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Case reports in neurocritical and neurohospitalist care, volume III - 2023

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Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-4685-7
DOI 10.3389/978-2-8325-4685-7

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Case reports in neurocritical and neurohospitalist care, volume III - 2023

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Citation

Ruland, S., Schneck, M. J., eds. (2024). *Case reports in neurocritical and neurohospitalist care, volume III - 2023*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-4685-7

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frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 02 June 2023
DOI 10.3389/fneur.2023.1144970

OPEN ACCESS

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RECEIVED 28 January 2023
ACCEPTED 17 May 2023
PUBLISHED 02 June 2023

CITATION
Diao J and Zhou Q (2023) Toxic encephalopathy and peripheral neuropathy of poisoning by Avermectin Pyridine: a case report and a review of the literature. *Front. Neurol.* 14:1144970. doi: 10.3389/fneur.2023.1144970

Toxic encephalopathy and peripheral neuropathy of poisoning by Avermectin Pyridine: a case report and a review of the literature

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Background: Avermectin Pyridaben (AVP) is an insecticide with extreme neurotoxicity in human, causing critical symptoms such as nausea, vomiting, coma and respiratory failure within a short time after oral ingestion. Neurological sequelae or even death may occur because of delayed treatment or excessive toxic dose.

Case presentation: We report a 15-year-old girl who presented with coma, respiratory failure, limb weakness, ataxia symptoms after ingestion of a toxic dose of AVP. Soon after the poisoning, the patient was treated with life-saving mechanical ventilation and haemodialysis. Subsequently brain Magnetic Resonance Imaging (MRI) and nerve conduction study (NCS) and electromyography (EMG) demonstrated toxic encephalopathy and peripheral nerve injury. Over the next 2months the patient's limb function gradually recovered under treatment with hyperbaric oxygen, glucocorticoid pulses and neurotrophic drugs.

Conclusion: This case documents a rare presentation of toxic encephalopathy complicated with peripheral neuropathy following AVP poisoning. Seven other similar cases of poisoning in terms of common symptoms and effective treatment have also been summarised for providing clinicians with experience in diagnosis and therapy.

KEYWORDS

Avermectin and Pyridine, toxic encephalopathy, peripheral neuropathy, therapy, case report

Introduction

As a pesticide commonly used in agriculture, Avermectin Pyridaben is a mixed preparation consisting of 0.3% Avermectin and 10.2% Pyridaben. Avermectin which can be extracted from fermenting of *Streptomyces avermitilis*, presents the chemical structure of a large ring lactone compound, killing insects by the effect of preventing the transmission of electrical impulse which stimulate gamma-aminobutyric acid (GABA) receptors and paralysing nerves (1). Pyridaben is a highly lipohpilic compound with higher bioactivity, lower toxicity, and excellent selectivity compared to benzenoid (2) and can be generated by Intermediate Derivatization Methods (IDM) and terminal group replacement method (TRM) (3), it also can induce neurotoxicity by inhibiting mitochondrial respiration and disrupting oxidative stress and ubiquitin-proteasome system dysfunction (4, 5). The Food and Agriculture Organization of the United Nations (FAO) states that the human intake of Pyridaben should not exceed 0.405 mg/kg in 1 day. With the widespread use

of AVP in agriculture, there has been a gradual increase in the incidence of pesticide poisoning, which in severe cases can be life-threatening. This paper reports a case of toxic encephalopathy with peripheral nerve injury after AVP poisoning, which recovered after treatment with hyperbaric oxygen, hormone and neurotrophic therapy. In addition, the symptoms and treatment of seven other similar poisoning cases are discussed in this paper, aiming to increase awareness of the safety of using AVP and to summarise experience in the diagnostic treatment of this type of poisoning.

Case report

A female adolescent aged 15 years manifested symptoms of nausea, vomiting, dyspnea and unconsciousness an hour subsequent to the inadvertent ingestion of 50 mL of AVP (comprising 0.3% Avermectin and 10.2% Pyridaben) at home. Two hours later she experienced a state of shock and was admitted to a nearby hospital. She had no previous medical history. Her vital signs showed dilated, non-reactive pupils and no spontaneous breathing. Her blood pressure (BP), pulse rate (PR), respiratory rate (RR), temperature and blood glucose (BS) were 65/30 mmHg, 74 bpm, 18/min with balloon-assisted ventilation, below 35°C, and 26.4 mmol/L, respectively. An arterial blood gas (ABG) analysis showed metabolic acidosis with respiratory alkalosis (pH = 6.77, pO_2 = 242 mmHg, pCO_2 = 26.2 mmHg, HCO_3 = 12.3 mmol/L, BE = -15 mmol/L, Lactate beyond the max range). The 12-lead electrocardiogram was normal. Other laboratory exams are presented in Table 1.

Haemodialysis and mechanical ventilation were adopted in the treatment and, in the meantime, norepinephrine (0.2 μg/kg/min) was used to maintain the blood pressure. Having been transferred to ICU, she was treated with normal saline (1 L/d), intravenous pantoprazole (0.1 g q12h) and citicoline (0.25 g qd) which could protect gastic mucosa and the brain. On next day of admission, she regained consciousness, but still be weak, felt powerless and be in mechanical ventilation requirement. Her neurological examination revealed positive Babinski signs, grade IV muscle strength and ataxia in both lower limbs, and no ataxia, grade V muscle strength in both upper limbs, and no abnormalities on sensory examination such as depth sensation, positional sensation, pain and temperature sensation in the limbs. The examination suggested her pyramidal tract involvement, which prompted a request for a brain MRI, but it was not done due to her unpredictable condition. On the day 4 of ICU treatment, the patient was extubated and transferred to the general ward for continued treatment on the day 5. A list of vital signs care during ICU treatment can be found in Table 2. After ten-day treatment at the local hospital, the patient's BP, PR, RR, BS, O2 saturation, temperature, and ABG indicators returned to the normal range. Then she was transferred to our hospital for lower limb ataxia and positive Babinski signs, which suspected neurological impairment and confirmed by brain MRI NCS and EMG.

Her brain MRI showed abnormal signals in the internal and external capsules of the basal ganglia bilaterally, confirming toxic encephalopathy (Figure 1). Combined with the patient's respiratory failure after poisoning, the possibility of hypoxia-induced encephalopathy cannot be ruled out. NCS and EMG evoked potential testing suggested peripheral neuropathy of both lower limbs, including axonal damage to motor and sensory nerves (Table 3). Based on her weight of 52 kg the management of her neurological impairment was as follows: Intravenous dexamethasone sodium phosphate injection was given for 11 days (10 mg*5 days, 7.5 mg*3 days, 5 mg*3 days), then switched to oral methylprednisolone tablets with an initial dose of 40 mg/d, and the dose was reduced to one slice a week until the drug was stopped. Glucocorticoid therapy was administered for a duration of 3 months in order to mitigate the effects of inflammation and cerebral oedema. Hyperbaric oxygen (HBO) therapy lasted for 10 days with parameters set at 0.25 MPa and 60 min/d to reduce cerebral hypoxia, but was eventually discontinued due to financial constraints (6). Mecobalamin (0.5 gr qd) and vitamin B1 (0.1 gr qd) injections were used to promote regeneration of peripheral injured nerves and

TABLE 1 On-arrival laboratory test results.

Laboratory test	Result (normal range)
White blood cells (×1,000/mm^3)	11.2 (4.5–11)
Hemoglobin (g/L)	97 (110–150)
Hematocrit (percent)	32 (35–45)
Platelet count (×1,000/mm^3)	448 (150–450)
Urea (mmol/L)	4.0 (1.7–8.3)
Creatinine (umol/L)	39 (40–84)
Aspartate transaminase (U/L)	18 (0–40)
Alanine transaminase (U/L)	20 (6–29)
Lactate dehydrogenase (U/L)	229 (80–240)
Creatine phosphokinase (U/L)	43 (0–180)
Alkaline phosphatase (IU/L)	80 (15–140)
Total bilirubin (umol/L)	6.8 (5.1–28)
Direct bilirubin (umol/L)	1.1 (0–10)
Serum sodium (mmol/L)	136 (131–148)
Serum potassium (mmol/L)	3.9 (3.5–5.3)
Prothrombin time (seconds)	11.3 (10–14)
International normalized ratio	0.94 (0.8–1.5)
Partial thromboplastin time (seconds)	30 (22–38)
Reticulocytes	1.4 (0.5–1.5)
Arterial PH	6.77 (7.35–7.45)
Arterial pCO2 (mmHg)	26.2 (35–45)
Arterial pO2 (mmHg)	242.5 (90–100)
Arterial HCO3 (mmol/L)	12.3 (22–27)

TABLE 2 Changes in vital signs in the intensive care unit within 5days after poisoning.

	1	2	3	4	5
BP(mmHg)	65/30	98/67	101/65	104/68	96/66
R(times/min)	18	18	18	18	17
T(°C)	35	36.1	36.3	36.5	36.4
P(bpm)	74	70	68	69	67
Life support interventions	MV + VA	MV + VA	MV	MV	/

BP, blood pressure; R, respiratory frequency per minute; T, body temperature; P, pluse rate; MV, mechanical ventilation; VA, vasoactive agent.

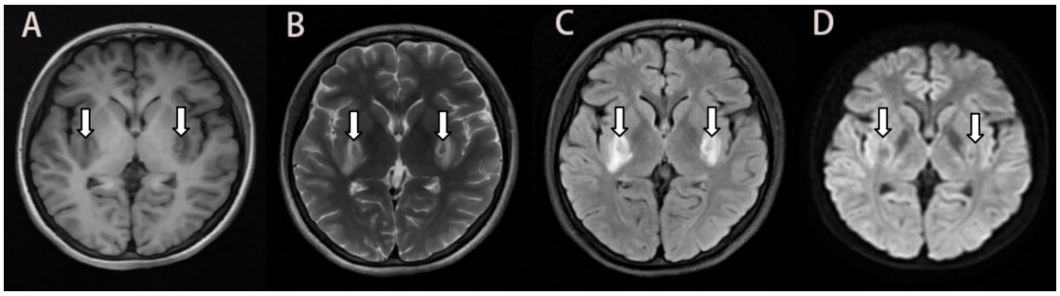

FIGURE 1
MRI 10days after ingestion showing bilateral symmetrical lesions in the basal ganglia. Abnormal isointensity on T1-FLAIR **(A)**, and heterogeneous intensity on T2 propeller **(B)**, and hyperintensity on T2-FLAIR **(C)**, and no significant hypersignal on DWI **(D)**. MRI: magnetic resonance imaging; FLAIR: fluid attenuated inversion recovery; DWI: diffusion-weighted imaging.

TABLE 3 The amplitude (Amp) of sensory and motor neuropathy in NCS and EMG.

Amp	Suralis sensory (μV)			Peroneus Motor (mV)		
Stimulation times	T1	T2	T3	T1	T2	T3
RT	6.4↓	3.1↓	2.8↓	5.0	8.1	4.7
LT	5.9↓	3.8↓	2.2↓	0.4↓	0.9↓	0.5↓

RT, right lower limb; LT, left lower limb; T1, 10 days after poisoning; T2, 2 months after poisoning; T3, 4 months after poisoning. The sensory nerve stimulation site was the ankle and the recording site was the foreleg. The motor nerve stimulation site was fibula superior and the recording site was extensor digitalis brevis. Conclusion: NCS and EMG-T1 showed axonal damage in the sensory nerves of the both lower limbs and the motor nerves of the left lower limb. NCS and EMG-T2 and T3 showed axonal damage in the sensory nerves of the both lower limbs. Due to the different machines used in each NCS and EMG test, the accuracy of stimulation site, depth and recording time will vary between operators. The measured NCS and EMG value can only be used as a qualitative criterion for the presence or absence of nerve damage and cannot used as a quantitative assessment index of improvement or deterioration. Therefore, the results of the NCS and EMG report should be taken as the final standard.

continued for 1 month (7, 8). The patient complied with medical advice and did not have any adverse effects during treatment.

She was reexamined by brain MRI, NCS, and EMG 45 days after glucocorticoid treatment and 4 months after poisoning, respectively. The brain MRI showed a remarkable reduction in the size of the lesions and the FLAIR hyperintensities in both basal ganglia regions, together with the observation of gliosis in the adjacent affected areas (Figures 2, 3), but NCS and EMG showed persistence of motor and sensory axonal damage in the lower limbs (Table 3). Her neurological examination showed a positive Babinski sign, no ataxia and normal muscle strength of the limbs.

