Mg supplements and those receiving placebo.
Wong et al. (2010) [70]	To identify the response of patients with subarachnoid hemorrhage after intravenous infusion of $MgSO_4$ compared with placebo	Phase-3, randomized, double-blind, controlled, multicenter, double-blind trial.	327 Patients enrolled. Similar results were found in the $MgSO_4$ intravenous infusion vs. saline group (OR, 1.0; 95% CI, 0.7–1.6) at 6 months.	No significant benefit of $MgSO_4$ administration for neuroprotection in subarachnoid hemorrhage was identified.
Takeuchi et al. (2021) [71]	To determine the results of intracisternal infusion of $MgSO_4$ combined with intravenous hydrogen therapy in patients with severe subarachnoid hemorrhage.	Randomized, double-blind, controlled clinical trial	Of 37 patients, no complications were observed with cisternal infusion or associated with hydrogen administration. - Rupture in 1 patient, $Mg+H_2$ group - Meningitis in 1 patient in the control group, 2 in the $Mg+H_2$ group, 1 patient in the $Mg+H_2$ group - Chronic hydrocephalus in 4 patients in the control group, 5 in the Mg group, 4 in the $Mg+H_2$ group	Early initiation, after surgery, of $MgSO_4$ infusion was found to reduce the incidence of cerebral vasospasm and cerebral ischemia in patients with subarachnoid hemorrhage.

$MgSO_4$, magnesium sulfate; Mg, magnesium; K, potassium; OR, odds ratio; CI, confidence interval.

gard to the secondary outcomes, there was no significant difference in the Glasgow Outcome Scale score between the treatment and control groups. It is due to the above that attempts have been made to introduce $MgSO_4$ as a neuroprotective agent with very heterogeneous results so that an accurate clinical recommendation can be given [77].

FUTURE PERSPECTIVES

Studies on the description of Mg in the physiology of the central nervous system, as well as its therapeutic utility in neurocritical care, are almost nonexistent at present. It is necessary to come up with new lines of research aimed at exploring the effect of Mg in central nervous system tumors, acquired metabolic disorders, neurogenetic diseases, neuronutrition, neurorehabilitation, and infectious diseases. Being an affordable mineral, it is postulated as a therapeutic option applicable in low-level healthcare contexts for the stabilization of neurocritical patients while they are being evaluated by a specialized department.

CONCLUSIONS

In a review of the different neuropathological conditions, a direct relationship between the physiological mechanisms of $MgSO_4$ and multiple pathophysiological phenomena can be observed. Therefore, current evidence allows us to observe that $MgSO_4$ can be an important part of the treatment of this type of pathology. Even so, in certain situations, for greater acceptance of its use, it is necessary to design studies of better quality to optimize the therapeutic objectives and, in this way, be able to obtain standardized schemes in the future for better results in its implementation.

ARTICLE INFORMATION

Ethics statement

Not applicable.

Conflict of interest

No potential conflict of interest relevant to this article.

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Neuroleptic malignant syndrome cases in a Moroccan intensive care unit: a retrospective analysis and literature review

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Background: Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening neuropsychiatric emergency. The aim of our study was to update our bedside procedures by investigating NMS cases managed in the intensive care unit (ICU).
Methods: This retrospective study included all NMS patients admitted to our hospital between January 2012 and December 2019. The variables analyzed included demographics, diagnosis, therapeutics, and outcomes.
Results: This study included 20 patients, with an average age of 36.6 years. The male to female ratio was 1:4. No patient had a history of NMS, and 60% of the patients had schizophrenia. First-generation neuroleptics (NLs) were the most commonly prescribed drugs (80%). The mean time between the introduction of NLs and onset of symptoms was 7.6 days. Rigidity was observed in 90% of the patients, hyperthermia and neuropsychic syndrome in 65%, and dysautonomia in 50%. The creatine phosphokinase level in all patients was four times the normal value. Mechanical ventilation was required in 20% of the patients and hemodialysis in one patient. None of the patients received specific therapy. The mean duration of ICU stay was 10 days. The mortality rate was 10%,, mainly associated with renal failure. The analysis of the predictors of mortality was limited by the size of our cohort.
Conclusion: NMS is a rare condition requiring multidisciplinary implementation of contextualized and updated procedures. Early detection and supportive treatment could improve the prognosis in resource-limited settings, where specific treatments are not available. Predictive risk factors should be investigated in larger multicenter cohorts.

Keywords: Neuroleptic malignant syndrome; Intensive care unit; Antipsychotics; Mortality; Treatment

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction mainly related to the use of antipsychotic agents (first-or second-generation neuroleptics [NLs]). It is characterized by a myriad of clinical signs, including altered mental status, muscular rigidity, hyperthermia, and dysautonomia. This life-threatening neuropsychiatric emergency is rare, with an estimated incidence of 0.2% among NL users [1], and requires early therapeutic management and intensive care for potentially severe presentations. Mortality, caused by dysautonomic and systemic complications (infections, venous thromboembolism, rhabdomyolysis, acute renal failure,

respiratory failure, etc.), decreased by 76% since the first reports in the 1960s; the current mortality rate is estimated at 10%–20% [2,3]. This is indicative of greater awareness, earlier diagnosis in both emergency settings and psychiatric wards, and interventions that are more aggressive than before. Since NMS requires a high degree of clinical suspicion for diagnosis and treatment, itis rightly a syndrome more often considered in differential diagnosis than is actually diagnosed. Moreover, considering its low incidence, there is limited evidence in the literature. Although the management of NMS is mostly performed in critical care settings, the issue is either not addressed or poorly addressed in the guidelines of the international and national scientific societies of intensive care and emergency medicine. This study aimed to analyze the NMS cases in our hospital to improve clinical decision-making based on the updated and contextualized bedside procedures.

METHODS

Study design and setting

This retrospective, observational, monocentric study evaluated patients aged ≥16 years who were admitted to our intensive care unit (ICU) between January 2012 and December 2019. The diagnosis of NMS was based on the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) of the American Psychiatric Association [4] (Table 1). The diagnosis of NMS was made based on the presence of exposure to a dopaminergic antagonist within the last 72 hours, a suggestive symptomatology, and negative examination results for infectious, toxic, metabolic, and neurologic causes. The study setting was a 14-bed medico surgical adult ICU in a tertiary university hospital in Morocco.

Data collection

Study data were collected retrospectively from both paper charts and electronic medical records of patients using HOSIX (SIVSA Soluciones Informáticas, Vigo, Spain) electronic data capture tools present at our university hospital. The variables analyzed included demographic characteristics, patient's history and comorbidities, all drugs involved, diagnostic parameters, therapeutics, and evolution.

Statistical analysis

Statistical analysis of the parameters was performed using IBM SPSS ver. 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the baseline patient characteristics. The results are expressed as numbers and percentages for qualitative variables and as means ± standard deviations for the quantitative variables. The quantitative and qualitative variables were compared using the two-sample *t*-test derived from Student *t* distribution and Fisher's exact test based on the N-1 chi-square test through univariate analysis. The statistical significance threshold was set at a *P*-value of 0.05. Analysis of predictive factors of mortality through multivariate analysis was not performed because of the limited number of patients in the "death" group, i.e., the group with deceased patients.

Table 1. Diagnostic criteria for neuroleptic malignant syndrome adapted from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [4]

Diagnostic criteria for neuroleptic malignant syndrome
Exposure to a dopaminergic antagonist within the last 72 hours
Suggestive symptomatology (no specific criteria)
• Hyperthermia >38°C at least twice
• Muscular rigidity or "lead-pipe" rigidity in generalized presentations
• Mental status alteration: delirium or altered consciousness ranging from stupor to coma
• Elevated CPK level, at least 4 times more than the normal value
• Autonomic dysfunction (lability and hypermetabolism):
Tachycardia, at least 25% over the baseline value
Diaphoresis
Increasing systolic or diastolic blood pressure by at least 25% from the baseline or blood pressure fluctuation by at least 20 mmHg for diastolic or 25 mmHg for systolic in the last 24 hours
Increase in respiratory rate of at least 50% over the baseline value
Urinary incontinence
Negative examination results for infectious, toxic, metabolic, and neurologic causes

CPK, creatine phosphokinase.

RESULTS

This study included 20 patients (16 males and 4 females) from the 6,090 patients admitted to our ICU between 2012 and 2019, with a mean age of 36.6 ± 19.5 years (range, 18–84 years). The underlying comorbidities in our population were schizophrenia (60%), bipolar disorder (20%), substance dependence (25%), mental retardation (10%), acute psychosis (10%), dementia (5%), and delirium (5%). None of the patients had a history of NMS. There were no other medical comorbidities, except for toxic addictions (smoking and cannabism) in five patients and psychomotor disability in two patients. In all the patients, NMS was caused due to the use of antipsychotic drugs. First-generation conventional NLs were the most commonly used drugs (80% of the patients) and mainly administered along with atypical NLs or other drugs (70% of the patients). Atypical NLs were used in 11 patients (55%). The medications used in our population included first-generation conventional NLs (haloperidol, 40%; levomepromazine, 35%; and chlorpromazine, 35%), second-generation atypical NLs (risperidone, 25%; olanzapine, 15%; and amisulpride, 10%), and other drugs (selective serotonin reuptake inhibitors [SSRIs], benzodiazepines, and anticholinergics). No case of dopaminergic agonist withdrawal was reported. The parenteral mode of administration was used in only four cases, and 10% of the patients required a rapid increase in NL doses. The mean time between the introduction of NLs and the onset of symptoms was 7.6 ± 7.1 days (range, 0–30 days). The mean time between symptom onset and hospital admission was 1.3 ± 1.5 days (range, 0–5 days). Rigidity was observed in 90% of patients, hyperthermia and neuropsychic syndrome in 65%, and dysautonomia in 50%. All patients presented a creatine phosphokinase (CPK) level four times more than the normal value. The average CPK was 4,810 ± 9,789 IU/L, with extremes ranging from 626 to 42,670 IU/L. The average Sachdev rating scale score on admission was 11 ± 3.09 (range, 3–14). Examinations for infectious, toxic, metabolic, and neurologic causes were negative in all patients. The distribution of patients according to different diagnostic criteria is presented in Table 2. Psychotropic treatment was stopped in all patients as soon as NMS diagnosis was suspected. Mechanical ventilation was required in 20% of the patients for a mean duration of 14.75 days (range, 1–28 days). Tracheotomy was performed in two patients on days 4 and 13 of intubation, respectively. All patients underwent respiratory physiotherapy and fluid resuscitation. A continuous intravenous infusion of nicardipine at a dose of 2–6 mg/hr was required in one patient. One patient needed catecholamines, while another needed hemodialysis. Diazepam, midazolam, or clonazepam against agitation were required in 25% of the patients. Contention was necessary in one patient. No patient was administered dantrolene or bromocriptine, and none received electroconvulsive therapy (ECT). The mean duration of ICU stay was 10 ± 15 days (range, 1–67 days). The overall outcome was favorable in 90% of the patients. The improvements in temperature, rigidity, CPK levels, and renal function varied (Table 3). One case progressed to persistent acute renal failure, classified as Risk; Injury; Failure; Loss; End stage kidney disease (RIFLE) 3. One case of cerebral hemorrhage due to ruptured arteriovenous malformation was recorded. The reintroduction of atypical NLs administered at low doses was conducted after a 15-

Table 2. Distribution of the patients according to different consensus diagnostic criteria

Consensus	Required criteria	Number of patients meeting the criteria (%)
DSM-5[a)]	No specific criteria	20 (100)
DSM-IV[b)]	Two of criteria A and at least two criteria B and criteria C and D	11 (55)
Nierenberg et al.'s diagnostic criteria[c)]	Essential criteria and 4 major or 3 major + 3 minor	13 (65)
Sachdev rating scale[d)]	Total score >8 and a score ≥2 in at least 3 domains	17 (85)

DSM, Diagnostic and Statistical Manual of Mental Disorders; CPK, creatine phosphokinase.
[a)]Hyperthermia, rigidity, mental status alteration, CPK elevation, sympathetic nervous system lability, and hypermetabolism after exposure to dopamine antagonist or dopamine agonist withdrawal, with a negative examination results for infectious, toxic, metabolic, and neurologic causes; [b)]Criteria A: muscle rigidity and hyperthermia associated with antipsychotic drugs use; criteria B: diaphoresis, elevated or labile blood pressure, tachycardia, incontinence, dysphagia, mutism, tremor, labile consciousness level ranging from confusion to coma, leukocytosis, and elevated CPK level; criteria C: symptoms in criteria A and B not due to another substance or due to neurologic or other medical conditions; criteria D: symptoms in criteria A and B not accounted for better by a mental disorder; [c)]Essential criteria: recent exposure to dopamine antagonist or dopamine agonist withdrawal; major criteria: fever >38°C without other causes, muscular lead-pipe rigidity, elevated serum CPK level (>3 times the normal value without any other cause), autonomic instability (two or more symptoms of sweating, tachycardia, and elevated or decreased blood pressure), and altered consciousness; minor criteria: other autonomic dysfunction (urinary incontinence, arrhythmias, or any one of sweating, tachycardia, and elevated or decreased blood pressure), other extrapyramidal signs (tremor, cog-wheeling, acute dystonic reaction, or choreiform movements), respiratory problems (severe dyspnea, tachypnea, respiratory failure, or hypoxemia), and leukocytosis; [d)]I: oral temperature; II: extrapyramidal symptoms (rigidity, dysphagia, and resting tremor); III: autonomic instability (increased systolic blood pressure, increased diastolic blood pressure, tachycardia, diaphoresis, incontinence, and tachypnea); IV: altered consciousness; V: catatonia/movement disorder; and VI: biology (elevated CPK level and leukocytosis).

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Table 3. Clinical and biological evolution of neuroleptic malignant syndrome cases

Improved parameter	Number of patients (n=20)	Mean time to improvement since NL discontinuation
Temperature (≤38°C)	20 (100)	3.8±1.3 (1–5)
No rigidity	18 (90)	5.2±2.2 (2–11)
CPK level ≤4 times normal value	14 (70)	5.9±2.3 (3–10)
Improved renal function	17 (85)	4.3±1.5 (3–6)

Values are presented as number (%) or mean±standard deviation (range).
NL, neuroleptic; CPK, creatinine phosphokinase.

day therapeutic interval in six patients (30%). No adverse effects were observed. The mortality rate was 10%, and the deaths were associated with renal failure complications. Two patients developed metabolic arrhythmias, mainly induced by refractory hyperkalemia and exacerbated by severe rhabdomyolysis. The mean time from ICU admission to death was 4±1.41 days (range, 3–5 days). When comparing the "death" (n=2) and "recovery" (n=18) groups, univariate analysis identified nine variables that were significantly ($P<0.05$) associated with mortality in NMS in our population (Table 4). The analysis of predictive factors of mortality through multivariate analysis was not possible given the limited number of patients in the "death" group.

DISCUSSION

This study, comprising 20 cases, is one of the largest cohorts of NMS patients in Morocco and one of the few studies conducted in ICUs. The incidence of NMS among NL users varies between 0.024% and 3% [5]. This is difficult to assess accurately due to population heterogeneity, variability in diagnostic criteria, and the methodological limitations of retrospective studies. In our study, NMS was predominant in young adult males, as similarly reported in the literature [6].

This can be explained by the higher skeletal muscle mass in males, and therefore more visible symptoms and more severe forms [7]; higher frequency of schizophrenia in males, and therefore a higher need for antipsychotics at elevated doses [8]; and sexual dimorphism in dopaminergic pathways, as suggested in recent studies [9].

NMS was first described in 1960 with haloperidol and was labeled as malignant by the Parisian group of the Sainte-Anne Hospital, analogous with the malignant syndrome of infectious diseases widely prevalent in the 1950s and 1960s [10].

However, any drug interfering with dopaminergic transmission can lead to NMS [11]. Combination of antipsychotic drugs, combined use of an antipsychotic with lithium or carbamazepine, abrupt discontinuation of a dopaminergic agonist such as levodopa in Parkinson disease patients, and the use of antiemetics such as metoclopramide have been reported to induce NMS. The combined use of several therapeutic classes of drugs seems to be associated with a higher risk of NMS, despite the higher affinity of conventional antipsychotics for dopaminergic D2 receptors [12,13]. In our series, no cases of dopaminergic agonist discontinuation were reported, and conventional NLs often combined with atypical NLs were most commonly used. Recently, more researchers have suggested "malignant extrapyramidal autonomic syndrome" diagnosis instead of NMS [14] to improve proactive screening in the absence of the use of antipsychotic drugs. The risk of NMS is higher within the first month of treatment at high doses, especially when administered parenterally or after a rapid dose change. Physical restraint during psychomotor agitation is often associated with high titration rates and parenteral therapies, and therefore increases the risk of NMS [15]. In our population, NMS occurred within a mean interval of 7 days (range, 24 hours–30 days), all doses were standard, and the parenteral route was only used in 20% of the cases. Therefore, NMS can occur at any time during treatment, even with standard doses, and regardless of the route of administration. Other risk factors have been reported, such as advanced age, comorbid medical conditions, mental retardation, history of NMS, and personal and/or family history of catatonia [16].

Regardless of the trigger mechanism (dopaminergic antagonism, dysautonomia, direct muscle toxicity of NL, etc.), the physiopathology of NMS is complex and involves a cascade of dysfunctions in multiple neurochemical and neuroendocrine systems, leading to end-stage hypermetabolic syndrome [8,17-19]. NMS is classically [1] characterized by four cardinal signs: hyperthermia, muscular rigidity, dysautonomia, and altered mental status. Neuropsychic syndrome usually precedes the systemic symptoms. Muscle rigidity can be generalized and could be symmetric (opisthotonos) or focal (blepharospasm, oculogyric crisis, and trismus). NMS hyperthermia usually presents high body temperatures, with no major peaks or fluctuations, no shivering, and unresponsiveness to conventional antipyretics. However, the clinical presentation of NMS can be heterogeneous and challenging (Table 5) [13,20-23]. Cases of NMS without muscle rigidity have

Table 4. Univariate analysis of risk factors for mortality in the NL malignant syndrome cases (n=20)

Parameter	Death (n=2)	Recovery (n=18)	*P*-value
Age (yr)	71.5±16.3 (60–83)	32.7±15.8 (18–84)	0.004
Male sex	2 (100)	14 (78)	0.630
Mean time to consultation (day)	0.5±0.7 (0–1)	1.5±1.5 (0–5)	0.360
Admission from domicile	1 (50)	5 (27.7)	0.520
Duration of NL treatment (day)	7.0±1.4 (6–8)	9.1±7.9 (1–30)	0.710
GCS on admission	13.00	13.64±1.49 (10–15)	
Heart rate on admission (beats/min)	85.00±7.07 (80–90)	98.88±24.92 (56–140)	0.450
Diastolic blood pressure (mmHg)	80.00±14.14 (70–90)	78.05±11.77 (60–100)	0.450
Systolic blood pressure (mmHg)	130.00±14.14 (120–140)	138.61±24.24 (90–200)	0.630
Temperature (°C)	37.65±0.92 (37–38.3)	38.11±1.06 (35–39)	0.560
Dysautonomia	0	13 (72.2)	0.110
Rigidity	2 (100)	16 (88.8)	0.800
Quick SOFA score	1.00±1.00 (0–2)	0.88±0.75 (0–2)	0.830
Sachdev rating scale	12.50±1.50 (11–14)	11.00±3.19 (3–14)	0.520
CPK (IU/L)	21,964.00±29,282.70 (1,258–42,670)	2,904.00±4,265.86 (626–19,176)	0.005
CPK-mb (IU/L)	647.50±846.40 (49–1,246)	86.72±71.45 (24–327)	0.002
WBC count ($\times 10^3/mm^3$)	9.70±1.97 (8.38–11.17)	11.31±5.04 (4.89–25)	0.660
AST (IU/L)	366.00±376.18 (100–632)	71.22±62.84 (17–296)	0.002
ALT (IU/L)	148.50±136.47 (52–245)	41.72±33.71 (10–155)	0.006
Creatinine (mg/L)	102.00±134.35 (7–197)	8.55±2.22 (5–14)	0.001
Blood urea nitrogen (mg/L)	2.45±3.02 (0.29–4.60)	0.33±0.28 (0.09–1.23)	0.002
Prothrombin (%)	56.50±9.19 (50–63)	87.05±8.72 (69–100)	0.000
Platelet ($\times 10^3/mm^3$)	97.00±29.69 (76–118)	246.05±78.25 (147–444)	0.017
Blood potassium (mmol/L)	4.80±2.80 (2.8–6.8)	3.86±0.54 (2.7–5.1)	0.152
NL discontinuation time (day)	2.0±1.4 (1–3)	2.9±1.3 (0–6)	0.367
Mechanical ventilation	2.0 (100)	2 (11.11)	0.030
Hemodialysis	1 (50)	0	0.100
Pulmonary infection	0	3 (16.6)	0.710
Thromboembolic complication	0	0	
ICU stay (day)	3.50±2.12 (2–5)	10.83±16.11 (1–67)	0.538

Values are presented as mean±standard deviation (range) or number (%).
NL, neuroleptic; GCS, Glasgow coma scale; SOFA, Sequential Organ Failure Assessment; CPK, creatine phosphokinase; CPK-mb, creatine phosphokinase-myoglobin binding; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine aminotransferase; ICU, intensive care unit.

been reported in the literature [24,25] as well as in this study (10% of the sample). Other extrapyramidal motor symptoms, such as tremor, chorea, akinesia, mutism, dysarthria, dysphagia, and other dystonic movements, may guide the diagnosis, but they are inconstant and non-specific. Approximately 20% of the patients had dysphagia or mutism, while hyperthermia was reported in only 65%. Apyretic NMS cases can be explained by the early diagnosis of NMS and/or a delayed onset of hyperthermia when compared to early symptoms such as rigidity [21]. Non-typical presentations are mostly associated with atypical NLs [26]. This is consistent with our study findings, where in the absence of rigidity and hyperthermia were observed respectively in 25% and 50% of the cases using atypical NLs compared to 0% and 33.3% of the cases using conventional NLs.

Although no biomarkers are specific, laboratory assessment is necessary to support the diagnosis of NMS by excluding other diagnoses and to assess complications. Rigidity and hyperthermia lead to muscle damage and rhabdomyolysis (elevated CPK levels and myoglobinemia) with a risk of hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, heart rhythm disturbances, disseminated intravascular coagulation, and renal failure [27]. The CPK level is considered both a diagnostic and prognostic marker of NMS (especially if CPK >1,000 IU/L), as well as a monitoring factor to assess the course and effectiveness of the treatment (kinetics). A mild or no increase in the CPK level may be idiopathic or related to the early stages of NMS, where rigidity

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Table 5. Heterogeneity of the clinical-biological presentation of neuroleptic malignant syndrome in different studies

Study	Country	Cohort size (no. of cases)	Hyperthermia (%)	Muscular rigidity (%)	Mental status alteration (%)	Diaphoresis (%)	Mutism (%)	Tachycardia (%)	Tremor (%)	Dysphagia (%)	Elevated blood pressure(%)	Hypotension (%)	Blood pressure lability (%)	Urinary incontinence (%)	Hypersalivation (%)	Leukocytosis (%)	High CPK levels (%)
This study	Morocco	20	65	90	65	10	20	40	15	15	50	5	20	0	20	55	100
Sahin et al. [13]	Turkey	18	100	94.4	83.3	83.3	83.3	72.2	61.1	55.6	50	16.7		27.8			100
Tural et al. [20]	Turkey	36	100	100	100	86.1	61.1	80.6	41.7	52.8			55.6	44.4	25	75	83.3
Levenson [21]	USA	53	98	89	84	67		91	45				74	21		79	97
Gupta et al. [22]	India	15	100	100	100	26.6			93.3		13.3		86.7				100
Lang et al. [23]	Germany	390	87.7	85.9	35.6	43.6	32.1	62.1	26.9	14.8			41.5	14.6		38.2	70.5

CPK, creatine phosphokinase.

is absent or poorly developed and maybe associated with physical restraint and intramuscular injections, especially in catatonic psychotic patients. Leukocytosis with or without inversion of the formula is also common because of sympathetic hyperactivation even in the absence of infection [27].

The 2017 study by Gurrera et al. [28] showed that the 2011 consensus diagnostic criteria [29] incorporated in DSM-5 were superior to those of DSM-IV [30] but required clinical validation. The DSM-IV, Nierenberg scale, and Sachdev rating scale confirmed the diagnosis of NMS in only 55%, 65%, and 85% of our cases, respectively (Table 2). The DSM-5 consensus (Table 1) [4] does not require major and minor criteria and seems more likely to identify non-typical NMS presentations. It seemed appropriate to base the NMS diagnosis on the DSM-5 criteria in our daily practice. NMS is an exclusion diagnosis, even with well-defined diagnostic criteria [11]. Patients taking NLs may present a pathological condition unrelated to their usual drug use, and some differential diagnoses are potentially life-threatening, including meningoencephalitis, epilepsy, toxic or septic encephalopathy, malignant hyperthermia, heat stroke, serotonin syndrome, and malignant catatonia [31]. Brain scan, lumbar puncture, toxicological screening, electroencephalogram, and metabolic and infection testing may be necessary to rule out disorders that are more critical. Some differential diagnoses are less known to intensivists and require expertise and multidisciplinarity. In fact, NMS can easily be confused with other dysautonomia diseases (serotonin syndrome, malignant catatonia, or clozapine-induced hyperthermia) where rigidity, hyperpyrexia, dysautonomia, and polymedications are common. In our series, SSRIs were used in 15% of the cases at non-toxic doses in combination with NLs. Serotonin syndrome is related to selective toxicity of SSRIs but is characterized by tremor, hyper-reflexia, myoclonus, ataxia, more gastrointestinal symptoms (diarrhea, nausea, and vomiting), less rigidity, and hyperthermia [32]. Malignant catatonia is characterized by prodromal behavioral symptoms (psychosis, agitation, and catatonic excitement) and motor symptoms (dystonia, waxy flexibility, and repetitive stereotyped movements). Because catatonia symptoms are present in NMS too, distinguishing between the two is difficult [23]. Clozapine-induced hyperthermia, a known and variable side effect of clozapine, is considered a clinical presentation of NMS by some authors [33].

The severity of NMS is associated with the onset of life-threatening complications related to the physiopathology of the disease, long ICU stay, and immobility [3,31]. The Sachdev rating scale [34] allows for the diagnosis of NMS, severity assessment, and follow-up. A total score >8 and a score ≥ 2 in at least three of the six categories establish the diagnosis of NMS. Other complica-

tions not considered in the Sachdev rating scale are addressed in the organ failure scores usually used in intensive care and emergency settings, i.e., the quick-Sequential Organ Failure Assessment (SOFA) and SOFA scores. The quick-SOFA score is an easily reproducible clinical score in an emergency setting with a significant prognostic value. It includes three items: hypotension (systolic blood pressure ≤100 mmHg), high respiratory rate (≥22 breaths/min), and altered consciousness (Glasgow coma scale score ≤14). The SOFA score is used for the severity assessment and follow-up of critically ill patients in daily practice. The Sachdev rating scale requires further clinical validation in various populations and more demanding assessment, but it could be an interesting follow-up marker in the ICU setting.

Treatment must be initiated as soon as NMS is suspected [31]. These patients require monitoring and intensive care, which cannot be provided in the psychiatric ward. Both delayed diagnostic and therapeutic management and inadequate management settings have been recognized as the prognostic factors for morbidity and mortality [3]. This observation in our practice has led to a close collaboration between the two departments of psychiatry and emergency/intensive care that involves emergency care training for psychiatrists, multidisciplinary meetings, and rigorous transfer regulation of suspected cases of NMS. Considered a prognostic factor [3], the causal psychotropic treatment was discontinued in all our patients as soon as NMS was suspected. Resuscitation measures and specific therapies are shown in Table 6 [3,31,35,36]. Given the rarity of NMS and the acute nature of its onset, the current recommendations are based on a low level of evidence. Randomized controlled trials are lacking, and the main treatment guidelines are based on case studies, meta-analyses, or expert opinions [36]. In addition, recommendations must be adapted to the local specificities. Dantrolene [37,38] is a muscle relaxant antagonist of the ryanodine-1 receptors of striated muscles and is recommended in hypermetabolic forms of NMS (hyperthermia and rigidity). None of our patients was administered dantrolene, as it was unavailable. The central active dopaminergic agonists (bromocriptine, amantadine, or levodopa) have been reported to reduce the recovery time and mortality [38]; however, these molecules are used outside marketing authorization, and the treatment duration is not defined. ECT stimulates serotoninergic and dopaminergic neurotransmission and is currently the gold standard in cases non-responsive to specific pharmacological treatments [11,36]. However, the following imperatives need to be clarified: definition of pharmacological treatment failure, electrode positioning, and the intensity, frequency, and duration of sessions. Current guidelines recommend 6–10 bilateral ECT sessions [39]. It is performed under general anesthesia, and its requirements include pre-anesthetic assessment, optimal anesthetic platform, vigilance, and anesthesiologist-operator communication. Some anesthetic agents should be used with caution. Sevoflurane, succinylcholine, or their combination is associated with malignant hyperthermia; hence ,they should be avoided. The current availability of sugammadex makes rocuronium an interesting alternative to succinylcholine [40]. ECT is performed a tour center under sedation without intubation, but none of our patients received it as a treatment for NMS.

The reintroduction of psychotropic treatment in patients who need it but are at a risk of NMS recurrence is a real dilemma for clinicians. Recurrence risk is unpredictable, and relapse rates are highly variable [41]. When reintroduction is considered, the following recommendations [2,42] are essential to minimize the recurrence risk without canceling it: interval of at least 2 weeks, complete resolution of symptoms, use of different and less powerful molecules, avoiding lithium and parenteral therapies, slower titration schemes, prevention of dehydration, and close monitoring. Long-term ECT appears to be an interesting alternative. In our study, the reintroduction of NLs was performed in six patients (30%), using atypical molecules at low doses after a therapeutic interval of 15 days. No adverse events were reported.