Discussion

Avermectin can stimulate gamma-aminobutyric acid (GABA) receptors in the central nervous system to produce inhibitory neurotransmitters (9) and reduce cell viability and adenosine triphosphate (ATP) production by affecting mitochondrial function, thereby impairing the function of other organelles, leading to an imbalance in intracellular calcium homeostasis and eventually leading to cell necrosis (10). Pyridaben, an inhibitor of mitochondrial oxidation complex I, can significantly increase the production of reactive oxygen species (ROS) during part of the action period (11), which can induce apoptosis by affecting mitochondrial function, inducing ROS, inducing calcium imbalance, increasing the endoplasmic reticulum stress response, and promoting apoptosis (12). The patient reported taking 50 mL of a mixture of Avermitin 150 mg and Pyridine 15,100 mg and was found to have symptoms of toxic encephalopathy, and Peripheral neuropathy was found the next day after rescue. This is similar to the case of Avermectin poisoning with neurological injury-related sequelae reported by Song, which suggests that simultaneous central and peripheral neuropathy may have a poor prognosis (13). The poison reaches the brain tissue through the blood, inhibits mitochondrial function, and leads to tissue hypoxia and necrosis. Gray matter is more vulnerable to anoxic or ischemic insults due to its higher metabolic demands for oxygen and glucose, and deep gray nuclei are often involved in acute severe brain tissue hypoxia, which is associated with poor prognosis (14–16).

This paper presents a discussion regarding a total of eight patients who suffered from poisoning, each exhibiting varying degrees of symptoms related to neurological damage include ataxia, muscle weakness, coma, blepharoptosis, hypoesthesia and myoclonus et al. (Table 4) (13, 17–22). In addition to nervous system symptoms, gastrointestinal irritation symptoms were common, and more than half of the patients had respiratory system involvement. One patient had allergic symptoms, and another one had cerebral haemorrhage, multiple organ failure and eventually died. The dose of poisoning, the rescue time and the presence or absence of major organ damage were the main factors influencing prognosis.This paper presents an overview of treatment methods for AVP poisoning, as no singular antidote for its mitigation is currently available.

Toxins should be removed from the body as soon as possible after poisoning. Activated charcoal gastric lavage, intestinal perfusion, hemodialysis and other methods could be used to avoid the occurrence of MOF. At the same time, vasoactive drugs were used to maintain blood pressure in the normal range, and mechanical ventilation support was given to patients with dyspnea. Patients with toxic encephalopathy can use glucocorticoid to control the inflammatory response of cells, reduce brain edema, and prevent compression of the surrounding normal brain area. Hyperbaric oxygen therapy (HBO) inhibits neutrophil adherence to the walls of ischemic vessels, which decreases free radical production, vasoconstriction and tissue destruction (14). Patients with Peripheral neuropathy should be given timely nutritional nerve treatment to prevent irreversible sequelae. Liver damage, pulmonary infection,

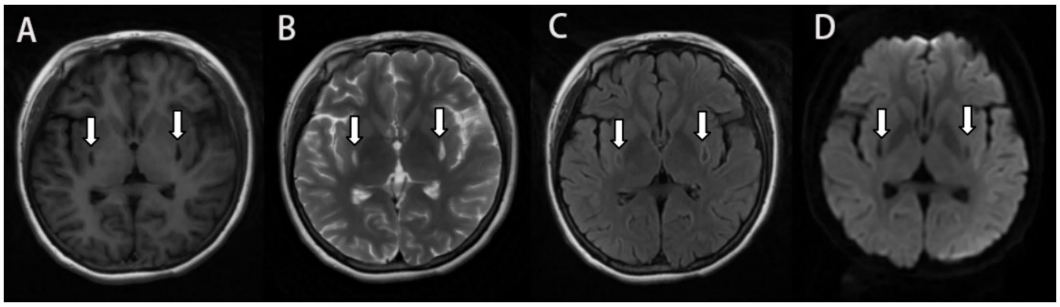

FIGURE 2
MRI 2months after ingestion showing encephalomalacia in the bilateral basal ganglia with surrounding gliosis and the lesion size was smaller than before. Symmetrical small patchy with long T1 long T2 signal on T1 Flair **(A)** and T2 propeller **(B)**, and hyperintense in the edge of the lesion on T2-FLAIR **(C)**, and no significant hypersignal on DWI **(D)**.

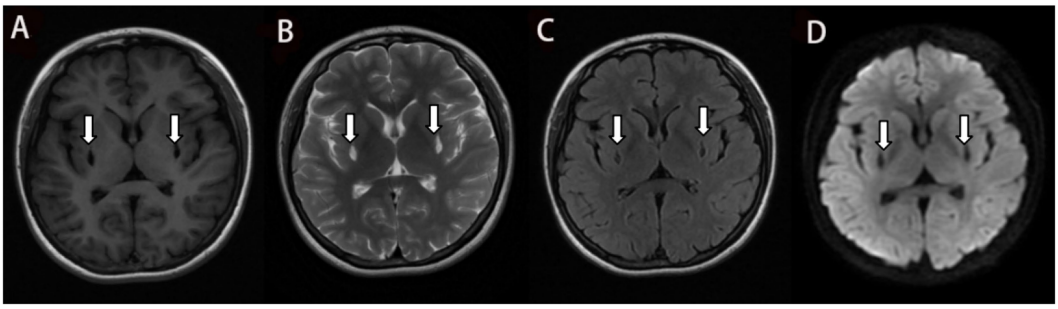

FIGURE 3
The T1 Flair **(A)**, T2 Propeller **(B)** and DWI **(D)** in the MRI 4 months after ingestion show similar to Figure 2. and the gliosis around the lesion is less than before which is shown in the T2 Flair **(C)**.

TABLE 4 Summary of 8 cases of AVP related poisoning.

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8
Author	Karatelike H	Wenjie W	Aminiahidashti H	Sung YF	Soyuncu S	Jiezheng D	Jianian D	Our case
Age/Sex	30/M	47/M	42/M	76/M	25/W	28/W	28/W	15/W
Pesticide-dose	A-12 mg/kg	A u	A-51.42 mg/kg	A-414.2 mg/kg	A-108 mg/kg	A + P-100 mL	P-20 mL(15%)	0.3%A + 10.2%P-50 mL
Onset/Escape	<3 h/27 h	N/5 h	2.5 h/24 h	1 h/9 days	<3 h/u	2 h/16 h	2 h/Death	1 h/24 h
GAS	9	10	u	3	6	4	u	3
BP-PO2(mmHg)	120/60-u	135/90-u	80/65-u	94/49-195(MV)	102/59–68.5	85/54–58	65/26–33	65/30–242.5(MV)
Neurological	Ataxic, Blepharoptosis	/	Muscle weakness, Myoclonus	Coma, Myoclonus, Muscle weakness, Peripheral neuropathy	/	Coma	Coma, Cerebral hemorrhage, Toxic encephalopathy	Coma, Ataxic, Muscle weakness, Peripheral neuropathy, Toxic encephalopathy
Other symptoms	u	u	Fever, Diarrhea, Allergy	RF	N/V, RF	N/V, Pulmonary infection	N/V, MOF	N/V, RF, Shock
Main treatments	GL	GL, MV	GL, VA, H1-R blocker, H2-R blocker, Hormone	GL, VA, MV, H2-R blocker, Hormone	GL, MV	GL, MV, Anticholinergic, Antibiotics, Neurotrophic	GL, VA, Hemodialysis, CRRT	Enema, MV, VA, Hemodialysis, Hormone, Neurotrophic
Prognosis	R	R	R	S	R	R	D	R

M, Man; W, Woman; A, Avermectin; P, Pyridaben; u, unreported; H, Hypoactive; N, Negative; Onset/Escape, the time of onset and escape from life risk; N/V, Nausea/Vomiting; RF, Respiratory failure; MOF, Multiple organ function; GL, Gastric lavage; VA, vasoactive agent; MV, mechanical ventilation; CRRT, Continuous renal replacement therapy; R, Clinical Recovery; S, Severe sequelae; D, Death.

gastrointestinal ulcer, and allergy are all possible complications, and doctors need to predict the possible situation to reduce the incidence of complications.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Research ethics committee of the second hospital of shandong university. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JD collected the clinical information, and examination data and wrote the manuscript. QZ provides thesis guidance and financial support. All authors contributed to the article and approved the submitted version.

Funding

Supported by Natural Science Foundation of Shandong Province of China (ZR2021MH098).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TYPE Case Report
PUBLISHED 03 August 2023
DOI 10.3389/fneur.2023.1195008

OPEN ACCESS

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RECEIVED 27 March 2023
ACCEPTED 25 July 2023
PUBLISHED 03 August 2023

CITATION
Wang F and Darby J (2023) Case report: Central alveolar hypoventilation in a survivor of cardiopulmonary arrest.
Front. Neurol. 14:1195008.
doi: 10.3389/fneur.2023.1195008

Case report: Central alveolar hypoventilation in a survivor of cardiopulmonary arrest

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Introduction: Ondine's curse is a rare respiratory disorder that is characterized by central alveolar hypoventilation (CAH) during sleep. It is most commonly congenital. However, it can also be acquired very rarely. Herein, we report a young survivor who developed CAH following cardiopulmonary arrest.

Case presentation: A 35-year-old man was admitted to the Intensive Care Unit following unwitnessed cardiopulmonary arrest. Following resuscitative interventions, he remained comatose. Early diagnostic testing showed elevated neuronal specific enolase (28.7 ng/ml), absent cortical responses on evoked potential testing and MRI evidence of restricted diffusion in the cerebellum, hippocampi, juxtacortical white matter, superior cerebellar peduncles, dorsal pons, dorsolateral medulla, and upper cervical spinal cord. Ten days following admission, the patient remained comatose and underwent tracheostomy. He subsequently began to emerge from coma but had persistent unexplained hypotension and bradypnea necessitating ongoing vasopressor and respiratory support. Repeat MRI on hospital day 40 revealed residual FLAIR hyperintensities in the medulla within the nucleus tractus solitarius (NTS). After being discharged to long-term acute care facility, he was successfully liberated from mechanical ventilation 70 days post arrest.

Conclusion: We report the first survivor of cardiopulmonary arrest who was complicated by CAH and hypotension with MRI verified ischemic injury to the bilateral NTS regions. Despite this injury, ventilator and vasopressor dependency resolved over a period of 10 weeks. Our case highlighted the essential functions of NTS in regulating the respiratory and cardiovascular systems.

KEYWORDS

Ondine's curse, central alveolar hypoventilation, cardiac arrest and brain injuries, nucleus tracti solitarii, dysautonomia

Introduction

Ondine's curse is a rare but potentially lethal respiratory disorder that is characterized by central alveolar hypoventilation (CAH) or apnea during sleep. While usually congenital, it can be acquired from neurological disorders. We describe a young man who developed CAH after resuscitation from cardiopulmonary arrest.

Case description

A nonobese 35-year-old man with history of polysubstance use was transported to the Emergency Department following unwitnessed cardiopulmonary arrest. His initial rhythm was pulseless electric activity with return of spontaneous circulation after 25 min of chest compressions. Initial evaluation revealed an unremarkable electrocardiogram, undetectable blood glucose level and a Full Outline of UnResponsiveness (FOUR) score of 1 (E0M0B0R1). Urine toxicology was positive for cocaine and fentanyl. Neurological examination demonstrated generalized myoclonus and increased muscle tone in the lower extremities with sustained clonus at both ankles. Initial computed tomography (CT) head showed preserved gray-white differentiation and hypodensity in the left cerebellar hemisphere. He was further resuscitated in the intensive care unit (ICU) and subsequently cooled to 33°C for 24 h according to our institutional protocol. Neuron specific enolase was elevated at 28.7 ng/ml. Continuous electroencephalogram (cEEG) showed background suppression ratio of 85% which improved to 10% overnight (Figure 1).