Mortality rates in NMS range from 5% to 20%; death occurs most often in the course of multivisceral failure secondary to complications of NMS, mainly renal [2,3,13,43]. The main prognostic factors observed are acute renal failure, respiratory failure, sepsis, advanced age, and CPK levels [2,3,13,44]. The mortality rate in our study was 10%, and the deaths were related to rhabdomyolysis and renal failure. Advanced age, renal, hepatic, and hematological failure, as well as mechanical ventilation were significantly associated with mortality in our study based on the univariate analysis. Daily assessment of the SOFA score should be performed, and treatment that is more aggressive should target elderly and frail patients, especially those with limited physiological and nephronic reserves. Most episodes usually resolve within 2 weeks, but prolonged cases with residual catatonia and motor signs have been reported [42]. Recovery was longer in one of our cases, as it was complicated by meningeal hemorrhage [45]. Risk factors for the worsening of NMS include the use of conventional antipsychotic drugs and the presence of underlying structural brain pathologies. Most patients do not develop neurological sequelae, except in cases of severe hypoxia or prolonged hyperthermia [42]. This implies the importance of temperature control and optimization of oxygenation in NMS patients. These patients are considered to have brain injury, and management of secondary cerebral systemic aggressions is necessary. Interestingly, our patients' outcomes are consistent with those reported in the litera-

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Table 6. Resuscitation measures and specific therapies recommended in neuroleptic malignant syndrome [3,31,35,36]

Category	Resuscitation and specific therapy
Conditioning and monitoring	• Half-seated position, head at 45°
	• Standard monitoring: heart rate and rhythm, blood pressure, oxygen saturation, temperature, and urinary output
	• Two peripheral venous lines (18–16 gauge) and central venous lines
	• Biology: blood count+platelet count, liver function, renal function, hemostasis, electrolytes (kalemia, calcemia, phosphatemia, and magnesia), glycemia, C-reactive protein, arterial blood gases, lactates, urinary pH, procalcitonin
	• Nasogastric tube in case of swallowing disorder, hypersalivation, or consciousness alteration
	• Standard chest radiography
Fluid resuscitation and renal support	• Crystalloids: saline 0.9%, Ringer's lactate solution
	• 3–6 L/24 hr or more+monitoring
	• Renal objectives: urinary output 2–3 mL/kg/hr and urinary pH >6.5
	• Stop vascular filling in case of oliguria or if blood volume is optimized to avoid risk of overload
	• Avoid nephrotoxicity
	• Avoid colloids
	• Bicarbonates on a case-by-case basis
	• Dialysis
Cooling	• Ambient temperature around 23°C
	• Cooling blankets and ice blocks
	• Chest position elevated at 45° from bed level
Respiratory support	• Oxygen therapy
	• Respiratory kinesiotherapy: postural measures, incentive spirometry, and drainage of bronchial secretions
	• Tracheal intubation and mechanical ventilation
Agitation control	• Avoid restraint as much as possible
	• Benzodiazepines (lorazepam or midazolam): 1–2 mg intravenously every 4–6 hours (maximum 8 mg/day)
Antiarrhythmic and antihypertensive treatment	• Correction of hydroelectrolytic disorders
	• Antiarrhythmic therapies
	• Calcium inhibitors (do not combine with dantrolene)
Prevention of complications related to intensive care unit stay	• Stress ulcer prevention
	• Pharmacologic and/or mechanical thromboembolic prophylaxis
	• Prevention of decubitus complications: regular position changes, anti-bedsore mattress, motor kinesiotherapy, and early mobilization
	• Prevention of metabolic complications: energy intake based on 5% glucose serum with electrolytes+nutritional management: enteral (oral or by nasogastric tube) and/or parenteral administration
Specific therapy	• Bromocriptine 2.5–5 mg every 8 hours (oral or nasogastric tube) or amantadine 100 mg every 8 hours (oral or nasogastric tube)
	• Dantrolene 1 mg/kg every 4–6 hours intravenously for 48 hours (maximum 10 mg/kg/day)
	• Electroconvulsive therapy as second line therapy

ture, and no "antidotal" therapy was given to any patient. This highlights the importance of early diagnosis and supportive treatment in resource-limited settings where specific treatments are not available. However, early initiation of specific treatment, if available, may have affected the outcome of the deceased patients. Analysis of the predictive factors of mortality was not possible given the limited number of patients in the "death" group; however, through univariate analysis, this study identified the important complications that require close monitoring. The stated conclusions need to be verified using larger samples in future multicentric studies. Another limitation of the retrospective nature of this study is the lack of long-term follow-up of all the patients.

In conclusion, NMS is a diagnostic and therapeutic neuropsychiatric emergency. It requires clinical, multidisciplinary, and dynamic expertise to avoid overlooking atypical forms or differential diagnoses. The use of more flexible diagnostic criteria is essential to detect atypical forms, which are more frequent with second-generation antipsychotics and non-psychotropic drugs. The identification of prognostic factors specific to our context could improve the management, but this would require large national

multicentric cohorts for research. Nevertheless, advanced age, high CPK levels, and renal failure are the potential factors to be considered in future studies, and they require the clinician's full consideration during management. Finally, this study allowed us to update and contextualize our bedside procedures (Supplementary Material 1).

ARTICLE INFORMATION

Ethics statement

This study was approved by the local Institutional Review Board of Comite d'Ethique Hospitalo-Universitaire de Fes (IRB No. 16/21), and the need for informed consent from patients was waived.

Conflict of interest

No potential conflict of interest relevant to this article.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.18700/jnc.210019.

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Bilateral posterior cerebral artery stroke following transtentorial herniation caused by a subependymal giant cell astrocytoma in a patient with tuberous sclerosis: a case report

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CASE REPORT

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Background: Acute increased intracranial pressure (IICP) is a life-threatening condition that requires urgent treatment. Rapid IICP with hydrocephalus may be complicated by ischemic stroke, convulsions, loss of consciousness, brain herniation, and death. Extremely rare complications include intracranial vessel entrapment and ischemic stroke due to sudden IICP in cases with benign tumors.
Case Report: We report a case of bilateral posterior cerebral artery region infarction and complicated hydrocephalus with subependymal giant cell astrocytoma in a patient with tuberous sclerosis.
Conclusion: We postulate that the temporary IICP induced by seizure led to transient bilateral posterior cerebral artery entrapment, causing ischemic stroke without vascular occlusion.

Keywords: Tuberous sclerosis; Astrocytoma; Stroke; Intracranial pressure; Hydrocephalus

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder, first described by Bourneville [1]. TSC patients present with three distinct intracranial lesions: subcortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGA) [1,2]. Despite its benign histopathology, SEGA can result in a variety of severe events that may substantially increase the mortality and morbidity of TSC patients [3]. This is due to their preferential proximity to the foramen of Monro, which can get blocked during tumor growth, causing obstructive hydrocephalus [4]. Obstructive hydrocephalus can be complicated by convulsions, loss of consciousness, brain herniation, and death [5].

Usually, SEGA grows very slowly, rarely inducing acute increased intracranial pressure (IICP), which can be life threatening [6]. Intracranial vessel compression induced by IICP in SEGA patients has not been reported. We report a rare case of acute bilateral occipital lobe infarction due to SEGA presenting with acute obstructive hydrocephalus.

CASE REPORT

A 33-year-old man was brought to the emergency room (ER) with altered mental status. He had a history of recurrent seizures and mental retardation related to TSC first diagnosed at the age of 17 years, when contrast-enhanced T1-weighted imaging revealed a 1.4×0.9-cm^2 intraventricular tumor (Fig. 1A). The patient visited the hospital frequently with generalized seizures and changes in mental status. At the age of 31 years, he developed decreased appetite, fatigue, somnolence, and projectile vomiting. T1-enhanced images revealed a 4×6.1×5.5-cm^3 well-defined mass in the midline of the lateral ventricle (Fig. 1B). Fluid-attenuated inversion recovery imaging revealed marked ventricular dilatation with a high-signal halo around the lateral ventricles, suggesting

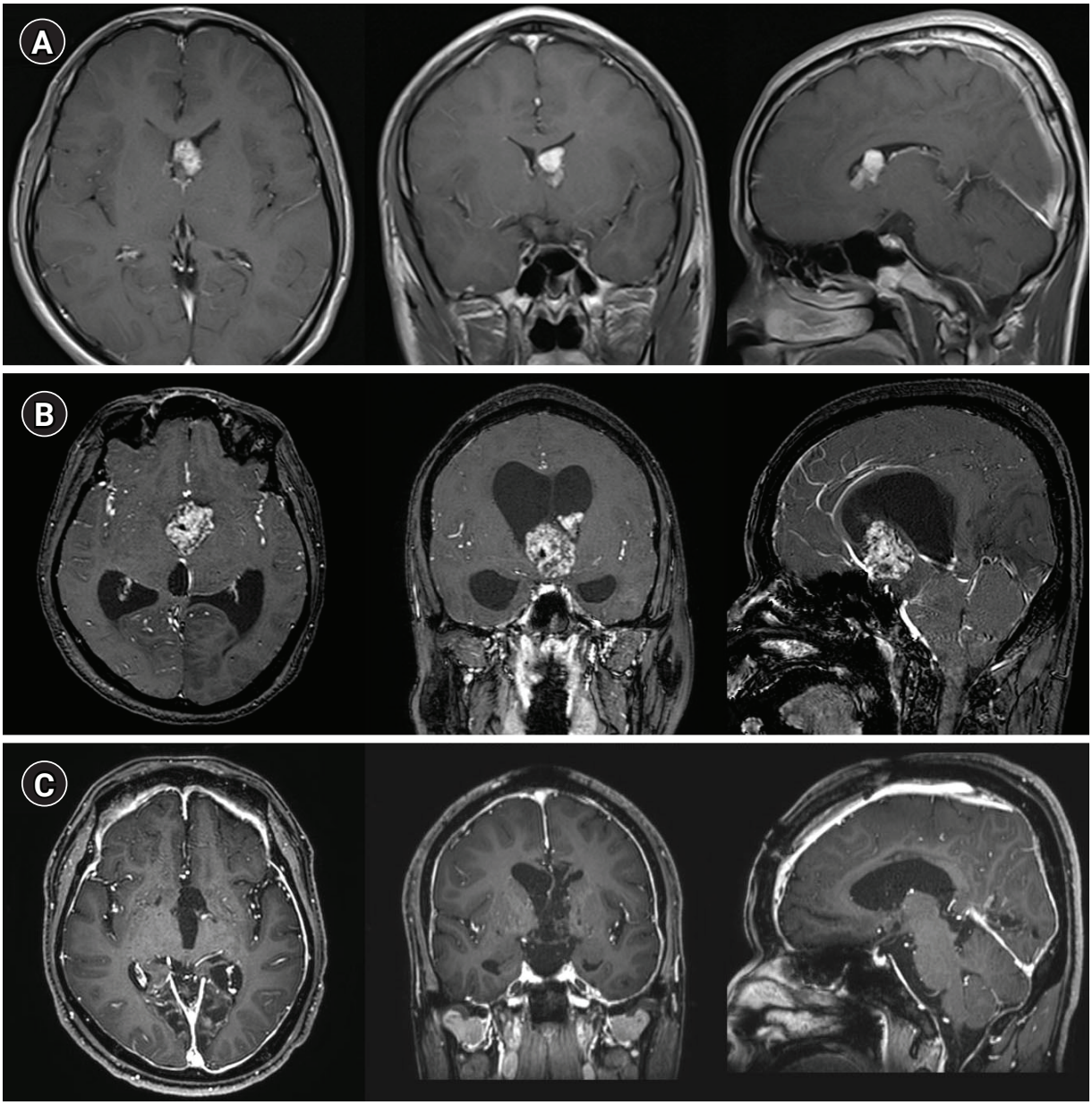

Fig. 1. (A) The axial/coronal/sagittal contrast-enhanced T1-weighted sequence from 16 years earlier showed a solid homogeneous lesion in the left lateral ventricle, extending toward the foramen of Monro without hydrocephalus. (B) Immediately preoperatively, the contrast-enhanced T1-weighted sequence showed marked heterogeneous enhancement and proximal aqueduct occlusion with marked hydrocephalus. Coronal and sagittal magnetic resonance imaging images showed marked dilatation of the lateral and third ventricles, with a normal-sized fourth ventricle. Note the downward bowing of the third ventricle floor with expanded infundibular and optic recesses. (C) Postoperative contrast-enhanced T1 axial scans showed no residual tumor with marked meningeal enhancement.

hydrocephalus. Marked growth of the ventricular lesion was noted.

The patient's symptoms usually improved after seizure control. This time, however, there was failure of recovery of consciousness after monitoring in the ER for 3 hours. At the time of admission, his blood pressure was slightly elevated at 150/90 mmHg, but other vital signs were normal. A neurological examination revealed that the patient was stuporous and unable to open his eyes on command. There was no apparent limb weakness and he showed an avoidance response to painful stimuli. Both pupils were 5 mm in diameter and showed decreased light reactivity. Direct ophthalmoscopy suggested papilledema with no evidence of disc cupping or atrophic changes. Diffusion-weighted imaging showed diffusion restriction of both occipital lobes suggesting acute ischemic stroke (Fig. 2A). Digital subtraction angiography showed maintained patency and normal caliber of both posterior cerebral arteries (PCAs) without significant perfusion defect (Fig. 2B).

The patient was diagnosed with bilateral occipital lobe infarction due to obstructive hydrocephalus and referred to neurosurgery. First, a ventriculoperitoneal shunt was inserted in the ER to relieve the IICP. The patient underwent a bifrontal craniotomy, and the tumor was exposed via an interhemispheric transchoroidal approach. The mass originated from the anterior wall of the third ventricle and extruded into the left lateral ventricle via the foramen of Monro. The mass was yellow to pinkish with moderate vascularity. Gross total resection was achieved after identifying the opening of the cerebral aqueduct.

Histological evaluation of the mass led to the diagnosis of SEGA. Hematoxylin and eosin staining showed large polygonal cells resembling astrocytes or ganglion cells. The tumor cells had abundant, finely granular eosinophilic cytoplasm with large round to oval nuclei and prominent nucleoli (Fig. 3A and B). Immunohistochemistry was positive for S-100 and glial fibrillary acidic protein (Fig. 3C and D). A 12-lead electrocardiogram, transthoracic echocardiogram, and heart rhythm monitor during the intensive care unit admission were normal. There was no significant evidence of hypercoagulable state in the initial young age stroke evaluation. On discharge from the hospital, the patient had recovered all symptoms except for cortical blindness. One year postoperatively, magnetic resonance imaging (MRI) showed complete resection of the SEGA and resolution of the hydrocephalus (Fig. 1C). However, the visually evoked potential was still absent in both eyes. Despite patency of the PCAs, the visual loss did not show recovery.

DISCUSSION

SEGA is a low-grade astrocytoma that arises within the cerebral ventricles in patients with TSC [3] . Although SEGA can occur in the absence of TSC, it quite frequent in TSC, occurring in 5%–20% of TSC cases [2]. It is generally benign, as the lesions grow slowly and rarely infiltrate the adjacent brain tissue [4]. However, in case of uncontrolled hydrocephalus, TSC may lead to progressive obstructive hydrocephalus and transtentorial herniation [7]. Although the related symptoms are usually mild and can be relieved by emergency shunt insertion, acute IICP can be fatal [6].

The distinguishing feature of our case was that the flow in both

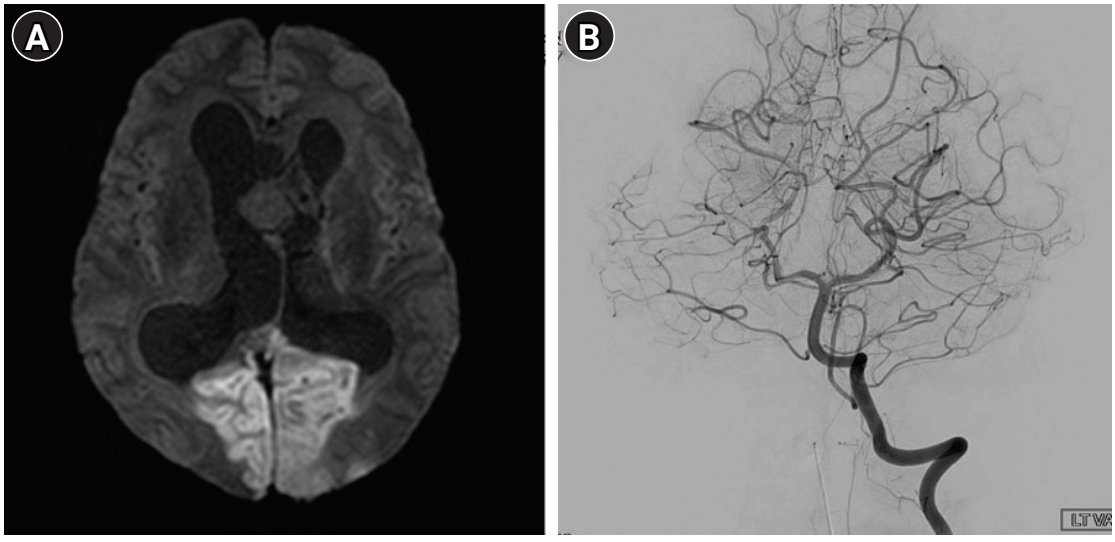

Fig. 2. (A) Diffusion-weighted image showed hyperintensity suggesting acute ischemic stroke in the region of the bilateral posterior cerebral artery (PCA). (B) Conventional angiography showed patency of the lumens of both PCAs, which have normal diameters.

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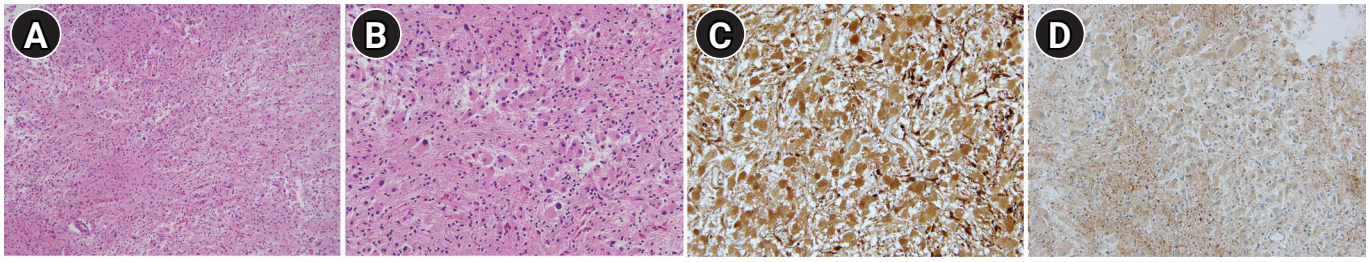

Fig. 3. (A, B) Microscopically, the tumor comprised mainly of large polygonal cells resembling astrocytes or ganglion cells. The tumor cells have abundant, finely granular eosinophilic cytoplasm with large round to oval nuclei and prominent nucleoli (H&E, A: ×100, B: ×200). (C, D) Tumor cells show positive immunoreactivity for S-100 and glial fibrillary acidic protein (immunohistochemical stain, ×200).

PCAs was maintained after an irreversible ischemic stroke. Considering the growth rate of SEGA, the entrapment or compression of intracranial vessels by transtentorial herniation is extremely rare. This suggests that other factors contributed to the temporary deterioration following IICP. Recurrent seizures are common in patients with TSC, with a reported prevalence of 62%–93% [4]. Excessive IICP in TSC patients is thought to cause and exacerbate seizure attacks, and several studies have suggested that seizures can lead to transient rapid IICP [8].

Therefore, it is theoretically possible that seizures and IICP may exacerbate each other. The cerebral infarction in both PCAs without definite arterial occlusion on conventional angiography suggests a temporary interruption during the instantaneous IICP associated with seizure. Consequently, the interaction between the bilateral rostrocaudal descent and horizontal midline shift led to compression of both PCAs [7].

The enlarged lateral ventricle independently worsened the compartment pressure via the "accordion" effect [9]. The combined forces associated with the midline shift and ventricular enlargement resulted in descent of the medial temporal lobe, causing impingement of the PCA on the rigid tentorial edge. In this process, acute IICP in hydrocephalus most often involves the PCAs [9]. Considering the anatomical course of the PCAs as they pass back up over the medial edge of the tentorium, ischemic stroke related to hydrocephalus may develop in the PCA region rather than the anterior circulation [10]. The cause of extension of the infarcted lesion limited medial occipital lobe was probably associated with collateral flows of anterior circulation and, the direction of PCAs. More medially developed PCAs have been presumed to affect the medial occipital lobe during arterial entrapment.

No case of hydrocephalus and IICP caused by SEGA leading to ischemic stroke has been reported previously. The differentiation of epilepsy from an IICP crisis is not always obvious, but is mandatory. Careful neurological examination and MRI, including diffusion imaging and gadolinium enhancement, are crucial examinations during differential diagnosis, and both should be included in the diagnostic protocol of stroke with the slightest sign of brain tumor. Patients presenting with TSC with SEGA causing obstructive hydrocephalus is an extremely rare cause of ischemic stroke associated with malignant IICP.

ARTICLE INFORMATION

Ethics statement

Ethics approval from Institutional Review Board of Jeju National University Hospital was granted in accordance with national requirements (IRB No. 2021-12-011), and the need for written informed from a patient was waived.

Conflict of interest

No potential conflict of interest is relevant to this article.

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Successful treatment with rituximab in a patient with lupus cerebritis and posterior reversible encephalopathy syndrome: a case report

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CASE REPORT

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Background: Neuropsychiatric systemic lupus erythematosus (NPSLE) has a diverse and broad spectrum of severity and prognosis, with some devastating manifestations. However, its diagnosis and treatment remain unclear and controversial.
Case Report: A 19-year-old woman with SLE presented with fever, headache, quadriparesis, and tremor. Brain magnetic resonance imaging (MRI) showed sulcal enhancement in the cortical sulcus, and intravenous methylprednisolone (500 mg/day) and immunoglobulin (2 g/kg for 5 days) were started under the suspicion of aseptic lupus meningitis. However, the patient's neurologic symptoms worsened; brain MRI showed a newly developed brain parenchymal lesion, suggesting lupus cerebritis and posterior reversible encephalopathy syndrome. Two cycles of rituximab (850 mg/day, 1-week interval) were administered for the treatment of refractory NPSLE. Her neurologic symptoms gradually improved after the second cycle, and she was discharged with minimal neurologic symptoms.
Conclusion: Rituximab may be a therapeutic option for refractory lupus cerebritis. Further research is needed to accurately determine its efficacy.

Keywords: Neuropsychiatric systemic lupus erythematosus; Posterior reversible encephalopathy syndrome; Rituximab

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect any organ in the body. Neuropsychiatric involvement in SLE is common, and its estimated prevalence ranges from 37% to 95% [1]. The diagnosis of neuropsychiatric SLE (NPSLE) was proposed by American College of Rheumatology in 1999 for 19 categories of NPSLE that included central nervous system manifestations, such as aseptic meningitis, cerebrovascular disease, demyelinating disease, headache, movement disorder, myelopathy, seizure disorder, cognitive dysfunction, mood disorder, and psychosis, as well as peripheral nervous system manifestations, such as acute inflammatory demyelinating polyradiculoneuropathy, autonomic disorder, mononeuritis, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy [2]. More recently, neuropsychiatric syndromes such as cerebral venous thrombosis, posterior reversible encephalopathy syndrome (PRES), optic neuritis, progressive multifocal leukoencephalopa-

thy, and idiopathic intracranial hypertension have been added to the classification of NPSLE [3,4]. As stated above, the clinical manifestations of NPSLE are diverse and heterogeneous, and NPSLE remains a diagnostic and therapeutic challenge [3]. Furthermore, the occurrence of similar phenomena because of steroid treatment or concomitant diseases such as hypertension and hyperlipidemia makes the diagnosis of NPSLE more difficult [4].

Lupus cerebritis is a poorly defined disease entity, described by some researchers as a former term for NPSLE [3]. However, others have referred the evidence of cerebral parenchymal damage with cerebrospinal fluid (CSF) inflammation in the absence of stroke and vasculitis as lupus cerebritis [5]. Herein, we report a severe case of lupus cerebritis that was treated successfully with rituximab.

CASE REPORT

A 19-year-old woman presented to the emergency department with fever, headache, nausea, quadriparesis, and tremor. She had been diagnosed with SLE 19 months previously with the findings of discoid rash, non-erosive arthritis, leukopenia, low complement level, positive anti-dsDNA, positive anti-Smith antibody, and negative antiphospholipid antibodies, and she was treated with oral prednisolone at a dose of 15 mg/day and hydroxychloroquine at a dose of 200 mg/day. She had been experiencing inattention, anxiety, insomnia, compulsive behavior (frequent hand washing), tremor, and apraxia for 10 days before admission. Neurologic examination revealed decreased muscle strength in all extremities (Medical Research Council [MRC] grade 4) with normoactive deep tendon reflexes. She also had bulbar symptoms such as dysarthria, dysphagia, and dysphonia accompanied by jaw weakness. Initial brain magnetic resonance imaging (MRI) showed normal fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 1A) with sulcal enhancement in cortical sulcus and cerebellar folia on FLAIR enhancement study (Fig. 1B). Laboratory findings showed leukopenia (3,000/mm^3), normal platelet count (211,000/mm^3), increased erythrocyte sedimentation rate (56 mm/hr), normal C-reactive protein level (< 0.3 mg/dL), negativity for antiphospholipid antibodies, anti-dsDNA antibody negativity, and normal complement level (C3, 94 mg/dL; C4, 19.4 mg/dL), indicating rather low disease activity. CSF analysis revealed normal opening pressure (120 mmH_2O), increased white blood cell count (9/mm^3), elevated protein level (93 mg/dL), and lower glucose level (69 mg/dL) compared to serum glucose level (126 mg/dL). Under the suspicion of aseptic meningitis due to SLE, methylprednisolone was started at a dose of 500 mg/day; however, 2 days after starting methylpred-

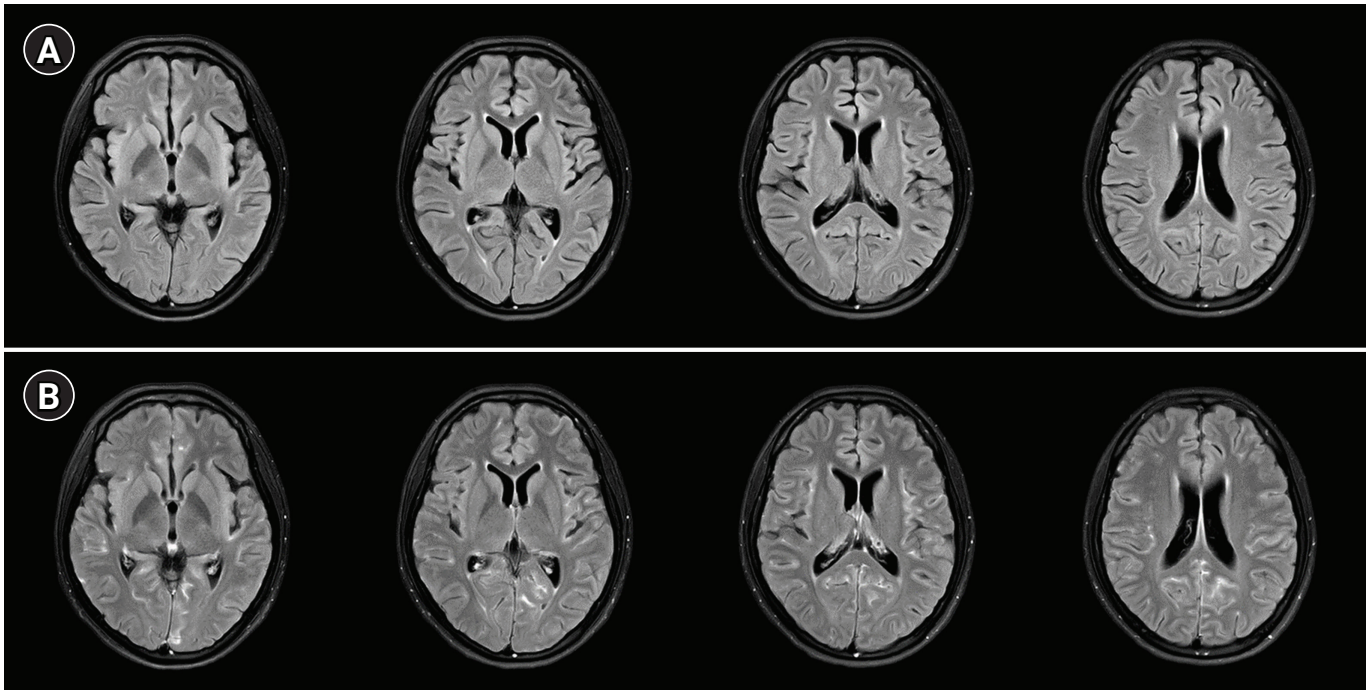

Fig. 1. Initial brain magnetic resonance imaging. (A) Fluid-attenuated inversion recovery (FLAIR) image revealed no abnormal signal intensities. (B) FLAIR-enhanced image revealed multifocal sulcal enhancement in the cortical sulcus, suggesting lupus meningitis.

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nisolone, her tremor and the weakness of the extremities worsened, and she was treated with intravenous immunoglobulin (2 g/kg/day) for 5 days along with steroid. On the fifth day of immunoglobulin administration, her vital signs became unstable; blood pressure increased to 153/129 mmHg, and pulse rate increased to 160 beats per minute without improvement of the neurologic symptoms. Additional brain MRI revealed high signal intensities in the occipital region on T2 and FLAIR imaging, suggesting PRES, as well as focal high signal in the right basal ganglia. Moreover, no basal ganglia lesion was observed on diffusion-weighted imaging and normal angiography. These findings suggested the diagnosis of lupus cerebritis and PRES induced by the disease itself or immunoglobulin (Fig. 2). She received symptomatic treatment for hypertension and tachycardia. Simultaneously, she was treated with two cycles of rituximab (850 mg/day for 8 hours) with an interval of 1 week for the newly developed lesions. Although there was no clear improvement in the patient's neurological findings after the first cycle of rituximab, the tremor and weakness of the extremities and bulbar muscles gradually improved after the second cycle. Twenty days after the last rituximab treatment, she was discharged with improved neurological and psychiatric symptoms (Fig. 3). At 3-month follow-up, brain MRI showed a complete reversal of the occipital and basal ganglia signals (Fig. 4), and she resumed normal daily activity.