On hospital day 3, his FOUR score improved to 9 (E4M0B4R1) while cEEG revealed continuous reactive background with theta-delta slowing. His eyes opened spontaneously, but he did not react to noxious stimuli. Somatosensory evoked potential (SSEP) revealed bilaterally absent cortical potentials. Given the discrepancy between neurological examination, cEEG and SSEP findings, magnetic resonance imaging (MRI) of brain and cervical spine revealed symmetrical diffusion restriction with surrounding edema in the juxtacortical white matter, hippocampi, superior cerebellar peduncles, dorsal pons, dorsolateral medulla within the nucleus tractus solitarius (NTS), and cerebellum. Punctate hyperintensities were apparent in the left ventral spinal cord at C3-C4 on fluid-attenuated inversion recovery (FLAIR) sequences indicating subacute infarct (Figures 2A,B). There were no vascular abnormalities identified on magnetic resonance angiogram (MRA) of head and neck vessels.

On hospital day 10, repeated SSEP again showed bilaterally absent cortical potentials. After discussion with family, tracheostomy and percutaneous endoscopic gastrostomy tubes were placed. His arousal continued to improve over time and began to track with his eyes and eventually was able to follow commands and communicate. Despite his improving neurological condition, unexplained hypotension requiring vasopressors as well as bradypnea necessitated retention in the ICU. While he was able to breathe voluntarily, his involuntary respiratory rate consistently ranged from between 4 and 6 times per minute with symptomatic hypercarbia developing after variable periods of unassisted breathing. While the administration of pseudoephedrine improved his blood pressure, a trial of theophylline as a respiratory stimulant was ineffective in preventing the development of symptomatic hypercarbia.

On hospital day 42 repeat MRI revealed persistent FLAIR abnormalities in the dorsolateral medulla, caudal pons and cerebellar hemispheres, and resolution of FLAIR abnormalities in the hippocampi, juxtacortical white matters and upper cervical cord (Figures 2C,D). Given his overall improvement in neurological condition and imaging findings, he was transferred to a long term-acute care facility for ongoing ventilator weaning 50 days after hospital admission. Pseudoephedrine was subsequently discontinued with normal blood pressure. He was successfully liberated from mechanical ventilation approximately 70 days after arrest.

Discussion

Ondine's Curse was first described by Severinghaus and colleagues in patients who had undergone bilateral spinothalamic tract

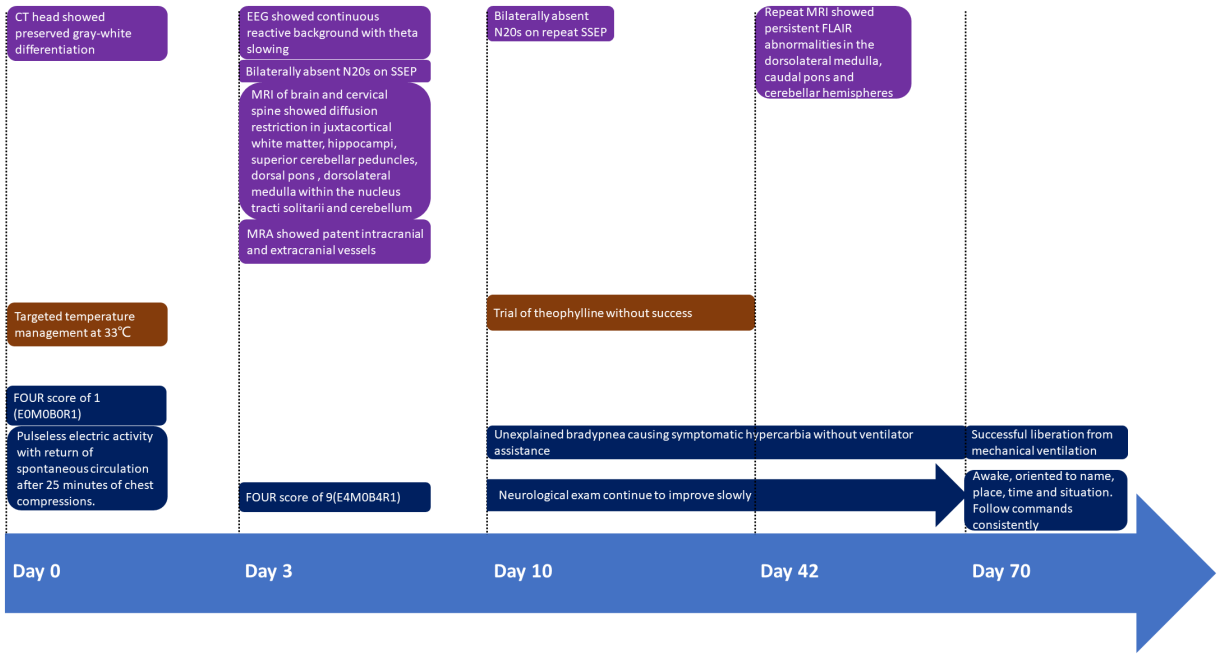

FIGURE 1
Timeline of presentation and outcome in this case. FOUR Score: Full Outline of UnResponsiveness (FOUR) score of 1 (E0M0B0R1); E, eye response; M, motor response; B, brainstem reflexes; R, respiration pattern.

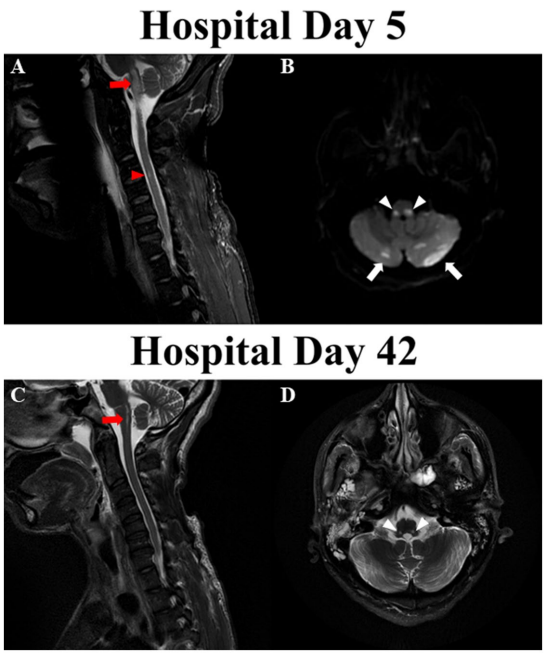

FIGURE 2
Magnetic resonance imaging of brain and cervical cord. **(A)** Fluid-attenuated inversion recovery (FLAIR) abnormalities in medulla oblongata (red arrows) and ventral aspect of C3-C4 cervical cord (red arrowheads) on hospital day 5. **(B)** Diffusion restriction in dorsolateral medulla (white arrowheads) and bilateral cerebellar hemispheres (white arrows) on hospital day 5. **(C)** Improvement in the FLAIR signal in the medulla oblongata (red arrow) and resolution of FLAIR abnormality in cervical cord on hospital day 42. **(D)** Remnant T2 signal abnormalities in the regions bilateral nucleus tracti solitarii on hospital day 42.

cordotomies who had retained voluntary respiratory function but poor responsiveness to inhaled carbon dioxide (1). Interchangeably, CAH describes impaired ventilatory function secondary to an underlying neurological disorder affecting sensory, motor or integration pathways of brainstem respiratory centers (1–8).

The neuronal control of respiration is complex and integrated with other autonomic systems. Respiratory control neurons are localized to three main areas within the brainstem: (1) the dorsal respiratory group (mainly inspiratory) located in the dorsal medulla within the NTS; (2) the ventral respiratory group, a column of inspiratory, expiratory and rhythm-generating neurons extending from the first segment of cervical spinal cord to below the facial nuclei; (3) the parabrachial/Kölliker-Fuse complex located in dorsolateral upper pons which controls switching between inspiration and expiration (9). The NTS is also the main area for cardiorespiratory control (9). NTS receives afferent sensory information from peripheral and central chemoreceptors as well as from stretch receptors in the lungs. It then sends information to respiratory motor centers to regulate respiration (10). The NTS also receives afferent information from arterial baroreceptors and cardiac receptors to regulate blood pressure and heart rate with multiple efferent projections to the medulla and pons.

CAH is more frequently congenital than acquired and attributed to a mutation in the PHOX2B transcription factor gene within neurons of the retrotrapezoid nucleus in the ventral respiratory group disrupting central and peripheral chemosensitivity (11).However, traumatic, ischemic, and inflammatory insults to the brainstem can also cause acquired CAH (1–8). Although the respiratory centers receive bilateral reciprocal inputs, patients with unilateral caudal brainstem lesion have been reported to develop CAH (1, 2, 4, 5, 8). Damage to C2 nerve fibers were also implicated in patients developing CAH after high cervical cord injury (12). Moreover, brainstem ischemia or hypoperfusion can also result in acquired CAH (13). In an autopsy report of five patients with acute heart failure and prolonged hypotension, including one patient with cardiopulmonary arrest, bilateral isolated NTS lesions were identified with signs of neuronal excitotoxicity at autopsy (14). The authors proposed that NTS possibly resides in the watershed area of anterior spinal artery (ASA) and posterior inferior cerebellar artery (PICA), which makes them susceptible to ischemic injury during prolonged hypoperfusion. Furthermore, hyperexcitability of NTS neurons in the setting of decreased pH and/or carbon dioxide retention might precipitate secondary injuries.

Herein we report a case of CAH in a young survivor following cardiopulmonary arrest with MRI evidence of bilateral NTS injury. He had CAH with primary respiratory acidosis while preserving the ability of voluntary breathing. His brain MRI showed bilateral symmetrical lesions in the NTS areas, which explained both CAH and dysautonomia with low blood pressure (15). The exact etiology of these lesions might be difficult to pinpoint because his cardiopulmonary arrest was confounded by critical hypoglycemia and substance intoxication. However, here we propose that hypoperfusion from cardiopulmonary arrest is likely the culprit. Firstly, the patient had signs of ischemia in the ASA and PICA territories regardless of patent vessels. Transient drug-induced vasospasm might be another precipitating factor as cocaine is known to cause diffuse vasospasm, even though we did not discover any vascular abnormalities on MRA. Nevertheless, the NTS probably suffered from critical hypoperfusion because it locates in the watershed area of ASA and PICA. Moreover, NTS neurons are hyperexcitable in the setting of acidemia and hypercapnia which might lead to excitotoxicity and exacerbates secondary injuries. Lastly, critical hypoglycemia and drug intoxication might have amplified the excitotoxicity and secondary injuries.

Conclusion

We report a survivor of cardiopulmonary arrest who was complicated by CAH and hypotension with MRI verified ischemic injury to the bilateral NTS regions. Despite this injury, ventilator and vasopressor dependency resolved over a period of 10 weeks. Our case highlighted the essential functions of NTS in regulating the respiratory and cardiovascular systems.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FW: study concept and design, data acquisition, first draft, and literature review. JD: study concept and design, literature review, and revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Case Report
PUBLISHED 04 August 2023
DOI 10.3389/fneur.2023.1219372

OPEN ACCESS

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RECEIVED 09 May 2023
ACCEPTED 10 July 2023
PUBLISHED 04 August 2023

CITATION
Wang PW, Chung MH, Feng SW, Liao HC, Wu YC, Hueng DY, Yang YJ and Ju DT (2023) Case report: Ruptured internal carotid artery fusiform aneurysm mimicking pituitary apoplexy after stereotactic radiosurgery. *Front. Neurol.* 14:1219372. doi: 10.3389/fneur.2023.1219372

Case report: Ruptured internal carotid artery fusiform aneurysm mimicking pituitary apoplexy after stereotactic radiosurgery

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Pituitary adenomas are benign tumors of the anterior pituitary gland for which surgery or pharmacological treatment is the primary treatment. When initial treatment fails, radiation therapy should be considered. There are several case reports demonstrating radiation-induced vascular injury. We report an adult patient who presented with headache and diplopia for 6 months and a sellar tumor with optic chiasm compression. The patient received transnasal surgery, and the tumor was partially removed, which demonstrated adenoma. Stereotactic radiosurgery (SRS) was arranged. However, owing to progressive tumor growth, the patient received further transnasal surgery and stereotactic radiosurgery (SRS). After 14 years, the patient reported the sudden onset of headache and diplopia, and a ruptured fusiform aneurysm from the left internal carotid artery with pituitary apoplexy was diagnosed. The patient received transarterial embolization of the aneurysm. There were no complications after embolization, and this patient was ambulatory on discharge with blindness in the left eye and cranial nerve palsies. Aneurysm formation may be a complication of SRS, and it may occur after several years. Further research is needed to investigate the pathogenesis of radiosurgery and the development of cerebral aneurysms.