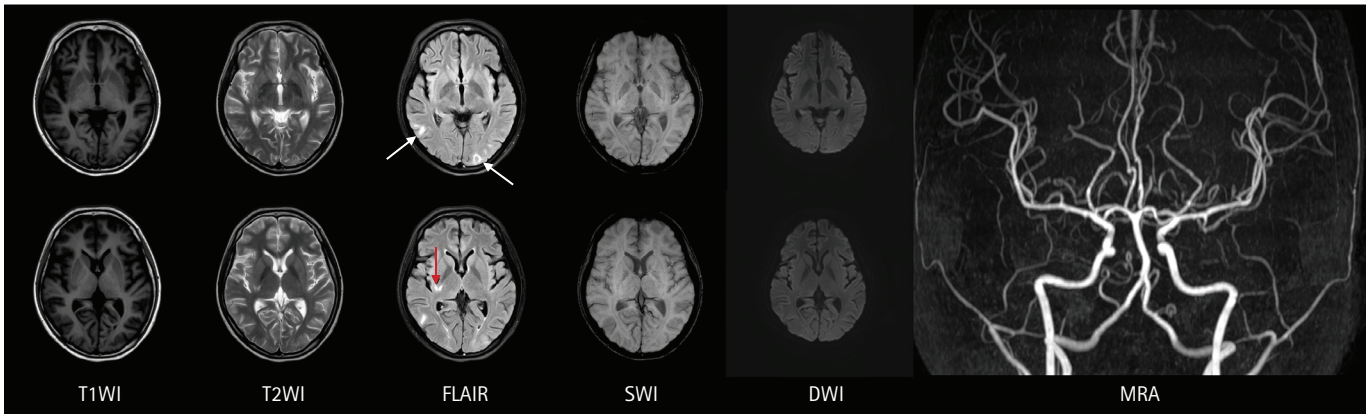

Fig. 2. Brain magnetic resonance imaging after intravenous methylprednisolone and immunoglobulin treatment. Fluid-attenuated inversion recovery (FLAIR) image revealed possible posterior reversible encephalopathy syndrome (white arrows) and possible lupus cerebritis in the right basal ganglia region (red arrow). Diffusion weighted imaging (DWI), susceptibility-weighted imaging (SWI), and time-of-flight magnetic resonance angiography (MRA) showed no evidence of ischemic and hemorrhagic vascular lesions.

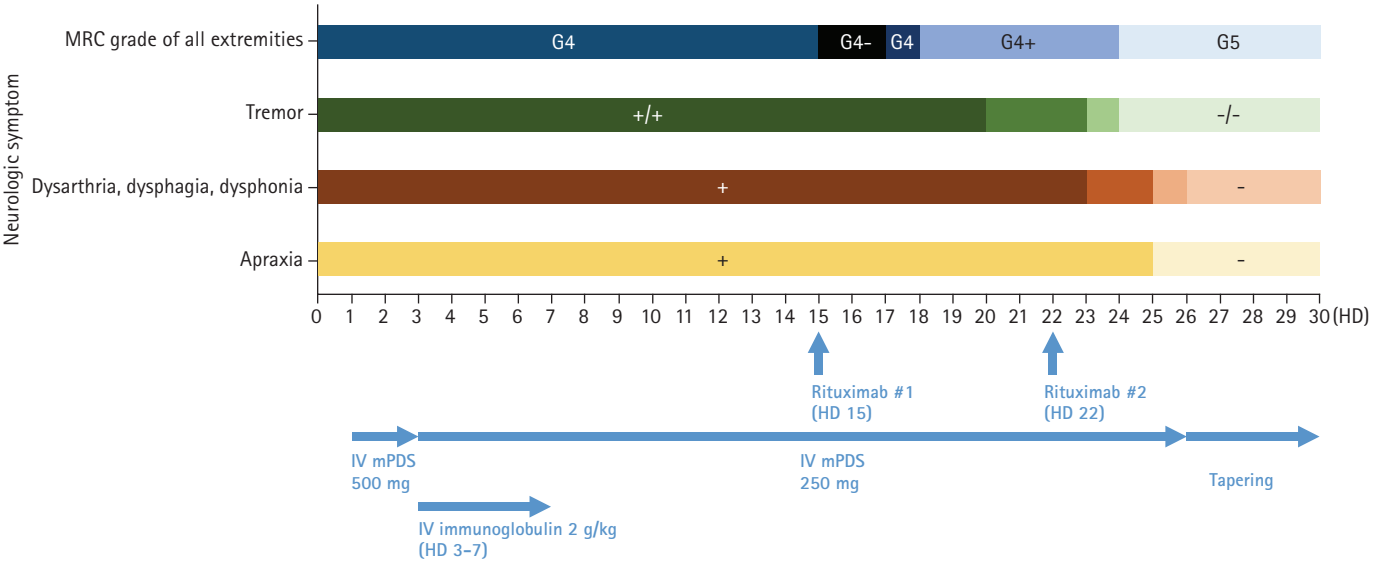

Fig. 3. Clinical course of the patient. MRC, Medical Research Council; HD, hospital day; IV, intravenous; mPDS, methylprednisolone.

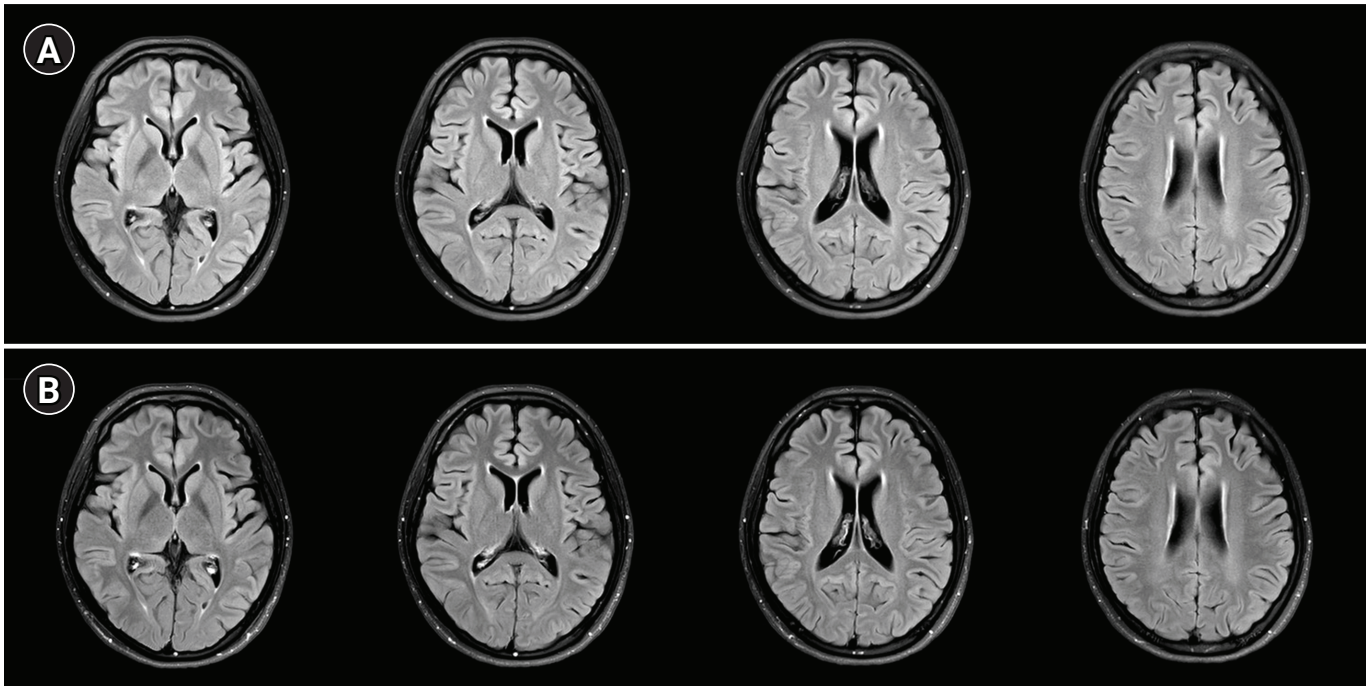

Fig. 4. Brain magnetic resonance imaging performed 3 months after rituximab treatment. Fluid-attenuated inversion recovery (FLAIR) image (A) and FLAIR-enhanced image (B) showed no abnormalities.

DISCUSSION

Here, we present the case of a young woman with lupus cerebritis and PRES who had been previously diagnosed with SLE. Unlike intravenous methylprednisolone and immunoglobulin, two cycles of intravenous rituximab successfully reversed her neurologic and psychiatric symptoms. Furthermore, her radiologic abnormalities along with neuropsychiatric symptoms were completely reversed 3 months after symptom onset.

Neuropsychiatric involvement in patients with SLE has been directly linked to SLE (primary NPSLE) or to other factors such as medicines, systemic diseases, and concomitant psychiatric disorders (secondary NPSLE) [6]. Although the pathogenesis of primary NPSLE is not fully understood, immune or inflammation-mediated blood brain barrier disruption with active generalized disease (inflammatory NPSLE) and thrombotic cerebrovascular disease with antiphospholipid antibody (thrombotic NPSLE) have been suggested to cause primary NPSLE [7,8]. Nevertheless, it is important to manage neuropsychiatric manifestations in SLE patients because they are associated with increased risk of death and worse functional outcome [9,10]. However, the diagnosis of NPSLE remains challenging even for experienced physicians because there is no specific biomarker for NPSLE. Therefore, researchers have attempted to developed various models or algorithms involving disease activity, imaging techniques, and CSF examinations to assist clinicians in diagnosing NPSLE [11]. Our patient was simultaneously diagnosed with lupus cerebritis (primary NPSLE) and PRES (secondary NPSLE) based on clinical findings, brain MRI, and CSF examination. Although rituximab is considered as second-line therapy for inflammatory NPSLE that shows no clinical response to methylprednisolone [4,12], it was more common and easier to use intravenous immunoglobulin, which is consider as third-line therapy for inflammatory NPSLE, in our hospital. However, in this case, intravenous immunoglobulin was not effective, and it might have induced PRES. Nevertheless, we anticipated that immunotherapy against lupus cerebritis and symptomatic treatment with blood pressure lowering for PRES would reverse the patient's neuropsychiatric symptoms, and this proved to be the case.

The treatment of NPSLE is challenging, and no specific guidelines for the treatment of NPSLE have been established. This could be due to the obscure and complex pathophysiology of NPSLE as well as the fact that well-designed clinical studies are limited by small sample sizes [13]. Nevertheless, it is most important to diagnostically decide whether the neuropsychiatric symptoms are caused by primary NPSLE and the dominant category of NPSLE (inflammatory vs. thrombotic). An inflammatory cause is considered in case of young patients , NPSLE occurrence close to the time of SLE diagnosis, increased lupus activity or

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flare, antiphospholipid antibody-negative patients, worsening neuropsychiatric symptoms, NPSLE relapses, and abnormal results of CSF examination and brain MRI , and immunosuppressive treatment is recommended in such cases [13]. In inflammatory NPSLE, the first-line treatment of choice is high dose intravenous methylprednisolone. A randomized clinical trial demonstrated that intravenous cyclophosphamide (0.75 g/m^2) combined with methylprednisolone was more effective than intravenous methylprednisolone alone [14]. However, because cyclophosphamide is difficult to use and has many side effects, physicians generally hesitate to use it. Despite the lack of evidence from randomized clinical trials, B-cell depleting agents (rituximab; an anti-CD20 monoclonal antibody) are widely used to successfully treat refractory NPSLE in patients who do not respond to first-line therapy [15]. In this case, the patient's clinical symptoms also gradually improved to complete remission after two cycles of rituximab separated by an interval of 1 week (Fig. 4). Her brain MRI findings also improved 3 months after rituximab therapy.

Accurate diagnosis and treatment of NPSLE are crucial for managing every neuropsychiatric event in patients with SLE. Rituximab may be an effective treatment for refractory inflammatory NPSLE.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Institutional Review Board of Hanyang University Hospital (IRB No. HYUH 2021-10-015). Informed consent from a patient was waived by the IRB.

Conflict of interest

No potential conflict of interest relevant to this article.

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Which one to do first?: a case report of simultaneous acute ischemic stroke and myocardial infarction

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CASE REPORT

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Background: Although there are common risk factors for acute ischemic stroke and myocardial infarction, simultaneous onset of both diseases is uncommon. Here, we present a case of acute cerebral infarction with concurrent fatal myocardial infarction.
Case Report: A 54-year-old man presented with left hemiparesis, gaze preponderance to the right side, and visual and tactile extinction. Computed tomography angiography showed occlusion of the right middle cerebral artery. ST-elevation myocardial infarction was suspected on electrocardiography. After the injection of intravenous tissue plasminogen activator, thrombectomy was attempted first, and the coronary angiogram was planned after recanalization of the cerebral artery. However, thrombectomy was discontinued because of cardiac arrest. Despite extracorporeal membrane oxygenation and emergency percutaneous coronary intervention, the patient died of multiorgan failure.
Conclusion: Double primary acute ischemic stroke and myocardial infarction are rare but may be fatal due to the narrow therapeutic time window for both diseases. Careful consideration of the urgency of cardiac status is essential.

Keywords: Ischemic stroke; Myocardial infarction; Thrombectomy; Percutaneous coronary intervention; Cardiocerebral ischemic attack

INTRODUCTION

Acute ischemic stroke (AIS) and acute myocardial infarction (AMI) are life-threatening conditions that may lead to permanent morbidity or disability. Although there are many shared risk factors [1-3], simultaneous onset of both AIS and AMI is uncommon. In such rare circumstances, physicians are left with a dilemma of treating one condition may delay the treatment of the other condition. Here, we present a case of acute cerebral infarction that occurred concurrently with fatal AMI at the same time.