KEYWORDS

fusiform aneurysm, radiosurgery (SRS), pituitary tumor, apoplexy, internal carotid aneurysm

Case description

An adult patient in their 40's reported progressive headaches, vision loss in the left eye, and diplopia for 6 months. Magnetic resonance imaging (MRI) revealed a sellar tumor with parasellar and suprasellar extension and optic chiasm compression (Figure 1A). No endocrine abnormalities were noted, and neurosurgical treatment was suggested owing to the development of neurological symptoms. This patient underwent transnasal transsphenoidal surgery, and the sellar tumor was partially removed (Figure 1B). The surgical pathology report showed adenoma, and fractionated radiotherapy with 4,500 cGy that was divided to the anterior, left, and right parts of the tumor in 24 sessions was performed. However, progressive tumor enlargement was seen in follow-up imaging studies, and headache had developed. This patient underwent further transnasal transsphenoidal surgery with debulking of the tumor, and stereotactic radiosurgery (X-knife) with 1,200 cGy delivering 90% isodose volume that covered 98% of tumor volume was performed. An annual follow-up image demonstrated no interval change

in tumor size and no vascular abnormalities (Figures 2A–D). However, 14 years after SRS, the patient was sent to our emergency department due to the sudden onset of headache, dizziness, diplopia, and blindness in the left eye for 1 day. In the emergency department, a loss of pupillary light reflex in the left eye, and oculomotor nerve and abducens nerve palsies were found.

Diagnostic assessment

A hematoma at the sellar turcica and an intraventricular hemorrhage were found on brain computer tomography (CT) (Figure 3A). A cerebral angiogram revealed a fusiform aneurysm measuring 1.55 x 1.45 cm arising from the cavernous segment

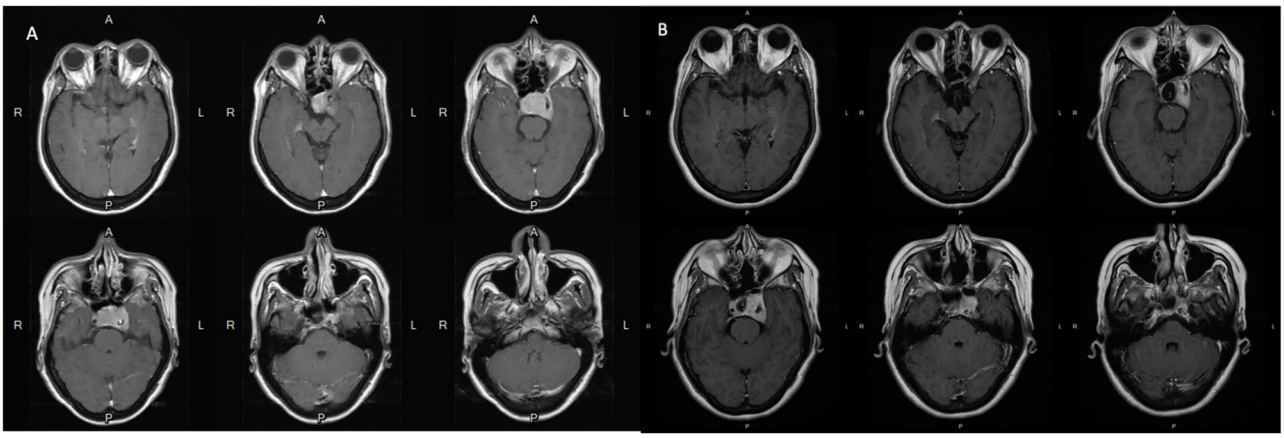

FIGURE 1
(A) Pre-operative MRI scans with contrast show the pituitary tumor measured 3.6 cm x 2.35 cm x 2.83 cm causes erosion of the sellar floor and encasement of the left cavernous structure including the internal carotid artery. **(B)** Post-operative MRI scans with contrast show that the residual tumor is still located mainly in the left side of the sellar fossa and parasellar structures including the cavernous sinus and Meckel's cave.

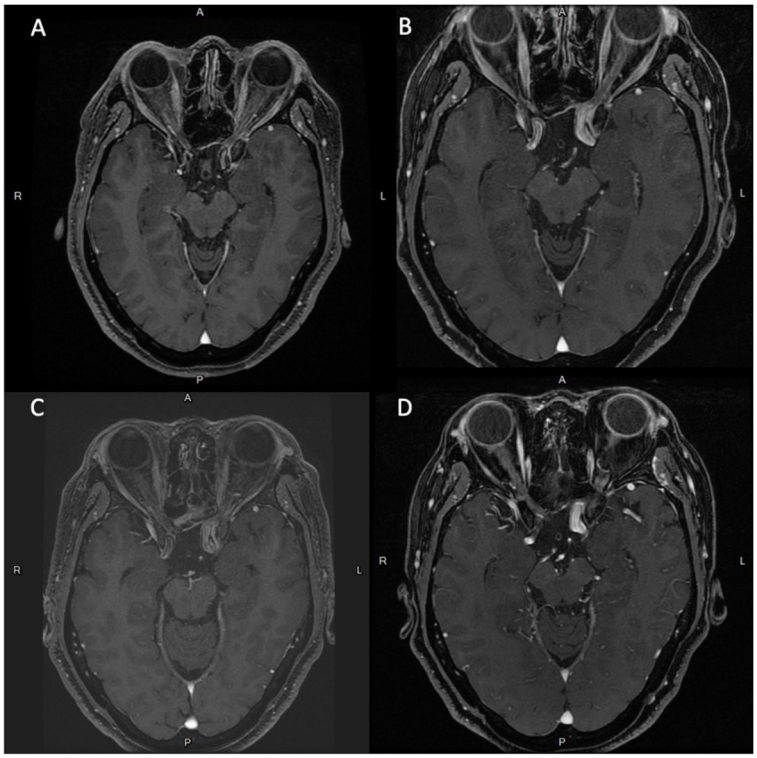

FIGURE 2
Series of brain MRI scans with contrast shows newly noted focal dilation of left cavernous ICA (diameter: 1.3 cm) and medial protrusion (0.75 cm) in the cavernous ICA. since 2020.06. **(A)** Brain MRI scans in 2008.10. **(B)** Brain MRI scans in 2018.01. **(C)** Brain MRI scans in 2019.06. **(D)** Brain MRI scans in 2020.06.

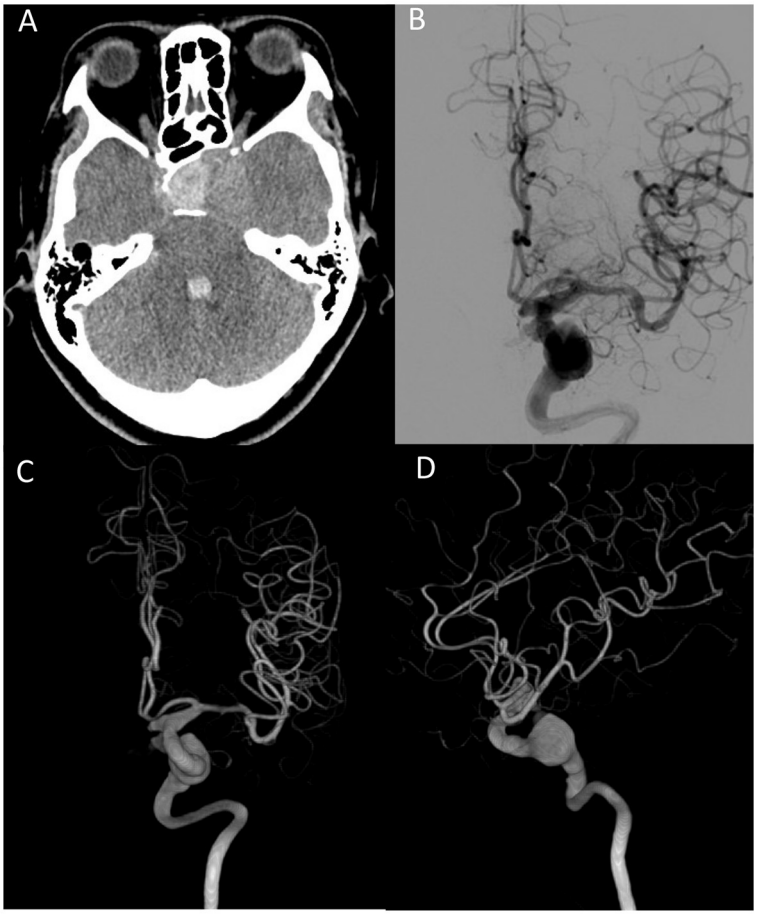

FIGURE 3
(A) Brain CT scan shows hemorrhage at the sellar turcica and intraventricular hemorrhage. **(B)** Fusiform aneurysm from the left ICA. Arrow indicates contrast extravasation. **(C)** Anterior–posterior view of 3-D reconstruction angiography. **(D)** Lateral view of 3D reconstruction angiography. ICA, internal carotid artery.

of the left internal carotid artery, with contrast extravasation from the aneurysm to the sellar turcica, and another saccular aneurysm measuring 0.7 x 0.6 cm arising from the left posterior communicating artery (Figures 3B–D). Because of the location (cavernous segment of the ICA) and shape of the fusiform aneurysm, it was difficult to approach and perform clipping or bypass surgery. This patient was treated with stent-assisted coiling embolization of the ICA aneurysm. A self-expandable stent was deployed spanning the left distal internal carotid artery at the C4 segment, covering the aneurysm orifice. A total of 32 coils were delivered into the aneurysm. There were no complications after embolization, and the patient was ambulatory on discharge with blindness in the left eye and cranial nerve palsies.

Discussion

SRS is used for several types of intracranial tumors. In 1968, Dr. Leksell treated the first pituitary macroadenoma with SRS, and many thousands of patients with pituitary adenomas have since been treated with SRS. The radiation effect stabilizes tumor growth with an average control rate of 68–100% and normalizes hormone levels. However, complications following radiosurgery for pituitary adenoma have been reported, including hypopituitarism, cranial nerve injury, adjacent vascular structure injury, and brain parenchyma injury. Injury to the cavernous segment of the internal carotid artery is rare, and only two cases of symptomatic carotid artery stenosis have been reported.

The definition of radiation-induced aneurysms is still under debate due to the absence of pathognomonic radiographic or histologic features. As a result, a more appropriate description would be aneurysms occurring in an irradiation field. Five cases of aneurysm formation after SRS for the treatment of intracranial tumors have been reported, four of which were acoustic neuromas and one was bilateral retinoblastoma (1). Ruptured anterior inferior cerebellar artery aneurysms occurred in the four patients with acoustic neuromas, and an anterior cerebral artery aneurysm occurred in the patient with retinoblastoma. Four of the five cases (80%) were alive after treatment, and the time between irradiation and the discovery of an aneurysm ranged from 6 to 11 years.

The pathophysiology and histologic changes in radiation-induced aneurysms are not well understood. A possible

explanation is that ionizing radiation causes cell death, leading to endothelial cell dysfunction, vasa vasorum injury, and accelerated atherosclerosis in acute and chronic time periods. This then resulted in intimal and adventitia injury of the artery, which Barletta et al. suggested are associated with fusiform aneurysm development (2). In addition, radiation can also induce inflammatory cytokine cascades, which persist for years (3). Chalouhi et al. (4) reported that inflammatory reactions associated with intracranial aneurysm formation begin with endothelial dysfunction, followed by the production of cytokines such as interleukin, tumor necrosis factor-alpha, matrix metalloproteinases, and prostaglandin E2. These inflammatory responses result in the disruption of the internal elastic lamina of vessels, vascular smooth muscle cell apoptosis, and the development of an aneurysm. Direct cell death and inflammatory responses after radiation may cause vessel wall injury and subsequent aneurysm formation.

Moreover, the incidence of intracranial aneurysms in patients with pituitary adenoma is 2.3–7.4% higher than in the general population and in patients with other brain tumors (5). However, apoplexy from a ruptured cerebral aneurysm is rare. Five cases in the literature reported the coexistence of ruptured aneurysms (5), located at the anterior cerebral artery and posterior communicating artery. Local circulatory stress, endocrinological effect, mechanical effect, and direct invasion have been proposed as possible mechanisms of aneurysm formation in patients with pituitary adenoma (5). However, our case is different from previous cases due to the unique location of the aneurysm, the absence of an endocrinological effect, and the fact that the aneurysm developed over a long time period. This time period reinforces that SRS was most likely the cause of the aneurysm rather than the adenoma itself.

The treatment of radiation-induced fusiform cerebral aneurysms is not well-established. Endovascular treatment with or without bypass procedures should be considered in these cases. However, several issues should be considered before treatment. First, the fragile radiation-induced aneurysm wall is prone to rupture, so the possibility of rupture during embolization should be considered. Second, stenosis of the internal carotid artery, middle cerebral artery, and anterior cerebral artery due to radiation may increase the risk of embolic events during catheter passage. Careful instrument manipulation with dual antiplatelet therapy and heparization is needed to prevent infarction events. Moreover, a regional radiation effect may increase the risk of recanalization and new aneurysm formation. Hence, these patients should be closely followed after the procedure.

Patient perspective

The actual pathogenesis of aneurysm formation after SRS is still under debate. The duration of aneurysmal formation following SRS to treat intracranial tumors can be several years. How long is the recommended follow-up after radiotherapy?

The fragile radiation-induced aneurysm wall is prone to rupture, so the possibility of rupture during embolization should be considered.

Patients with pituitary adenoma are at greater risk of aneurysm development. Due to the effect of radiation on cerebral vessels, the risk of aneurysm should be explained and well discussed before treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Tri-Service General Hospital Institutional Review Board (Approval No. A202215217). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PW, MC, and DJ were responsible for the study conceptualization. HL, YW, and SF were responsible for the study procedures. PW, YY, and DH analyzed and interpreted the study data. PW and DJ were the major contributors in writing the original draft. PW, MC, YY, DH, and DJ reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Neurology

TYPE Correction
PUBLISHED 10 October 2023
DOI 10.3389/fneur.2023.1301436

OPEN ACCESS

APPROVED BY
Frontiers Editorial Office,
Frontiers Media SA, Switzerland

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RECEIVED 28 September 2023
ACCEPTED 28 September 2023
PUBLISHED 10 October 2023

CITATION
Wang PW, Chung MH, Feng SW, Liao HC, Wu YC, Hueng DY, Yang YJ and Ju DT (2023) Corrigendum: Case report: Ruptured internal carotid artery fusiform aneurysm mimicking pituitary apoplexy after stereotactic radiosurgery. *Front. Neurol.* 14:1301436. doi: 10.3389/fneur.2023.1301436

Corrigendum: Case report: Ruptured internal carotid artery fusiform aneurysm mimicking pituitary apoplexy after stereotactic radiosurgery

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KEYWORDS

fusiform aneurysm, radiosurgery (SRS), pituitary tumor, apoplexy, internal carotid aneurysm

A corrigendum on
Case report: Ruptured internal carotid artery fusiform aneurysm mimicking pituitary apoplexy after stereotactic radiosurgery

by Wang, P. W., Chung, M. H., Feng, S. W., Liao, H. C., Wu, Y. C., Hueng, D. Y., Yang, Y. J., and Ju, D. T. (2023). *Front. Neurol.* 14:1219372. doi: 10.3389/fneur.2023.1219372

In the published article, there was an error in affiliation 2. Instead of "Department of Neurological Surgery, Tri-Service General Hospital, Taipei, Taiwan", it should be "Department of Neurological Surgery, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan".

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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TYPE Case Report
PUBLISHED 10 August 2023
DOI 10.3389/fneur.2023.1196431

OPEN ACCESS

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RECEIVED 01 April 2023
ACCEPTED 26 July 2023
PUBLISHED 10 August 2023

CITATION
Wang H, Lin Q, Wang F, Yi Y, Xu X, Jiang J and Deng Q (2023) Case report: A rare case of cerebral herniation during glioma resection in a syphilis-positive patient.
Front. Neurol. 14:1196431.
doi: 10.3389/fneur.2023.1196431

Case report: A rare case of cerebral herniation during glioma resection in a syphilis-positive patient

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Acute intraoperative cerebral herniation is catastrophic in craniotomy and seriously affects the outcomes of surgery and the prognosis of the patient. Although the probability of its occurrence is low, it can lead to severe disability and high mortality. We describe a rare case of intraoperative cerebral herniation that occurred in a syphilis-positive patient. The patient was diagnosed with both glioma and syphilis. When the glioma was completely removed under the surgical microscope, acute cerebral herniation occurred. An urgent intervention in cerebral herniation identified a collection of colorless, transparent, and protein-rich gelatinous substances rather than a hematoma, which is a more commonly reported cause of intraoperative cerebral herniation in the literature. We have found no previous descriptions of such cerebral herniation during craniotomy in a patient with syphilis and glioma. We suspected that the occurrence of intraoperative cerebral hernia might be related to the patient's infection with syphilis. We considered the likelihood of an intraoperative cerebral herniation to be elevated when a patient had a disease similar to syphilis that could cause increased vascular permeability.

KEYWORDS

cerebral herniation, glioma, syphilis, vasculitis, craniotomy

Introduction

Acute intraoperative cerebral herniation is more common in brain trauma surgery but can occasionally occur in surgery for brain tumor resection. Based on prior literature search, the etiology of intraoperative acute intraoperative brain bulge encompasses the occurrence of hematoma in a distant location from the surgical site, acute cerebral edema resulting from obstruction of cerebral venous return during surgery in the patient (1). It seriously affects the prognosis of patients and does more harm than the disease itself. To the best of our knowledge, there are no previous descriptions of an acute intraoperative epidural lesions in a glioma patient with syphilis that resulted in acute cerebral herniation.

Case presentation

Clinical presentation

A 28-year-old woman was admitted to the hospital for mental disorders half a month prior. Severe headaches and visual hallucinations were the primary clinical manifestations without fever, heart murmur, skin lesionss, or hepatosplenomegaly. Motor and sensory examinations revealed normal results. The bilateral Babinski sign was negative.

Diagnosis and preoperative course

Magnetic resonance imaging (MRI) of the head showed a space-occupying lesions in the right frontal lobe (Figures 1A–C). The toluidine red unheated serum test (TRUST) titer was 1:8. The *Treponema pallidum* particle agglutination test (TPPA) was 1:80 positive, and serology was negative for human immunodeficiency virus (HIV). We could not perform a preoperative CSF examination on this patient, as we considered that she had features of increased intracranial pressure. At the same time, the patient was unable to cooperate with the lumbar puncture due to her psychiatric symptoms. She received penicillin G intravenously at a dosage of 2.4 million units per day for 14 days in order to rule out cerebral syphilis gumma (2). Mannitol is simultaneously infused intravenously to reduce her intracranial pressure. A follow-up computed tomography (CT) scan of the head after treatment showed that the lesions was almost unchanged from the time of admission.

Operation and pathological findings

A craniotomy was performed after signing the consent form.We used a large craniotomy with a bone flap that exceeded the extent of the patient's tumor edema. The operation went well, and the tumor was basically resected. When we were preparing to suture the dura mater, the patient suddenly developed an acute protrusion of the right frontal lobe within approximately 10 min. An emergency CT scan showed a low-density, spindle-shaped epidural lesions (Figures 1D,E). Decompression craniectomy and evacuation of the epidural lesionss were performed immediately. A large amount of colorless and transparent gelatinous substances were found in the epidural area of the patient (Figure 1F). It was easily evacuated by using a surgical aspirator. After the operation, the patient was in a coma for 3 days and gradually became conscious but was accompanied by left hemiplegia. The biochemical examination of exudate epidural fluid contains a large amount of proteins. The cytological examination of exudate epidural fluid contains a small amount of red blood cells. After the patient became conscious, her headache and the mental disorder of the patient were relieved. As soon as the patient's consent was obtained, we performed a lumbar puncture 2 weeks after her surgery. Cerebrospinal fluid (CSF) analysis revealed a white blood cell count of 20.2×10^6/L (85% lymphocytes and 15% monocytes), a red blood cell count of 1.03×10^9/L, a total protein level of 0.79 g/L, and a chloride concentration of 122.6 mmol/L. Her CSF analysis revealed that TRUST was negative and TPPA was 1:40 positive. Pathological examination showed H&E staining of a pleomorphic glial tumor with round tumor cells and high mitotic activity (Figure 1G). Immunohistochemistry showed that glial tumor cells were positive for GFAP (glial fibrillary acidic protein). Nuclear expression of ATRX

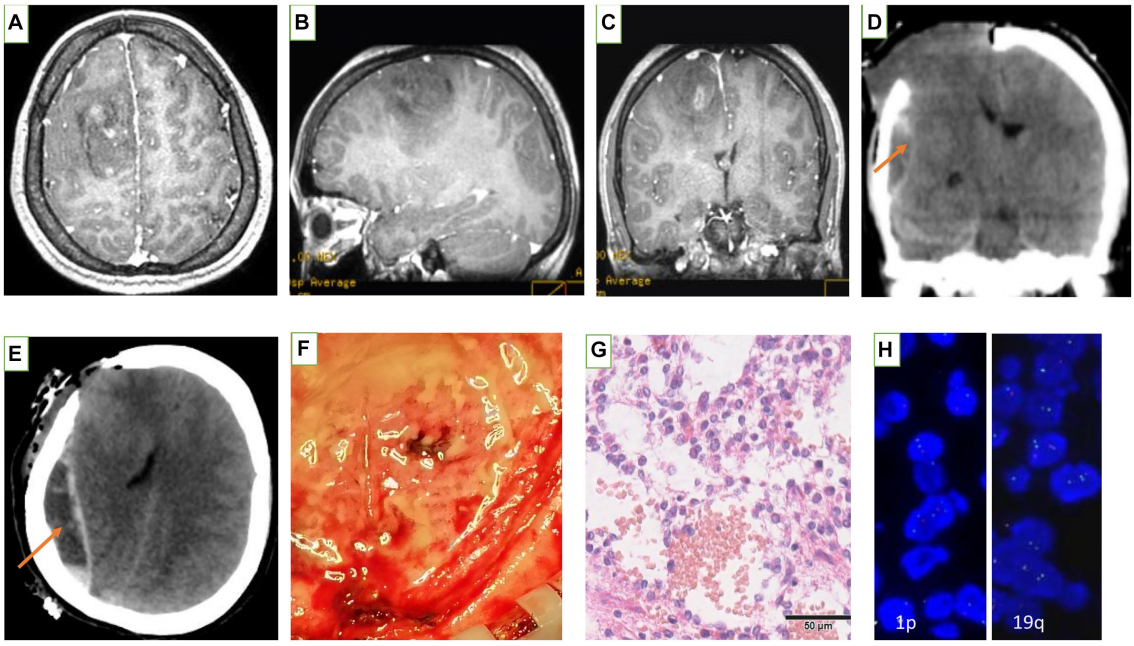

FIGURE 1
Images obtained from the preoperative cranial MRI: the right frontal lobe space-occupying lesions. **(A)** axial T1 enhanced, **(B)** Sagittal T1 enhanced, and **(C)** Coronal T1 enhanced. **(D,E)** Emergency cranial CT during the operation: found the low-density of the epidural behind the surgical area. (orange arrow). **(F)** Photo of the epidural during decompressive craniectomy: gelatinous substance in the epidural area. **(G,H)** Pathological examination confirm the right frontal lobe mass is anaplastic oligodendroglioma, IDH mutated, 1p/19q codeleted, (WHOIII): scale bar 50um.

(α-thalassemia/mental retardation syndrome X-linked) was retained, and IDH1 (isocitrate dehydrogenase 1) R132H mutant protein was expressed. The Ki-67 proliferative index was 5%. Analysis of 1p and 19q status revealed a combined loss of 1p and 19q. The right frontal lesions was graded as anaplastic oligodendroglioma, IDH mutated, 1p/19q codeleted, WHO III (Figures 1G,H).

Postoperative course

After the operation, the patient was in a coma for 3 days, gradually became conscious, and was discharged after 1 month of treatment but was accompanied by left hemiplegia. Because the patient lived in a remote village, the telephone follow-up revealed that she was able to walk with a cane. The patient currently felt headaches all the time and needed to be relieved by taking painkillers.