CASE REPORT

A 54-year-old man presented to the emergency room with left hemiparesis. Neurologic examination further showed gaze preponderance to the right side, central type left facial palsy, and visual and tactile extinction. He did not show asomatognosia or anosognosia. The National Institutes of Health Stroke Scale score was

17. The neurological deficit was first detected by a witness who reported him to the police because he had been driving his car and scratching the median strip. He was a smoker and had been taking medications for hypertension and diabetes mellitus. Brain computed tomography (CT) showed a focal low density in the right insula, corona radiata, and temporal lobe (Fig. 1A), and CT angiography showed occlusion of the M1 segment of the right middle cerebral artery (Fig. 1B). In the CT perfusion image, the T_{max} value was increased in the right middle cerebral artery and posterior cerebral artery territory due to the fetal posterior cerebral artery (Fig. 1C). Because he was alert and denied having any neurological symptoms when he started driving at 16:00, intravenous tissue plasminogen activator (tPA) was injected at 18:35. The door-to-needle time was 59 minutes. Initial electrocardiogram showed ST-segment elevation in leads II, III, and aVF with reciprocal ST depression in V_5 and V_6, suggesting acute inferior myocardial infarction (Fig. 2A). Although initial creatinine kinase (CK) and CK-myocardial band were within the normal range, troponin-I was elevated to 0.130 ng/mL and N-terminal-pro hormone B-type natriuretic peptide was elevated to 1,859 pg/mL. Endovascular thrombectomy (EVT) of the thrombus in the right middle cerebral artery was attempted first, planning the coronary angiogram after the recanalization of the cerebral artery, since the patient was alert and did not report any chest pain. However, thrombectomy was stopped without recanalization due to cardiac arrest during the procedure. Electrocardiography revealed a pulseless ventricular tachycardia. After cardiopulmonary resuscitation for 21 minutes, extracorporeal membrane oxygenation was performed. An emergency coronary angiogram showed a culprit lesion in the right coronary artery (Fig. 2B), with other coronary ar-

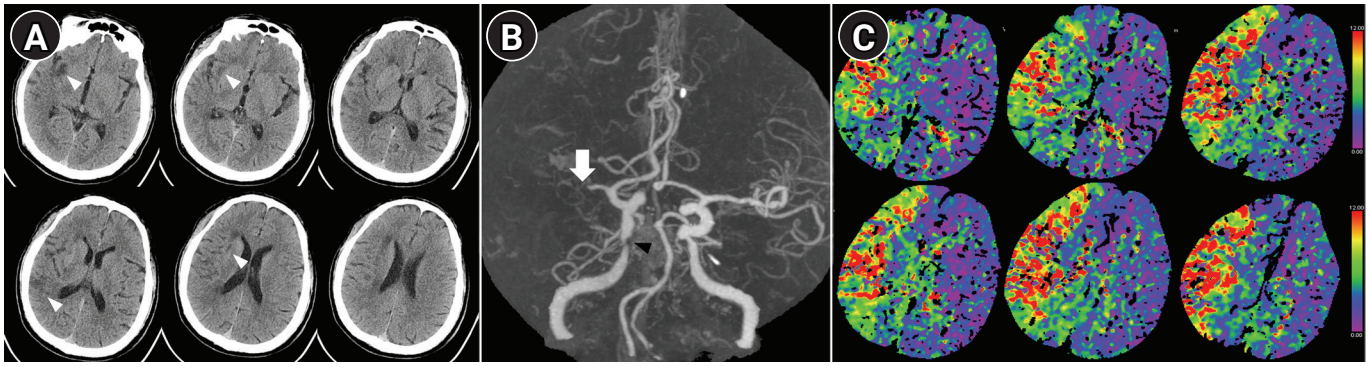

Fig. 1. (A) Brain computed tomography without enhancement demonstrates low density in the right insula, corona radiate, and temporal lobe (white arrowheads). Sulcal effacement is also noted in right frontal and temporal lobe. (B) Brain computed tomography angiogram demonstrates occlusion of the M1 segment of the right middle cerebral artery (white arrow). Severe stenosis is also noted in the right distal internal carotid artery (black arrowhead). (C) Perfusion image shows increased T_{max} value in the right middle and posterior cerebral artery territory.

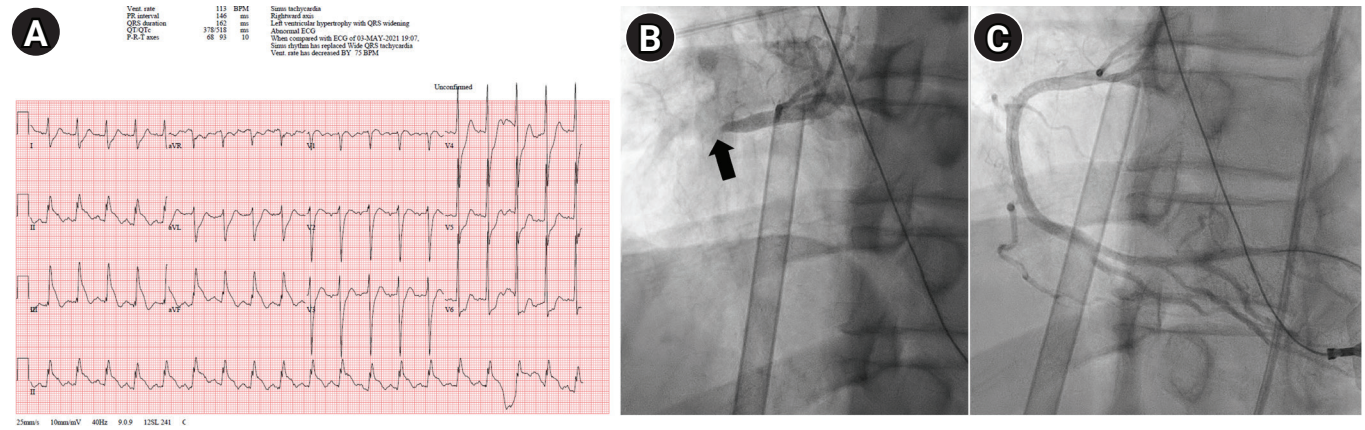

Fig. 2. (A) Electrocardiogram shows ST-segment elevation in II, III, and aVF with reciprocal ST depression in V_5 and V_6, suggesting acute inferior myocardial infarction. (B) Emergency coronary angiogram shows the culprit lesion in the right coronary artery before stenting (black arrow). (C) After percutaneous coronary intervention, recanalization of right coronary artery is achieved.

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teries remaining intact. Percutaneous coronary intervention (PCI) was performed for the occluded right coronary artery to achieve recanalization of the right coronary artery (Fig. 2C). Despite intensive medical care for 5 hours with inotropic agents, the patient died after gradual blood pressure drop and progression of multi-organ failure.

DISCUSSION

Concurrent AIS and AMI, in other words, a cardiocerebral ischemic (CCI) attack, is an infrequent but a challenging medical condition [4,5]. The mechanism of this life-threatening situation is unclear and may be multifactorial, from the increased risk of intracardiac thrombus formation due to left ventricular systolic dysfunction, to catecholamine-induced myocardial stunning due to the adrenergic surge associated with cerebral infarction, especially in the insular cortex [6,7]. Moreover, there have been several case reports of CCI attacks in special circumstances, such as aortic dissection, electrical injury, marijuana abuse, or underlying acute myeloid leukemia [8-10]. In some cases, a CCI attack may also occur due to atherosclerosis in the cerebral and coronary arteries, respectively [11].

Regardless of the mechanism, a CCI attack may be fatal because the treatment of both AIS and AMI has a narrow therapeutic time window. The acute treatment of one condition can result in a critical delay in the other treatment. Although intravenous alteplase injection may be helpful for both cerebral and myocardial infarction, intra-arterial reperfusion therapy for the cerebral artery prior to PCI can cause a delay in PCI, even leading to cardiac arrest, as in the present case. Meanwhile, PCI prior to cerebral reperfusion therapy can increase the risk of a large cerebral infarction, which can cause severe neurological deficits, cerebral edema, and even death. Moreover, the use of antiplatelets, which are essential after PCI, may be harmful when the cerebral infarction is too large, with a substantial risk of hemorrhagic transformation [5,11].

Despite such important clinical needs, there are no evidence-based guidelines or clinical studies on the management of the co-occurrence of AIS and AMI, especially in the priority of the treatment [7]. Most of the recent studies on CCI are case reports or case series describing various cerebral and myocardial infarct territories, heterogeneous timing and modalities of treatment, and consequent various outcomes [12,13]. Omar et al. [5] reported the case of a 48-year-old patient with inferior-posterior and right ventricular AMI concomitant vertebra-basilar territory AIS, who was treated with tPA and conservative management, and expired on the second day of hospital stay. In contrast, Yeo et al. [4] reported the case of a 53-year-old patient who was treated with PCI and stenting first, followed by EVT. The patient survived with aphasia and disability that required a wheelchair. In such case reports, the choice of treatment varies from conservative management with antithrombotics to aggressive management, such as PCI and EVT.

Because PCI and EVT are becoming more available these days, the choice of treatment for CCI is becoming more complex. A single-center case series reported that among nine patients who presented with synchronous onset of AMI and AIS, one patient underwent PCI, another patient underwent intravenous thrombolysis, and the others only received conservative management, leaving six survivors [13]. Meanwhile, in a meta-analysis of case reports and series describing the patient characteristics, investigations demonstrated, treatments, and outcomes [14], 10 out of the 44 enrolled patients died within a median of 2 days, despite the aggressive treatment of PCI with stenting in 15 patients, PCI without stenting in eight patients, thrombectomy of a coronary vessel in eight patients, and EVT in 10 patients. Even with emergent and aggressive treatments, the prognosis of CCI is still devastating. Moreover, the optimal order of PCI and EVT remains unclear.

Guidelines for the early management of patients with acute ischemic stroke, updated in 2019, recommend intravenous alteplase at the dose used for cerebral ischemia followed by PCI for hyperacute co-occurrence of AIS and AMI (class IIa; level of evidence C) [15]. However, the dosage needed for the management of AMI differs from that used in the treatment of AIS [12,13]. Moreover, tPA can increase the risk of cardiac wall rupture or tamponade in patients with AMI. Due to the lack of optimal treatment guidelines, careful consideration of the urgency of the cardiac status and tailored treatment strategies are essential in patients with simultaneous AIS and AMI. According to a case series report, most CCI patients (83%) presented only with neurological deficits without chest pain [13], as in our case. A high level of suspicion is necessary to improve the recognition and management of patients with CCI. Emergency bedside echocardiography can be helpful in evaluating cardiac function and deciding the order of treatment. Further large observational studies and randomized trials are need to be conducted in order to recommend the optimal treatment for this subset of patients.

ARTICLE INFORMATION

Ethics statement

In accordance with the principles of the Institutional Review Board (IRB) of National Health Insurance Service Ilsan Hospital that a case report of three or less cases does not require IRB ap-

proval, the need for IRB approval and informed consent from a patient was waived.

Conflict of interest

No potential conflict of interest relevant to this article.

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Journal of Neurocritical Care

Supranuclear oculomotor palsy in cerebral venous sinus thrombosis: a case report

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CASE REPORT

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Background: For certain ocular movement abnormalities, the exact neuroanatomical localization of the causative lesion is still not defined. Oculomotor apraxia, apraxia of eye opening and closing, and motor impersistence are rarely reported in acute stroke, particularly following venous stroke.
Case Report: A 34-year-old man presented with headache, vomiting, focal seizures with bilateral tonic-clonic movements, and altered sensorium. Magnetic resonance imaging revealed bilateral frontal and left parietal hemorrhagic infarcts, and contrast venography revealed superior sagittal sinus thrombosis. The patient received anticoagulant treatment with antiepileptics. On re-examination on day 3, the patient had a rare combination of apraxia of eyelid closure, motor impersistence, and oculomotor apraxia. By Day 10 of admission, all oculomotor abnormalities had subsided.
Conclusion: To the best of our knowledge, this is the first report of the combination of oculomotor apraxia and apraxia of eyelid closure with motor impersistence in a patient with cerebral venous sinus thrombosis.

Keywords: Sinus thrombosis; Apraxia; Frontal lobe

INTRODUCTION

Various eyelid and eye movement abnormalities have been attributed to different central nervous system lesions. Apraxia of eyelid closure (AEC), which is less common than apraxia of eyelid opening, is reported to occur in progressive supranuclear palsy, Creutzfeldt-Jakob disease, Huntington disease, amyotrophic lateral sclerosis, and acquired frontal and parietal lobe diseases such as stroke [1]. We report a case of cerebral venous sinus thrombosis with a rare combination of oculomotor apraxia (OMA) and AEC with motor impersistence (MI).

CASE REPORT

A 34-year-old right-handed man was admitted with a history of

acute onset severe holocranial headache, multiple episodes of vomiting, and focal seizures with bilateral tonic-clonic movements followed by altered sensorium for the past 4 days. There was no preceding history of fever, head injury, or chronic drug intake. The patient had no previous comorbidities. There was no significant family history for any similar illnesses.

On examination, the patient's Glasgow coma scale score was E2V1M4, body temperature 39°C, blood pressure 156/100 mmHg, and respiratory rate 18 per minute with normal oxygen saturation. His pupils were symmetrical and normally reactive to light without papilledema. There were decreased movements of all four limbs with bilateral extensor plantar responses. The remaining findings of the systemic examination were within normal limits.

His complete blood count, blood sugar levels, renal and liver function tests, chest radiography, and electrocardiography results were within normal limits. His D-dimer was 1,146 ng/mL (normal <255 ng/mL). Magnetic resonance imaging (MRI) of the brain revealed heterogeneous hyperintensity in the bilateral frontal and left parietal lobes on T2-weighted/fluid-attenuated inversion recovery images with blooming in susceptibility-weighted images; magnetic resonance venography revealed thrombosis of the anterior two-thirds of the superior sagittal sinus (Fig. 1). The patient was managed conservatively. His seizures were controlled with levetiracetam (1 g twice daily) and lacosamide (100 mg twice daily). He received low molecular weight heparin (100 U/kg) subcutaneous twice daily. Thrombophilia testing was positive for lupus anticoagulant. His serum homocysteine was 59.1 μmol/L (normal <12 μmol/L) and vitamin B12 was 121 pg/mL (normal >200 pg/mL). He was prescribed cyanocobalamin 1,000 μg, thiamine 100 mg, and pyridoxine 100 mg in combination daily for 7 days and then weekly. On day 3 of admission, his Glasgow coma scale score improved to E4V5M6 without any seizure recurrence. On re-examination, he could not comply with commands regarding eye closure, although reflex eye blinking was normal. He was fully conscious, alert, and cooperative, and followed commands such as mouth opening, tongue protrusion, and chewing, including complex multi-step commands. His visual acuity was 6/6 in both eyes, and there were no field defects. He was unable to maintain eyelid closure for more than a fraction of the second, though reflex blinking to visual, auditory, and corneal stimulation was normal, suggestive of AEC with MI. While sleeping, his eyes remained completely closed. In addition, his gaze was restricted in both horizontal and vertical directions, although the doll's eye sign, vestibulo-ocular reflex, compensatory head thrust, and intermittent reflexive saccadic movements in all directions in response to visual stimuli were present, suggesting OMA (Supplementary Video 1). No brainstem lesions were observed on the brain MRI (Fig. 2). Over a period of 1 week, the eyelid and oculomotor movement abnormalities resolved completely.