Discussion

Acute intraoperative cerebral herniation is an infrequent but catastrophic occurrence. According to previous reports, it often occurs in emergency surgery for severe craniocerebral trauma, and the common cause of intraoperative acute cerebral herniation is epidural or subdural hemorrhage during surgery (1). To date, a case of intraoperative cerebral herniation due to a large amount of colorless and transparent gelatinous substances has not been reported. Based on the patient's symptoms, serology, and CSF findings, we considered the patient to have neurosyphilis. According to previous reports, neurosyphilis can occur at any time after primary infection (3, 4). At the same time, the pathologic findings of meningovascular syphilis include diffuse thickening and lymphocytic infiltration of the meninges with superimposed arteritis (5, 6). The formation of the epidural gelatinous substance in this patient can be attributed to the following reasons. First, the decrease in intracranial pressure after tumor resection leads to an increase in volemia of the epidural blood vessels (7). Second, patients with neurosyphilis have vasculitic changes on the dural surface and increased vascular permeability (8) (Figure 2A). Glioma can form neovascularization with high defects, resulting in vessels with abnormal morphology and function (9). Third, leakage of plasma-protein-rich fluid accumulates in the epidural space, which is stirred repeatedly as the patient's cerebral pulsatility to form a gelatin-like substance (Figure 2B). According to the CT imaging and intraoperative images, the epidural collection is not only gelatinous but also has a blood component. Young and middle-aged postoperative patients with postoperative intracranial tumors often suffer from epidural hemorrhage because the dura mater is more loosely combined with the skull, and it is easier to peel off when the intracranial pressure changes. Therefore, epidural hemorrhage in remote sites is more likely to occur. In elderly patients, due to the large gap between the dura mater and the brain tissue and the poor compliance of the brain tissue in elderly patients, the intracranial pressure fluctuates significantly during the operation, which may easily lead to stretching and rupture of the bridging vein. Therefore, subdural hematomas in distant parts are more likely to occur (10, 11). Eventually, the gradually increasing epidural collection causes a malignant intraoperative cerebral herniation.

Conclusion

Our case is the first known case of a malignant bulge of the brain during craniotomy caused by the accumulation of a large amount of gelatinous substances. When cerebral herniation occurred, we intervened promptly and accurately, which ultimately led to the patient's survival. Despite the efficacy of the treatment for neurosyphilis in this particular patient, the irreversible harm inflicted by treponema pallidum on the blood vessels of the meninges necessitates caution among patients undergoing craniotomy, as cerebral bulges may arise during surgery, regardless of whether it occurs during the active phase of neurosyphilis or subsequent to treatment. In conclusion, it is strongly advised that neurosurgeons exercise utmost caution during craniotomy procedures conducted on patients presenting with treponema pallidum infection or any other medical condition that may potentially induce vasculitis. When these patients require a craniotomy, the likelihood of cerebral herniation during surgery will increase.

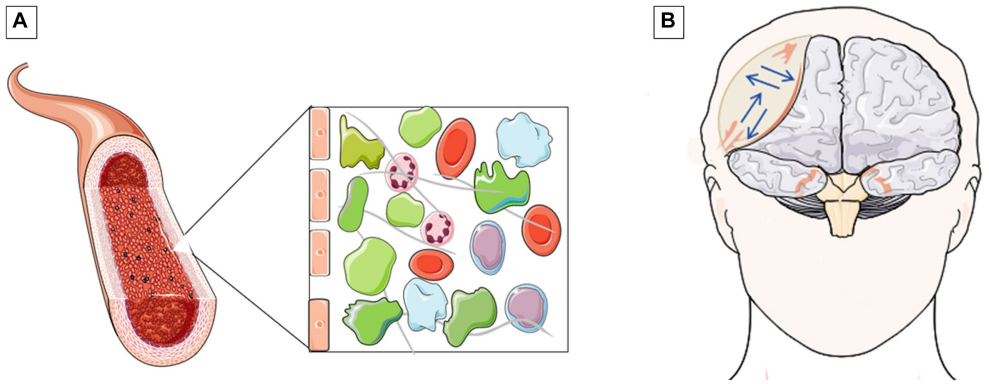

FIGURE 2
Schematic of inflammatory vascular exudation and schematic of the principle of epidural space occupying lesion formation. **(A)** Inflammation of blood vessels results in increased distance between endothelial cells. Eventually, a large amount of proteinaceous substances leak out of the blood vessels. **(B)** The exuded proteins churned in all directions with the frequency of the patient's cerebral pulsatility, eventually leading to the epidural mass effect (blue arrows).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/ participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

This work was supported by the Sichuan Province Key R&D Project (22ZDYF1826) and the 2021 hospital-level incubation Project of Yibin Hospital, West China Hospital of Sichuan University (2021FY15).

Conflict of interest

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frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 22 September 2023
DOI 10.3389/fneur.2023.1221810

OPEN ACCESS

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RECEIVED 12 May 2023
ACCEPTED 28 August 2023
PUBLISHED 22 September 2023

CITATION
Li W, Guo J, Wang L, Zhang T and Li T (2023) Acute spinal cord infarction secondary to ankylosing spondylitis: a case report and literature review.
Front. Neurol. 14:1221810.
doi: 10.3389/fneur.2023.1221810

Acute spinal cord infarction secondary to ankylosing spondylitis: a case report and literature review

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Introduction: Spinal cord infarction secondary to ankylosing spondylitis is a rare but severe disorder.

Case presentation: Here we present a case of acute spinal cord infarction in a 54 years-old man with a medical history of ankylosing spondylitis, scoliosis, and hypotension. The patient complained of a sudden onset of lower limb weakness. A physical examination showed that he suffered from a dissociative sensory disorder, paralysis, and concomitant sphincter disturbances. After undergoing a whole-spine MRI, he was diagnosed with an acute ischemic injury from T2 to T5. As he did not treat his ankylosing spondylitis, it later caused a spinal deformity, making the lumbar puncture technically challenging. However, using Taylor's approach, a CSF sample was successfully obtained. A CSF biochemical test ruled out myelitis, NMOSD, and MS. After receiving treatment with low-molecular-weight heparin, atorvastatin calcium, and methylprednisolone, his sphincter function gradually recovered, but his strength was only partially restored.

Conclusion: Although this is a rare entity, it is necessary for physicians to consider it when evaluating patients with a sudden loss of sensation and strength in their lower limbs.

KEYWORDS

spinal cord infarction, ankylosing spondylitis, autoimmune disease, Taylor's approach, vascular disease

1. Introduction

Spinal cord infarction (SCI) is less frequent than ischemic brain injury and represents only approximately 1% of all strokes. It also accounts for 8% of myelopathies (1, 2). It can leave patients with devastating neurological sequelae such as paraplegia, quadriplegia, and incontinence. There are usually no obvious inducing factors, the rate of misdiagnosis is high, and there is no unified treatment plan. In general, the common etiologies of SCI include atherosclerosis, embolism, vertebral dissection, fibrocartilaginous embolism, hypercoagulable states, vasculitis, vascular malformations, and vascular compression. Additionally, systemic conditions such as cardiovascular disease, hypercoagulability, and hypotension have common etiologies. However, approximately one-third of SCIs have no identifiable etiology. Therefore, this is considered an idiopathic or cryptogenic disease. The progression of acute SCI is slower than that of cerebral infarction, peaking within 12 h and developing for up to 72 h (3).

We treated a patient with a years-long history of ankylosing spondylitis who suddenly developed weakness in both lower extremities.

Common neurological complications of ankylosing spondylitis (AS) include stroke, cauda equina syndrome, and peripheral neuropathy (4, 5). However, AS associated with early-onset atherosclerosis has attracted the attention of doctors. Studies have shown that, compared with healthy people, patients with AS have a higher incidence of cardiovascular and cerebrovascular disease and mortality (6). They are more often associated with hypertension, metabolic syndrome, diabetes, and other risk factors.

Nevertheless, only a few cases of AS with SCI have been reported. The case we present may provide new insights into the possibility of a relationship between AS and SCI, whether secondary or combined.

2. Case presentation

A 54 years-old right-handed man was admitted to the Department of Neurology of The Second Hospital of Lanzhou University in September 2021 with a sudden onset of lower limb weakness. Four days before admission, the patient felt weakness in both lower limbs, more severe in the left leg, and was unable to walk. Two days later, the weakness in the right lower limb worsened, and he was unable to stand. He also presented with back pain, urinary retention, and constipation. The patient was a non-smoker with a medical history of scoliosis, hypotension, and AS, all of which were untreated. On examination, the subject's blood pressure was 75/50 mmHg. At that time, his weight was 40 kg, and his spine was deformed and curved. The neurological examination revealed that his speech, cognition, and cranial nerve function were normal. He had full strength bilaterally in all muscle groups in his upper limbs, with bilaterally brisk reflexes and normal muscle tone. Conversely, in his lower limbs, his muscle tone was significantly decreased, with tendon hyporeflexia. In both lower limbs, he had a flaccid tone with a Medical Research Council (MRC) grade 1/5 strength in the left leg and an MRC grade 2/5 strength in the right leg. He had dissociated sensory loss, and his superficial sensation was lost, with relative sparing of deep sensation below the level of the Th6 dermatome. Bilateral Babinski signs were present. The modified Rankin scale (MRS) score was 4/5.

Laboratory tests showed: C-reactive protein (CRP) 55.54 mg/L (normal range <6 mg/L), erythrocyte sedimentation rate (ESR) 23 mm/h (normal range <20 mm/h), immunoglobulin A (IgA) 4.5 g/L (normal range <4 g/L), D-dimer 1.13 mg/mL (normal range <0.5 mg/mL), γ-glutamyl transpeptidase (γ-GT) 268 u/L (normal range 10–60 u/L), alkaline phosphatase (ALP) 205 u/L (normal range 45–125 u/L), triglycerides (TG) 4.44 mmol/L, lipoprotein (a) [Lp(a)] 482 mg/L (normal range <400 mg/L), creatine kinase (CK) 365 u/L (normal range 50–310 u/L); HLA-B27 was positive. Homocysteine (HCY), hemoglobin A1c (HbA1c), antiphospholipid antibodies, thyroid function, and routine anticoagulant blood tests were normal. Electromyography (EMG) showed multiple sensory and motor nerve damages. A color Doppler ultrasound showed a thrombus in the intermuscular vein of the left lower limb.

An MRI of the whole spine was undertaken. On the sagittal T2, there was an abnormal intramedullary signal intensity from T2 to T5, with central cord swelling. Diffusion-weighted imaging (DWI) with an apparent diffusion coefficient showed restricted diffusion, which can be seen in patients with acute ischemia (Figures 1A–C). A spinal angiogram was recommended but declined by the patient.

Due to his AS, the patient had spinal deformities, ligament ossification, and spinal space occlusion (Figure 2A), which made lumbar puncture technically challenging. CT of the sacroiliac joint showed that he had bilateral sacroiliitis and calcification of the anterior and posterior longitudinal ligaments (Figure 1D). A chest CT showed abnormalities of the thoracic vertebrae and an old fracture of the ribs. Experienced anesthesiologists performed multiple lumbar puncture attempts in the left lateral position at different levels (L2_3 and L3_4), with both midline and paramedian approaches, but these failed. After five failed attempts, the Taylor approach was successfully used for lumbar punctures. After local anesthetic infiltration, a spinal needle was inserted 1 cm medial and 1 cm caudal to the posterior superior iliac spine, which was located immediately in front of the skin depression. On the first attempt, a needle was inserted toward the medial side of the head toward the L5_S1 space to obtain clear cerebrospinal fluid. Cerebrospinal fluid analysis showed a normal cell count (3 m/L) and an elevated protein level (0.72 g/L). The patient was negative for serum anti-aquaporin4 antibody (AQP4), oligoclonal band (OB), and glial fibrillary acidic protein (GFAP).

An MRI was performed to differentiate between possible inflammation and infarction. The MRI demonstrated restricted diffusion from T2 to T5. Combined with a severe acute deficit within hours, the subject was diagnosed with SCI.