DISCUSSION

The reported patient presented with acute-onset headache, focal with bilateral tonic clonic seizures, and altered sensorium. MRI brain revealed bilateral frontal and left parietal lesions with superi-

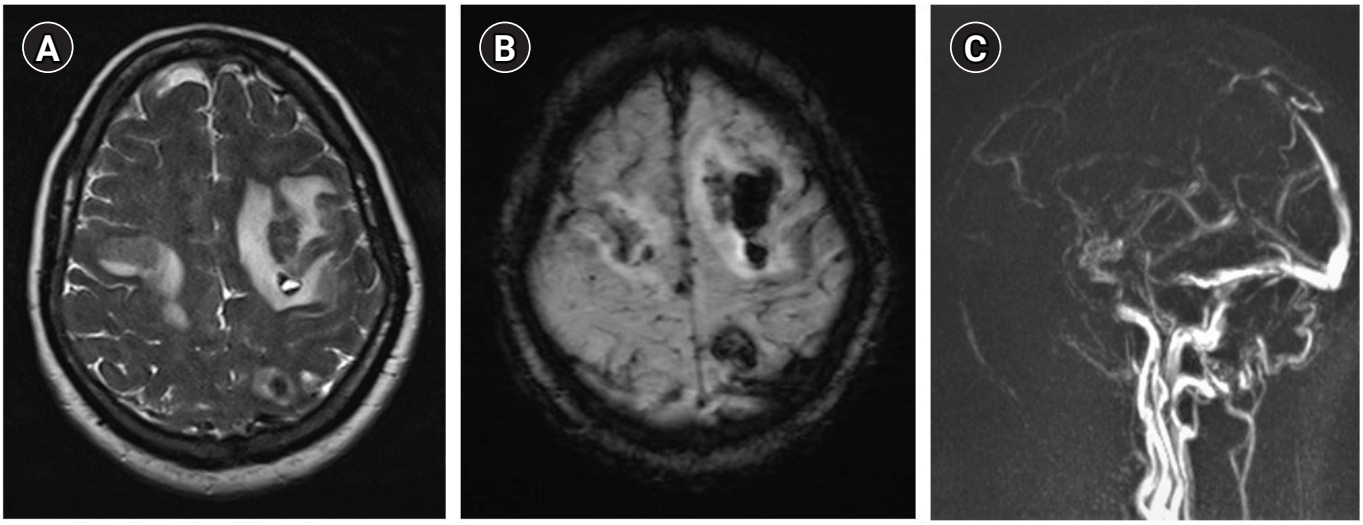

Fig. 1. Magnetic resonance imaging of the patient showing bilateral frontal and left parietal hyperintensity on T2-weighted images (A), blooming at the same sites on susceptibility-weighted images (B) suggestive of hemorrhagic infarct and thrombosis of the anterior two-third of the superior sagittal sinus (C) on contrast venography.

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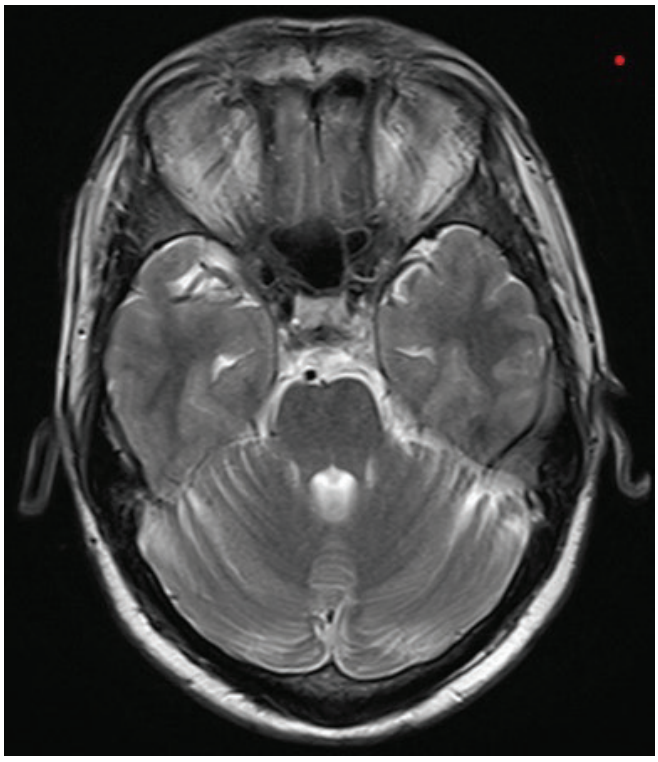

Fig. 2. Magnetic resonance imaging of the patient showing normal parenchyma at the pontine level.

or sagittal sinus thrombosis. Cranial nerve examination revealed a rare combination of OMA and AEC with MI.

The inability to perform voluntary eye closure on command while retaining spontaneous blinking was first described by Roth in 1901 as a "pseudobulbar paralysis" phenomenon and later coined as "apraxia of eyelid closure" by Lewandowsky in 1907 [2]. Which hemisphere is dominant in supranuclear control of eyelid movements is a matter of debate. In a systematic review, Nicoletti et al. described that all 15 patients with unilateral AEC had contralateral lesions, that is, a right hemisphere lesion, whereas a similar hemispheric lesion was observed in 90% (17/19) of patients with bilateral AEC [3]. They also mentioned that, in contrast to apraxia of eyelid opening, where subcortical structures are commonly affected, the frontoparietal cortex is predominantly involved in AEC. Functional MRI of the brain has explored the role of the frontal eye field (FEF), supplementary eye field (SEF), and posterior parietal cortex (PPC) in voluntary eye closure. Voluntary bilateral eye closure (blinking) activates the FEF and SEF but not the PPC. In contrast, voluntary unilateral eye closure (winking) activates a frontoparietal network involving the FEF, SEF, and PPC [4]. In the given case, bilateral AEC was probably due to involvement of the bilateral frontal cortex.

OMA was first described by Cogan [5] as the inability to generate horizontal saccades voluntarily in children with congenital OMA. Later, this abnormality was described in many other congenital and acquired neurological diseases [1]. Voluntary and reflexive saccades are generated in the FEF and interparietal sulcus, respectively. While horizontal saccades are initiated by the contralateral FEF and superior colliculus, vertical saccades are associated with activity in the FEFs and superior colliculi bilaterally [6]. Our patient had impaired horizontal and vertical voluntary saccades due to bilateral FEF involvement.

MI is defined as the inability to sustain a certain position or movement. This symptom was first described by Fisher [7] in patients with right hemispheric stroke. Patients with frontal or subcortical lesions were significantly more likely to demonstrate MI than those with posterior lesions. Moreover, lesions were more common in the right hemisphere than in the left hemisphere, supporting right hemispheric dominance [8,9]. Callosal lesions that disconnect the left hemisphere from right hemisphere inputs have also been associated with impersistence of the right limbs [10]. Our patient had eyelid and OMA with MI. Radiologically, the lesions were also located in the bilateral frontal and left parietal lobes, which are common sites responsible for such abnormalities.

In conclusion, non-motor signs of the eye have been previously reported in other pathologies involving the frontal and parietal cortices. However, to the best of our knowledge, this is the first case report of this combination of OMA and AEC with MI in a patient with cerebral venous sinus thrombosis.

ARTICLE INFORMATION

Ethics statement

Ethical approval for this study was not needed as per institutional ethics policy, as this study is a case report of a single patient and did not include protected health information, data analysis, or testing of a hypothesis. Written informed consent from a patient for the study and the publication was obtained.

Conflict of interest

No potential conflict of interest is relevant to this article.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.18700/jnc.210025.v001.

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Flaccid quadriparesis with raised creatine kinase in Guillain–Barré syndrome: a case report with review of literature

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CASE REPORT

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Background: Guillain-Barré syndrome (GBS) is an immune-mediated inflammatory polyneuropathy characterized by acute flaccid paralysis. Elevated creatine kinase (CK) levels in GBS have been reported to be transient, and levels vary from mild to severe. Herein, we report a case of GBS with elevated CK mimicking acute myositis.
Case Report: A 48-year-old man presented with pure motor flaccid quadriparesis. Power was 2/5 with hypotonia and areflexia in all four limbs. A nerve conduction study revealed reduced compound muscle action potential in all recorded motor nerves. Serum CK was 2,334 IU/L. The patient's symptoms progressed despite intravenous methylprednisolone administration. Cerebrospinal fluid (day 8) revealed albuminocytological dissociation, and electromyography (day 21) revealed spontaneous activity with neurogenic motor unit action potential suggestive of acute motor axonal neuropathy variant of GBS.
Conclusion: In a patient with elevated CK and ascending paralysis, differential diagnosis of GBS should be considered and cerebrospinal fluid study and electromyography should aid in confirming the diagnosis.

Keywords: Guillain-Barre syndrome; Flaccid quadriparesis; Creatine Kinase; Intravenous immunoglobulin

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute and fulminant polyradiculoneuropathy that is autoimmune in nature and characterized by acute flaccid paralysis, with or without sensory abnormalities. GBS is predominantly classified as demyelinating and axonal types. The three common subtypes are acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN) [1]. Creatine kinase (CK) catalyzes the breakdown of creatine and adenosine triphosphate into phosphocreatine and adenosine diphosphate [2]. This reaction is an essential step in cellular metabolism. CK can be elevated in various neuromuscular diseases, such as spinobulbar muscular atrophy, amyotrophic lateral sclerosis, and post-polio syndrome [3]. While cerebrospinal fluid (CSF) abnormalities in GBS are well known, serum abnormalities have also been reported. Although uncommon, one such serum abnormality is elevated CK levels. The level of CK in GBS may vary from mild to moderate depending on the severity of the illness [4-10]. Here, we report a case of GBS with elevated CK mimicking acute myositis.

CASE REPORT

A 48-year-old man presented with complaints of dull aching pain in the left calf muscle for the past 4 days. The next morning, he noticed weakness of both lower limbs while getting up from the squatting position. Twelve hours later, he also developed difficulty in raising his arms above his head, buttoning and unbuttoning his shirt and slippage of his slippers. Over the next 2 days, the patient became bedbound. He had occasional episodes of palpitations and diaphoresis. The patient did not complain of diplopia, chewing, or swallowing difficulty. There was no history of sensory, bowel, or bladder disturbances. He had an upper respiratory tract infection 6 days prior to the onset of illness, which subsided with symptomatic treatment.

He had a significant past history of ascending quadriparesis 3 years back, preceded by tingling sensations in both lower limbs. Later, he developed bulbar and respiratory muscle weakness. The patient was placed on mechanical ventilation and received a full course of intravenous immunoglobulin (IVIG). He was discharged after 1.5 months and had full functional recovery at the end of 3 months. There was no history of type 2 diabetes mellitus, hypertension, thyroid disorder, or coronary artery disease. History of trauma, toxin exposure, illicit drugs, or alcohol abuse was absent.

On examination (present admission), the patient was afebrile with a pulse rate of 72 beats per minute, blood pressure of 140/80 mmHg (no postural drop), respiratory rate of 18 breaths/min, and single breath count (SBC) was 14. No muscle tenderness was observed. The cardiovascular, respiratory, and abdominal examinations were normal. On neurological examination, he was conscious and oriented, and the cranial nerves were normal. Power was 2/5 at the shoulder, elbow, and wrist joints in the upper limbs and hip, knee, and ankle joints in the lower limbs with hypotonia and areflexia in all four limbs. The sensory examination results were normal.

Laboratory parameters revealed normal hemogram, renal and thyroid function tests. Random blood sugar 147 mg/dL, serum potassium 4.3 mEq/L (range, 3.5–4.5 mEq/L), alanine aminotransferase 138 IU/L (normal, 10–40 IU/L) and aspartate aminotransferase 127 IU/L (normal, 10–40 IU/L) with normal bilirubin levels were observed. Serum CK level was 2,334 IU/L (normal, 24–195 IU/L). The vasculitic profile, including antinuclear antibody, rheumatoid factor, anti-Ro, La, and angiotensin-converting enzyme levels were normal. Motor nerve conduction studies showed reduced compound muscle action potential with mild changes in distal latency, conduction velocity, and F-waves over the bilateral median and ulnar motor, common peroneal nerve, and posterior tibial nerves. The sensory nerve conduction studies were normal (Table 1). Serology for dengue, scrub typhus, and malaria was negative.

Considering a provisional diagnosis of acute myositis, intravenous methylprednisolone was initiated. However, the patient's symptoms progressed over the next two days. Power in the limbs was reduced to flicker movements and dyspnea was observed. SBC reduced to 10. Autonomic dysfunction was also observed in the form of tachypnea, diaphoresis, fluctuation in pulse rate, and blood pressure. Blood sugar levels also increased secondary to steroid infusion (random blood sugar, 390 mg/dL). CSF analysis done on the 8th day of onset of illness revealed elevated protein (63.5 mg/dL; range, 15–45 mg/dL) without pleocytosis. Hence, a final diagnosis of the AMAN variant of GBS was made. The patient was started on IVIG (2 g/kg over 5 days). His SBC improved gradually to 25 with improvement in autonomic symptoms and dyspnea over a period of 7 days, although he needed antihypertensives and subcutaneous insulin for a short period. The repeat serum CK level on day 20 was 192 IU/L. On day 21 of illness, electromyography (EMG) of the biceps and vastus lateralis revealed fibrillations and positive sharp waves with large amplitude and long duration polyphasic motor unit action potential (MUAP) with poor recruitment and incomplete interference suggestive of neurogenic MUAP, further confirming the diagnosis. The Hughes disability score at discharge was 2.

DISCUSSION

The present study reported a case of flaccid quadriparesis with elevated CK levels, mimicking acute myositis. CSF revealed albuminocytological dissociation, and EMG revealed spontaneous activity with neurogenic MUAP, which confirmed the diagnosis of GBS. Another unique feature of this case was recurrence of GBS, which is a rare phenomenon, occurring in only 2%–5% of cases. The exact pathophysiology of elevated CK in GBS remains poorly understood. Rapid and extensive denervation changes following severe axonal degeneration of motor nerve terminals might cause hyperexcitability of adjacent muscles and subsequent intramuscular CK release [4].

Table 2 highlights the published cases in the literature on GBS with hyperCKemia with/without other manifestations [4-10]. Satoh et al. [7] reported a case of cramping pain with prolonged elevation of serum CK levels in a patient with GBS. Saxena et al. [8] reported a patient with severe GBS and rhabdomyolysis. In a retrospective study of 72 patients, transient hyperCKemia in GBS was significantly associated with male sex and non-demyelinating electrodiagnostic subtype, but not with other clinical features, in-

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Table 1. Nerve conduction study of all four limbs of the case at the time of admission

Nerve	Stimulation site	Latency (ms)	Amplitude[a]	Conduction velocity (m/s)	F-wave (ms)
Right					
Median motor	D	3.9	3.2	49	32
	P	7.3	3		
Ulnar motor	D	3.4	3.4	50	34
	P	6.3	3.1		
Common peroneal	D	5.8	1.2	42	58
	P	10.9	0.9		
Tibial	D	5.9	2	40	58
	P	11.8	1.7		
Left					
Median motor	D	4.5	2.8	48	33
	P	7.9	2.3		
Ulnar motor	D	3.5	2.2	49	34
	P	7.2	1.9		
Common peroneal	D	6.2	1.5	41	59
	P	10.3	1.3		
Tibial	D	5.3	2.5	43	58
	P	12.5	2.1		
Right					
Median sensory		2.4	18	55	
Ulnar sensory		2.0	15	65	
Sural		2.6	13	46	
Left					
Median sensory		2.7	16	53	
Ulnar sensory		2.1	17	64	
Sural		2.3	12	46	

D, distal; P, proximal.
[a]Motor amplitude in millivolts, sensory in microvolts.

Table 2. Published literatures of GBS cases with raised CK levels

Study	No. of patients	Age (yr)	Sex (male:female)	CK level (IU/L)	CK measured from the day of onset of illness (day)	GBS variant (no. of patients)	Treatment given (no. of patients)
Ropper et al. (1984) [4]	29 (11 patients had raised CK)	NA	NA	141	NA	NA	NA
Scott et al. (1991) [5]	1	25	1:0	10,150	2	AMSAN	Plasmapheresis
Hanemann et al. (1999) [6]	1	49	1:0	817	3	AMAN	IVIG
Satoh et al. (2000) [7]	1	21	1:0	1,917	39	AMAN	Plasmapheresis+IVIG
Saxena et al. (2014) [8]	1	24	1:0	7,002	23	AMSAN	None
Choi et al. (2020) [9]	72 (Raised CK in 12)	59 (20–80)	10:2	996 (346–3,656)	8 (1–52)	Axonal (4)	IVIG (10)
						Equivocal (5)	None (2)
						Demyelinating (1)	
						Normal (2)	
Hosokawa et al. (2020) [10]	51 (Raised CK in 14)	41.2±10.2	12:2	612.1±459.1	11.1±7.3	AMAN	IVIG (11)
				431 (288-1,937)	10 (2-25)		IVIG+steroid (1)
							IVIG+plasmapheresis (1)
							None (1)
This study	1	48	1:0	2,334	4	AMAN	IVIG

Values are presented as median (range) or mean±standard deviation.
GBS, Guillain-Barré syndrome; CK, creatine kinase; NA, not available; AMSAN, acute motor and sensory axonal neuropathy; AMAN, acute motor axonal neuropathy; IVIG, intravenous immunoglobulin.

cluding disability or the nature of pain [9]. In another study of 51 patients, GBS patients with elevated CK levels represented a group of AMAN, and elevated CK tended to occur during the acute phase of AMAN following upper respiratory tract infection [10].

Elevated CK in a quadriparetic patient indicates muscle involvement. However, muscle injury may be secondary to severe denervation in acute motor neuropathy, which may be the primary pathology, as in our case, and EMG becomes imperative before planning any treatment decision. The optimal timing of electrodiagnostic studies in such a scenario would be 3–4 weeks after the onset of illness. EMG will provide more diagnostic information, as spontaneous activity will be more apparent.

In conclusion, this case highlights that in a patient with elevated CK and ascending paralysis, a diagnosis of GBS should be kept in mind, and CSF study and EMG should be performed to aid in the confirmation of the diagnosis.

ARTICLE INFORMATION

Ethics statement

Ethical approval for this study was not needed as per Institutional Ethics Policy as this study is a case report of a single patient and did not include protected health information, data analysis, or testing of a hypothesis. Written informed consent from a patient was obtained.

Conflict of interest

No potential conflict of interest relevant to this article.

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Posterior reversible encephalopathy syndrome as delayed neurological sequelae after carbon monoxide intoxication

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IMAGES IN NEUROCRITICAL CARE

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A 27-year-old woman attempted suicide and was diagnosed with acute carbon monoxide (CO) poisoning. Neurological examinations were normal except for confusion. Initial brain images showed no acute lesions (Fig. 1A) on the next day of admission. Twelve days after CO intoxication, severe headache, choreic movement of both upper extremities, and impaired visual acuity with optic ataxia, oculomotor apraxia, and simultanagnosia were observed. Cerebrospinal fluid findings showed pleocytosis (white blood cell, 135/mm^3) with elevated protein level (134.8 mg/dL). From the follow-up brain magnetic resonance imaging, she was diagnosed with posterior reversible encephalopathy syndrome (PRES) as delayed neurologic sequelae (DNS) after CO intoxication (Fig. 1B). With steroid pulse therapy, she had clinical improvement (Fig. 1C). During the acute phase of CO poisoning, brain MRI shows signal changes in the bilateral globus pallidus (GP) with cytotoxic edema [1]. PRES shows distinctive MRI findings of the parieto-occipital lesions with either vasogenic or cytotoxic edema or both [2]. A patient with DNS with PRES was reported without GP involvement [3]. However, in this case, DNS after CO intoxication affected not only the basal ganglia but also the parieto-occipital regions as PRES. Therefore, it is the reason that the patient presented with both chorea and Balint's syndrome simultaneously.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Institutional Review Board of Hanyang University Hospital (IRB No. 2021-10-012). The need for informed consent from a patient was waived by the IRB.

Conflict of interest

No potential conflict of interest relevant to this article.

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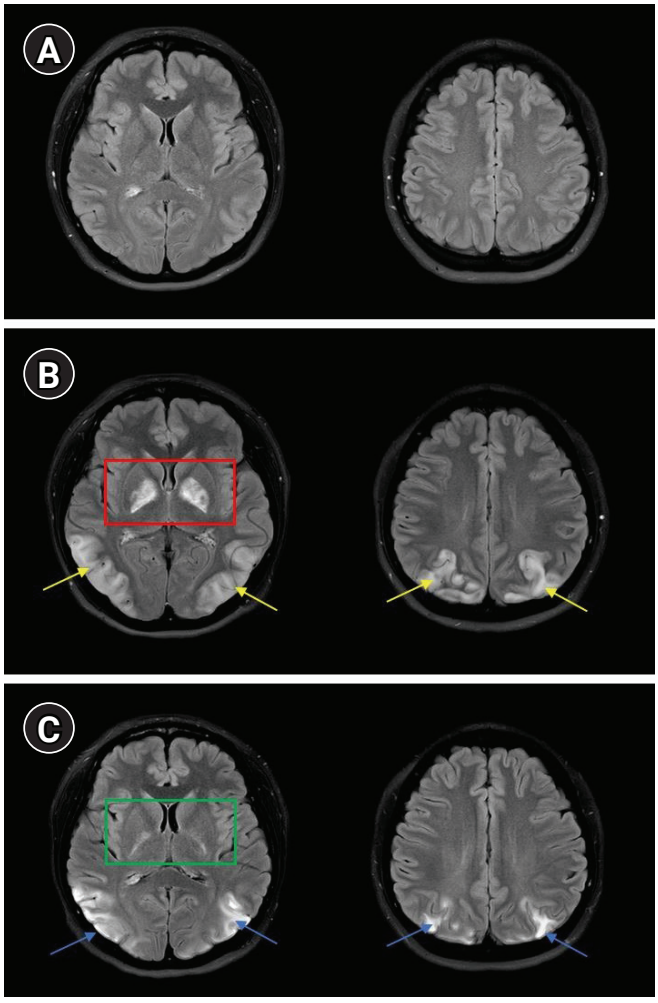

Fig. 1. Brain magnetic resonance imaging. (A) The day of carbon monoxide (CO) poisoning, fluid-attenuated inversion recovery (FLAIR) images showed no abnormal high signal intensity. (B) Twelve days from CO intoxication, FLAIR images showed high signal intensities in bilateral globus pallidus (red box) and both parieto-occipital cortex (yellow arrows), suggesting posterior reversible encephalopathy syndrome. (C) Twenty-five days after CO intoxication, follow-up FLAIR image was obtained from the outpatient visit, and it showed interval decrease of signal and volume in bilateral globus pallidus (green box) and temporo-parieto-occipital cortex (blue arrows).

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

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IMAGES IN NEUROCRITICAL CARE

Serial brain magnetic resonance imaging in a patient with invasive streptococcal infection with ventriculitis and choroid plexitis

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A 39-year-old previously healthy man visited the hospital with fever, myalgia, and vomiting. His systolic blood pressure was below 60 mmHg, and he was admitted to the intensive care unit with the suspicion of septic shock. After admission, *Streptococcus pneumonia* was found in his blood, and treatment with vancomycin 2 g/day and ceftriaxone 4 g/day was initiated. Following antibiotic treatment for 4 days, his mentation deteriorated to a stupor. Brain magnetic resonance imaging (MRI) indicated hydrocephalus, ventriculitis, and choroid plexitis (Fig. 1). Cerebrospinal fluid (CSF) examination showed normal opening pressure (180 mmHg), pleocytosis (white blood cell count, 280; neutrophils, 55%), high protein level (1,448 mg/dL), and low glucose levels (CSF, 54 mg/dL; serum, 135 mg/dL). Consequently, a high dose of steroids (dexamethasone, 40 mg/day) was prescribed together with antibiotics. After 14 days of antibiotic treatment, his general condition improved.

Brain MRI findings depicting pyogenic ventriculitis typically include ependymal thickening and enhancement with T2 prolongation surrounding the ventricle, hydrocephalus, and debris within the dependent aspect of the ventricles [1,2]. In addition, diffusion restriction and swelling of the choroid plexus are suggestive of choroid plexitis [2,3]. Although the MRI findings of our patient seemed more critical than previous reports, the patient experienced a good outcome with antibiotics [4].

ARTICLE INFORMATION

Ethics statement

This case was approved by the Institutional Review Board of the Hanyang University Hospital (IRB No. HYUH 2021-10-010). Informed consent from a patient was waived by the IRB.

Conflict of interest

No potential conflict of interest relevant to this article.

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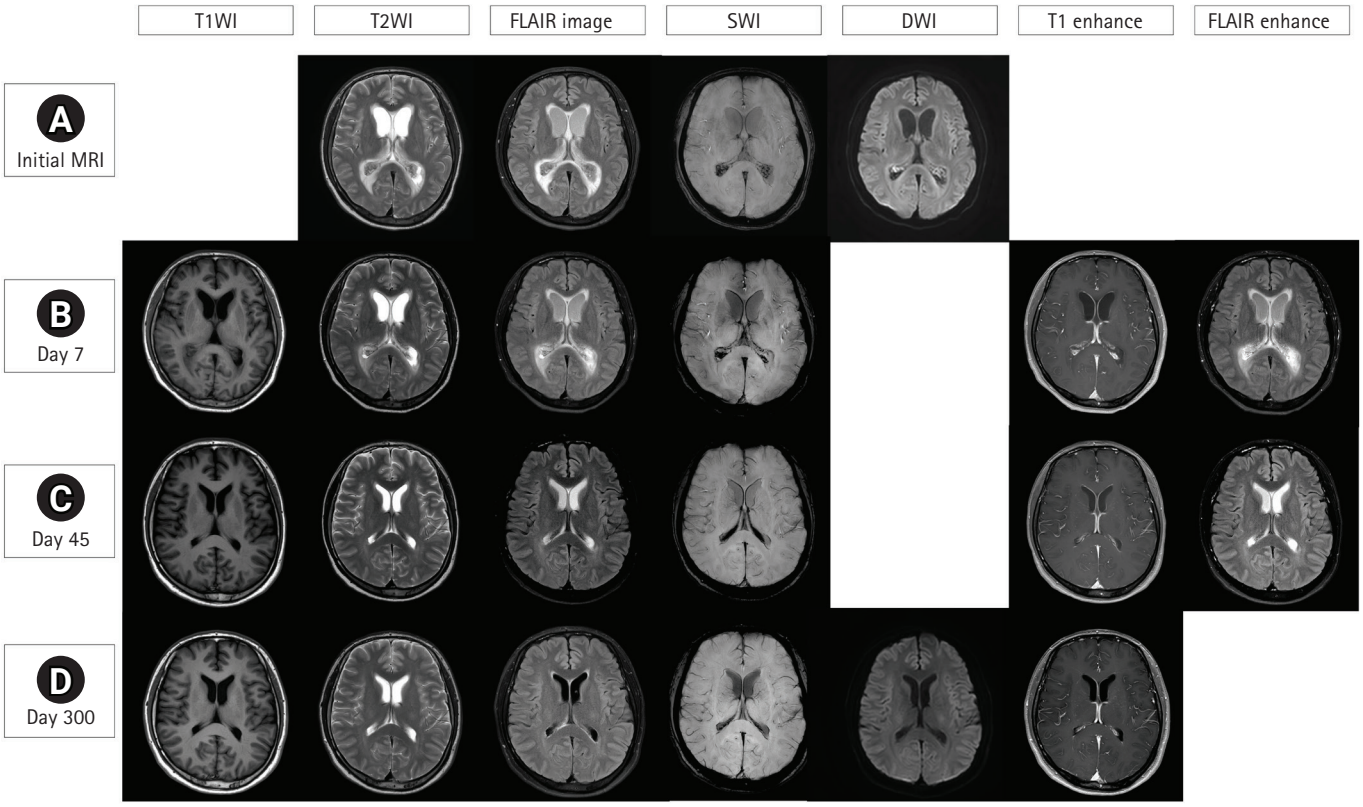

Fig. 1. Serial brain magnetic resonance imaging (MRI) findings of invasive streptococcal sepsis with ventriculitis and choroid plexitis. Initial brain images reveal hydrocephalus with severe interstitial edema and non-suppressed high-signal fluid in the lateral ventricle on fluid-attenuated inversion recovery (FLAIR) imaging, suggesting pyogenic ventriculitis. In addition, restricted diffusion on diffusion-weighted imaging (DWI) and low signal intensity on susceptibility-weighted imaging (SWI) in both choroid plexuses indicate choroid plexitis with hemorrhaging (A). Although the patient's mental status improved after administration of intravenous vancomycin and ceftriaxone, no significant change is observed in the brain MRI on day 7 after admission (B). The brain MRI of day 45 shows improved hydrocephalus, interstitial edema, ventriculitis, and choroid plexitis; however, a high signal of cerebrospinal fluid on FLAIR imaging is noted (C). Finally, on day 300, a normal brain MRI is observed (D).

YSK. Methodology: YSK. Project administration: YSK, JYL. Visualization: JYL. Writing–original draft: JC. Writing–review & editing: YSK.

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1. Kang J, Kang CH, Roh J, Yeom JA, Shim DH, Kim YS, et al. Feasibility, safety, and follow-up angiographic results of endovascular treatment for non-selected ruptured intracranial aneurysms under local anesthesia with conscious sedation. J Neurocrit Care 2018;11:93-101.
2. van den Bent MJ, Keime-Guibert F, Brandes AA, Taphoorn MJ, Eskens FA, Delattre JY. Temozolomide chemotherapy in recurrent oligodendroglioma [abstract]. Neurology 2000;54(suppl 3):12.
3. Di Luca DG, Mohney NJ, Kottapally M. Paroxysmal sympathetic hyperactivity with dystonia following non-traumatic bilateral thalamic and cerebellar hemorrhage. Neurocrit Care 2019 Feb 6 [Epub]. https://doi.org/10.1007/s12028-019-

00677-9.

- Book & book chapter

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

- Online source

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

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NOTICE

The revised instructions for authors will be applicable from September 2021.

Revision History

• Aug 2020
- Included a statement regarding IRB approval for case reports.
• Sep 2021
- Enhanced the description regarding institutional or ethical approval and informed consent.
- Added details regarding requirement of the manuscripts to adhere to recognized reporting guidelines relevant to the research design used and to submit a checklist as part of the initial submission.

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