We treated the patient with low molecular weight heparin (LMWH) for 1 month at the therapeutic dose, atorvastatin calcium (20 mg daily), and 160 mg intravenous methylprednisolone for 5 days, to reduce spinal cord edema. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for the symptomatic treatment of AS. After 2 weeks, a thoracic spine MRI showed a slightly decreased signal (Figures 2B–D). One month later, a reexamination of the lower vascular ultrasound showed unobstructed blood flow and resolution of venous thrombosis. After 8 weeks, the patient could walk with a medical walker. His MRS score was 3/5. A total of 6 months after the onset of his symptoms, he was able to walk independently and live without assistance. The treatment timeline is shown in Figure 3.

3. Discussion

Here we describe a case of acute SCI with a history of AS. The pathogenesis of acute SCI included aortic and venous pathology. In turn, the aortic pathology included mechanical radicular artery injury and spinal hypoperfusion. In a study of 131 patients with spontaneous spinal cord infarction (3), the suspected mechanism of SCI was idiopathic with atherosclerotic risk factors in 91 subjects (68%); fibrocartilaginous embolism, 19 (14%); aortic dissection, seven (5%); hypercoagulability, five (4%); vertebral artery dissection, four (3%); systemic hypotension, three (2%); cardioembolic, two (2%); and vasculitis, two (2%). Unfortunately, the patient refused to undergo a examination of spinal angiography. Thus, there is no direct examination results of the patient's vascular condition. The patient had a long history of hypotension. Combined with the patient's frail body habitus, we believe that his current blood pressure level was relatively normal for him. Additionally, there were no further apparent induced incidents such as diarrhea, reduced diet, or sweating, before the onset of this spinal infarction. Even though hypotension was probably not

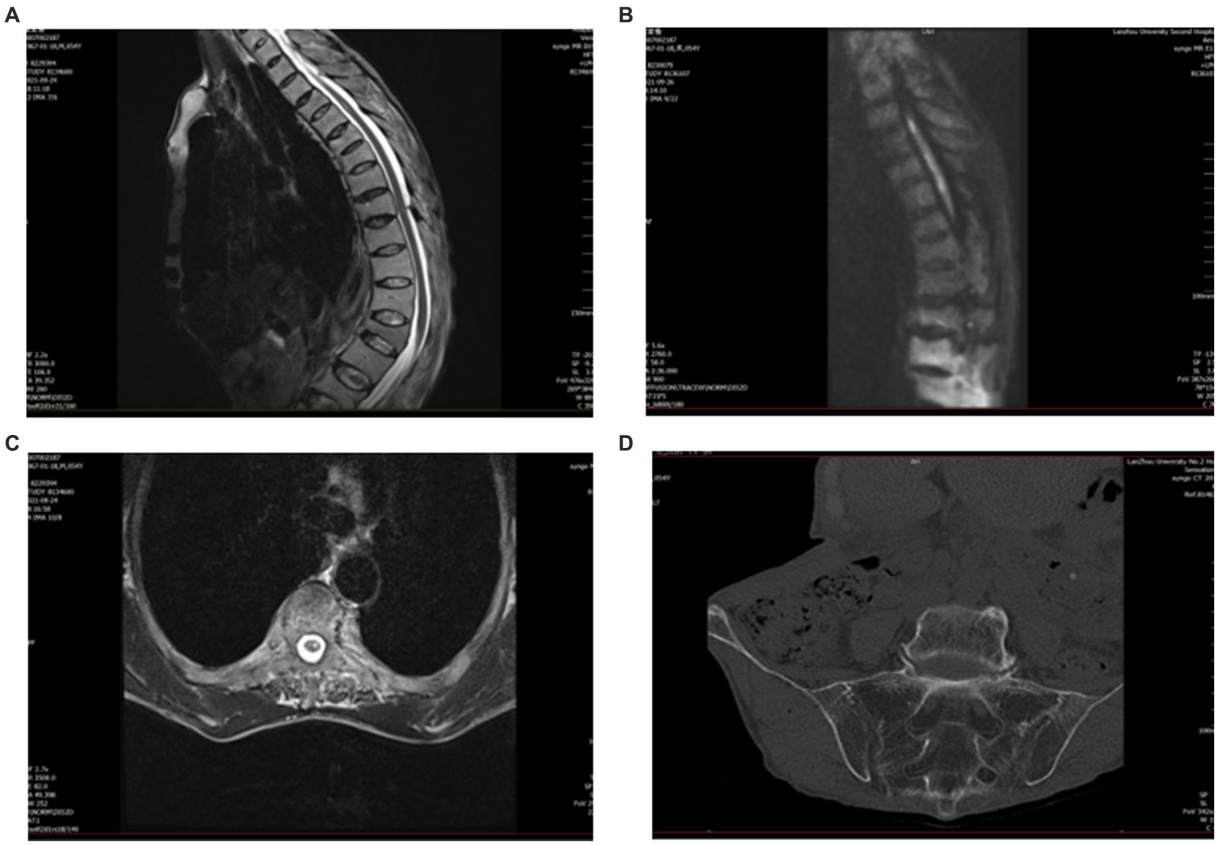

FIGURE 1
Pre-treatment magnetic resonance imaging (MRI). **(A)** Sagittal T2 cervical spine shows high signal T2–T5. **(B)** Diffusion-weighted imaging (DWI) shows restricted diffusion within the gray matter. **(C)** Axial T2 suggests a high signal centrally in the spinal cord. **(D)** CT of the sacroiliac joint shows bilateral sacroiliitis and calcification of the anterior and posterior longitudinal ligaments.

the main cause of infarction in this patient, it could be a significant contributing factor in combination with AS and radicular artery compression.

Ankylosing spondylitis is a chronic, progressive autoimmune rheumatic inflammatory disease. Patients with AS have an elevated risk of developing cerebrovascular disease. These factors include continuous systemic inflammation and lipid metabolism disorders (7). Chronic systemic inflammation may contribute to endothelial damage, diastolic dysfunction, and accelerated atherosclerosis. It may also lead to small-vessel inflammation. There are reports (8) suggesting that patients with AS have significantly higher levels of TG, HDL, and Lp(a), but these are potential contributing factors. Thus, patients with AS exhibit lipid metabolism disorders that work together with chronic systemic inflammation in the process of atherosclerosis. Our patient's high levels of CRP and ESR may indicate that his AS was active, although this is not definitive. His lipid levels [TG, LDL, and Lp (a)] were all high, suggesting that he had only lipid disorders.

This patient's EMG suggested peripheral neuropathy. This could be a complication of AS. There are probably several different mechanisms, such as demyelination, disruption of the blood supply (probably of arterial origin), and areas of arachnoiditis occurring earlier in the disease and resulting in atrophy. The latter is possible because patients usually develop their symptoms over a few months and then do not progress further (9).

There have been reports of cardiovascular disease associated with AS, and the pathogenesis of cardiovascular and cerebrovascular disease is similar, allowing the pathogenesis of spinal cord vascular disease. The related mechanisms include the following aspects: first, there is secondary systemic vasculitis. Second, AS accelerates the atherosclerosis in myelopathy. Finally, even though the patient's weight loss, chronic hypotension, chronic malnutrition, and other factors (e.g., chronic adrenal insufficiency in a chronically ill patient) may have contributed to spinal ischemia, AS was still the primary cause. Therefore, our patient was ultimately diagnosed with SCI secondary to AS.

Due to his kyphotic scoliosis, the conventional technique for lumbar puncture failed. Lumbar puncture with Taylor's approach targeting the L5-S1 interlaminar space was performed as an alternative. The reason is that targeting the L5_S1 interlaminar space provides a reliable alternative to the midline approach for lumbar puncture that is least affected by arthritic and degenerative changes (10).

Unfortunately, there are no universally accepted and effective methods to treat SCI. A few case reports advocate using IV thrombolysis in SCI patients in the hyperacute period (11, 12). However, no public data are available to support their use. In practice, treatment is usually based on the etiology of spinal cord ischemia. If no clear etiology is found, risk factor modification with blood pressure and glucose control, statins, and antithrombotics is often considered. We treated the patient with methylprednisolone, aiming to reduce the spinal cord edema. Due to his high D-dimer and deep venous

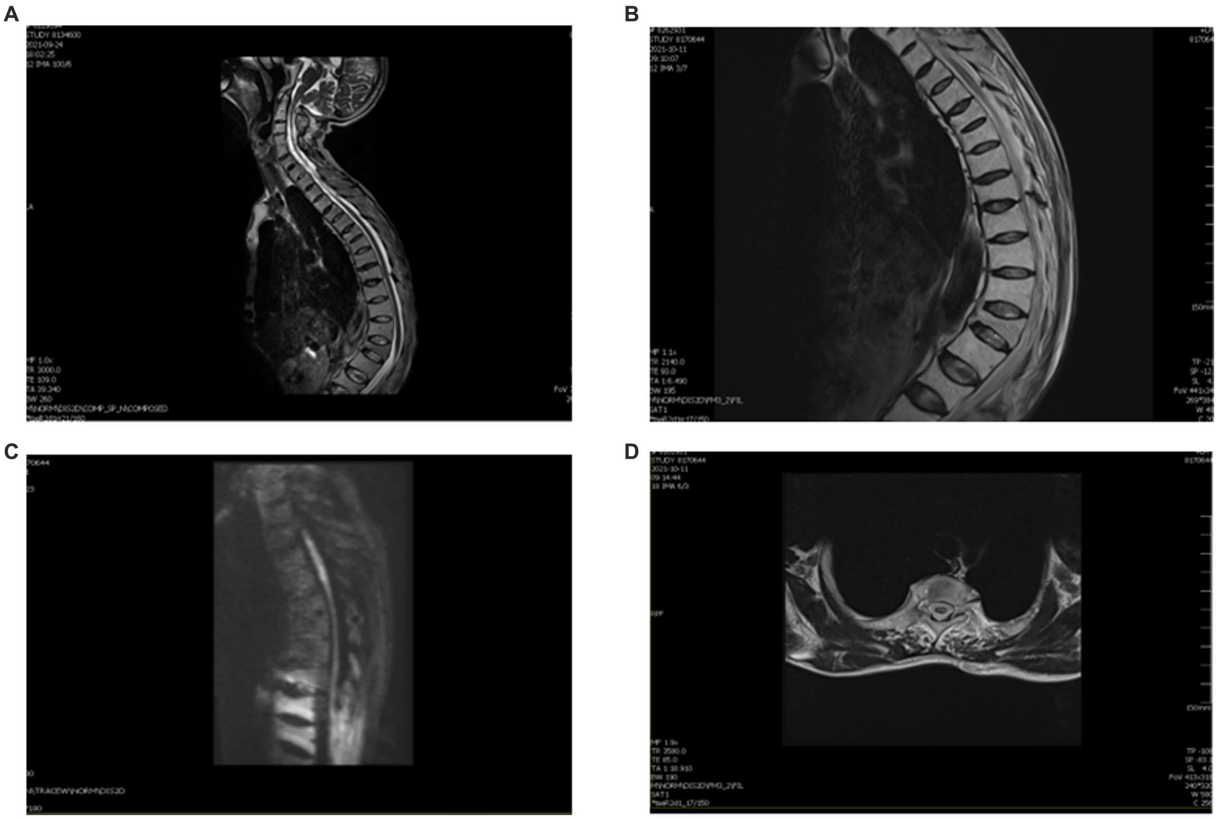

FIGURE 2
MRI of this patient after therapy. **(A)** Thoracic kyphosis with multiple vertebral wedgies at T4, T6, T7, T9, L1, and L3. **(B)** Sagittal T2 thoracic vertebrae T2–T5 are slightly hypersignal. **(C)** DWI shows a slightly elevated signal in the gray matter. **(D)** Axial T2 central hypersignal is less than before.

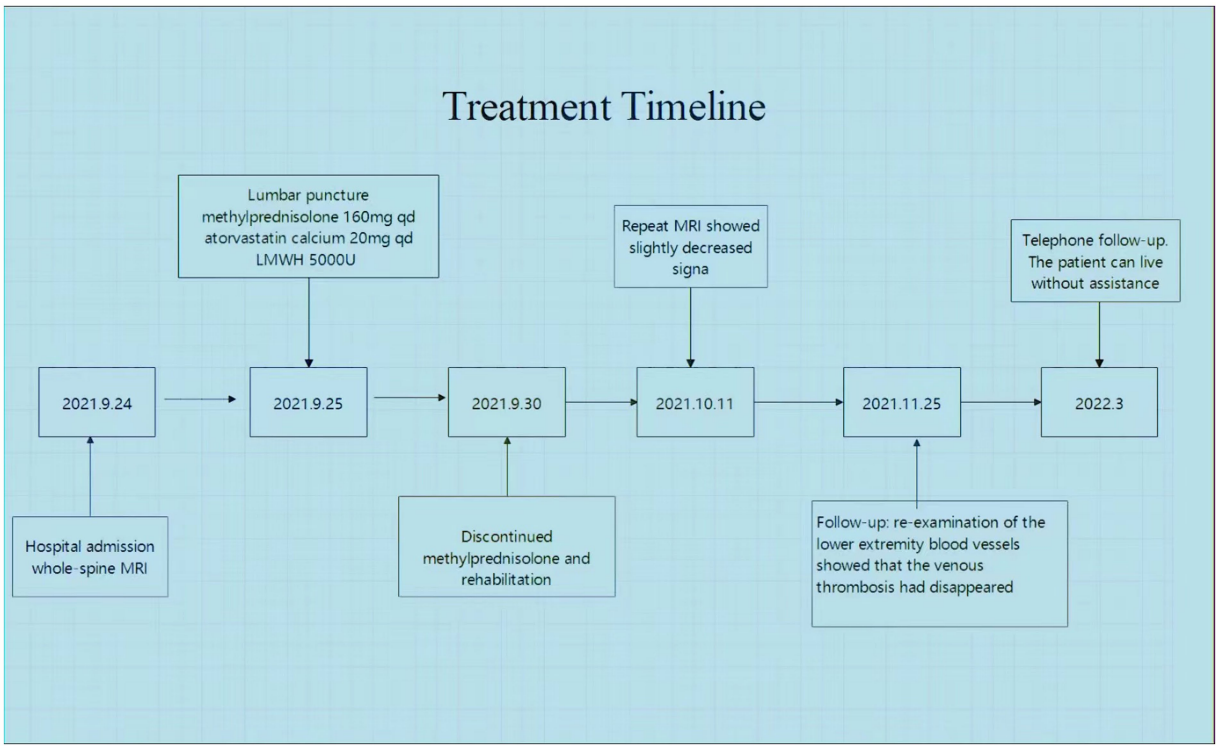

FIGURE 3
Treatment timeline of the patient.

thrombosis, we used antithrombotic therapy. With the applied therapy, his blood pressure increased to 110/70 mmHg.

We searched the PubMed database using the search strategy "(spinal cord infarction) and (ankylosing spondylitis)" and found seven items, one of which was relevant. Shim et al. (13) described a man with ankylosing spondylitis who developed multiple cerebellar infarctions due to vertebral artery obstruction and bulbar symptoms associated with atlanto-occipital subluxation and vertical subluxation. Although there are few reports on the correlation between spinal cord infarction and ankylosing spondylitis, there are many reports on spinal cord infarction.

Isolated posterior spinal cord infarction is rare, and vertebral artery dissection should be considered as an etiologic mechanism. Montalvo et al. (14) described a patient with an acute onset of flaccid quadriplegia. He regained complete muscle strength within 1 h. His MRI of the cervical spine showed a C3–C4 level consistent with ischemic stroke. MR angiography showed a vertebral artery dissection. The extensive collateral vascular network perfusing the spinal cord makes the incidence of spinal infarction low. Gu et al. (15) reported an acute spinal cord infarction due to a type B intramural hematoma of the descending aorta. The patient was able to walk with an elbow crutch after 2 years.

Recently, Zalewski et al. (3) proposed diagnostic criteria for SCI. These emphasize three major components: (1) clinical: rapid development of severe deficits within 12 h; (2) MRI spine: exclusion of compression (2A) with supportive features (2B), specific imaging findings (2C); and (3) CSF: emphasis on noninflammatory findings in most cases.

4. Conclusion

We presented a rare case of SCI related to AS, which was both interesting and significant. It may help clinicians have a better understanding of the potential for ischemic myelopathy associated with AS.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by The Ethics Committee of Lanzhou University Second Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JG, TL, and WL conducted the research, participated in data collection, and drafted the manuscript. JG, LW, WL, and TZ conceived and participated in the design. All authors contributed to the article and approved the submitted version.

Funding

This project was supported by Youth Foundation of Gansu Province (21JR7RA425).

Acknowledgments

The authors thank Scribbr (https://www.scribbr.com/) for the language editing service.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

SCI	Spinal cord infarction
AS	Ankylosing spondylitis
MS	Multiple sclerosis
NMOSD	Neuromyelitis optica spectrum disorder
MRC	Medical Research Council
MRS	Modified Rankin scale
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IgA	Immunoglobulin A
γ-GT	γ-glutamyl transpeptidase
ALP	Alkaline phosphatase
TG	Triglycerides
EMG	Electromyography
MRI	Magnetic resonance imaging
DWI	Diffusion-weighted imaging
AQP4	Anti-aquaporin 4 antibody
OB	Oligoclonal band
GFAP	Glial fibrillary acidic protein
LMWH	Low-molecular-weight heparin

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TYPE Case Report
PUBLISHED 24 October 2023
DOI 10.3389/fneur.2023.1216328

OPEN ACCESS

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RECEIVED 23 June 2023
ACCEPTED 04 October 2023
PUBLISHED 24 October 2023

CITATION
Qu H-L, Sun X-Y and Dai Y-J (2023) Central pontine myelinolysis: a rare finding in hyperosmolar hyperglycemia.
Front. Neurol. 14:1216328.
doi: 10.3389/fneur.2023.1216328

Central pontine myelinolysis: a rare finding in hyperosmolar hyperglycemia

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Central pontine myelinolysis (CPM) is a heterogeneous nervous system disease of pontine demyelination, usually caused by rapid correction of hyponatremia. In the present study, we report a unique case of a 46-year-old man with a hyperglycemic state complicated with CPM. MRI demonstrated a high signal on T2 and symmetric restricted diffusion in the pontine. In conclusion, the clinical case described confirmed that the hyperosmolar state inherent in hyperglycemia was a likely cause of CPM.

KEYWORDS

central pontine myelinolysis, hyponatremia, hyperosmolar, osmotic demyelination syndrome, blood glucose

1. Introduction

Osmotic demyelination syndrome (ODS) is a rare complication of hyperglycemia and refers to central pontine myelinolysis and extrapontine myelinolysis manifesting with quadriparesis and neurocognitive changes with characteristic changes in magnetic resonance imaging (MRI) (1). The clinical manifestations range from low level of consciousness to dysarthria and then to quadriplegia (2). ODS is usually associated with myelin destruction in the central pontine basement, also known as central pontine myelinolysis (CPM). Here, we report a unique case of a 46-year-old man with a hyperglycemic state complicated with CPM.

2. Case report

A previously healthy 46-year-old man presented with limb weakness and dysarthria for 20 days. There was no history of malnutrition, a known diagnosis of diabetes, alcohol abuse, or smoking. Medical examination showed the patient presented with a body temperature of 36.6°C, respiratory rate of 18 breaths/min, normal resting heart rate of 76 beats/min, and blood pressure of 116/68 mm Hg. No abnormalities were found during heart and lung auscultation, and the patient presented with a soft abdomen and no swelling in either lower limb. A neurological examination revealed that he had mild dysarthria. His muscle tone was normal, with bilateral severe limb weakness and power was grade 2–3 in all of his limbs. Limb reflexes were mildly decreased and plantar flexor and sensation were normal. The blood results showed the following a blood glucose level of 49.7 mmol/L (894.6 mg/dL) and a normal range of 4–7 mmol/L. The hemoglobin A1c was 16.34%, 3-hydroxybutyric acid was 0.5 mmol/L, and he had 1+ ketone (20–29 mg/dL) in his urine. Notably, at presentation, his serum sodium was 128 mmoL/L (128 mEq/L), with a normal range of 133–146 mmol/L, but his serum potassium was markedly low at 2.8 mmol/L (2.8 mEq/L), with a normal range of 3.5–5.0 mmol/L. The calculated serum osmolality was 325 mosm/kg. Normal saline (0.9% NaCl) and insulin therapy (0.1 U/kg/h) were

started and provided symptomatic treatment with potassium and sodium supplementation. After 6 h of admission, his blood glucose was 43.4 mmol/L (781.2 mg/dL) and serum sodium was 130 mmoL/L (130 mEq/L), whereas over the first 24 h of admission, his blood glucose reduced to 36.6 mmol/L (658.8 mg/dL), serum sodium increased to 135 mmoL/L (135 mEq/L), and 3-hydroxybutyric acid was 0.3 mmol/L. His blood glucose reduced to 25.6 mmol/L (460.8 mg/dL) over 48 h of admission and his serum sodium increased from 128 to 141 mmol/L (128 to 141 mEq/L). Over the first 48 h of admission, the patient's serum potassium increased from 2.8 to 4.9 mmol/L (2.8 to 4.9 mEq/L), 3-hydroxybutyric acid was 0.05 mmol/L with negative ketonuria, and the calculated serum osmolality was 327 mOsm/kg. The blood glucose level is shown in Figure 1. In order to exclude peripheral nerve diseases, including acute inflammatory demyelinating polyneuropathy, lumbar puncture and electromyography were performed, and the results showed no abnormalities. The patient gradually became sleepy after admission, and the Glasgow Coma Score fluctuated between 13 and 14. However, there were no significant changes in his limb muscle power assessment. Because of the neurological symptoms, the patient subsequently underwent a cerebral MRI, which demonstrated features of CPM (Figure 2). The patient's condition became stable and he was discharged to a rehabilitation institution. His blood glucose level was controlled with long-acting and short-acting insulin. In the following 6 months, his symptoms gradually improved and the power returned to grade 5 in all his limbs. The patient gradually resumed his daily activities without any residual symptoms (modified Rankin Scale [mRS] score = 0). Considering the clinical improvement of the patient and the absence of new neurological impairments, no repeated brain imaging was performed.

3. Discussion

CPM is a heterogeneous nervous system disease of pontine demyelination, usually caused by rapid correction of hyponatremia, and the correction speed exceeds 9 mmol/L/24 h (3, 4). In addition to rapidly correcting hyponatremia, other factors may be chronic alcoholism, hypernatremia, hypokalemia, hypophosphatemia, anorexia nervosa, and diabetes (5). Although rapid correction of hyponatremia is often considered a cause of CPM, considering the speed of initial serum sodium and electrolyte correction, our patient was unlikely to undergo rapid correction. Although the patient reported here presented with a serum sodium growth rate of 6.5 mmol/L/24 h, which did not exceed 9 mmol/L/24 h, we suggest that the inherent hypertonic state of hyperglycemia was more likely the cause of CPM. However, there are limited reports of associations between central pontine myelinolysis and derangement of glucose. It is reported that before the treatment of hyperglycemia and hyperosmolality (6, 7), there were cases of CPM, and our patient's CPM may also have been caused by hyperosmolality before correction. Several reports have described patients with CPM in association with a hyperosmolar hyperglycemic state or its correction (8–17). Since there was no obvious change in osmotic pressure before and after correction, we consider that the CPM of our patient was related to the hyperosmolar state inherent in hyperglycemia. A diagnosis of CPM secondary to hyperglycemia was made.

Hyperglycemia and diabetes ketoacidosis are rare causes of CPM, and its physiopathology is uncertain (12). The pathophysiology of CPM may involve the sudden contraction of brain cells, especially oligodendrocytes, and demyelination caused by a rapid increase of serum osmotic pressure due to rapid correction of hyponatremia. Two theories have been proposed to explain oligodendrocyte contraction and myelinolysis, which are sometimes related to the rapid increase of serum osmotic pressure, whether due to the increase of sodium or other reasons, such as hyperglycemia: (i) local inflammatory demyelination caused by blood–brain barrier damage and (ii) oligodendrocyte apoptosis caused by hypertonic stress caused by changes in serum osmotic pressure, which occurs too fast to allow changes in specific molecules (11, 16). Research has shown that long-term episodes of severe hyperglycemia may lead to osmotic stress. Due to the poor control of diabetes, the unstable fluctuation of blood glucose may further lead to an unstable osmotic environment and the inability of normal cell compensation (18). MRI changes related to ODS typically include high signal lesions on

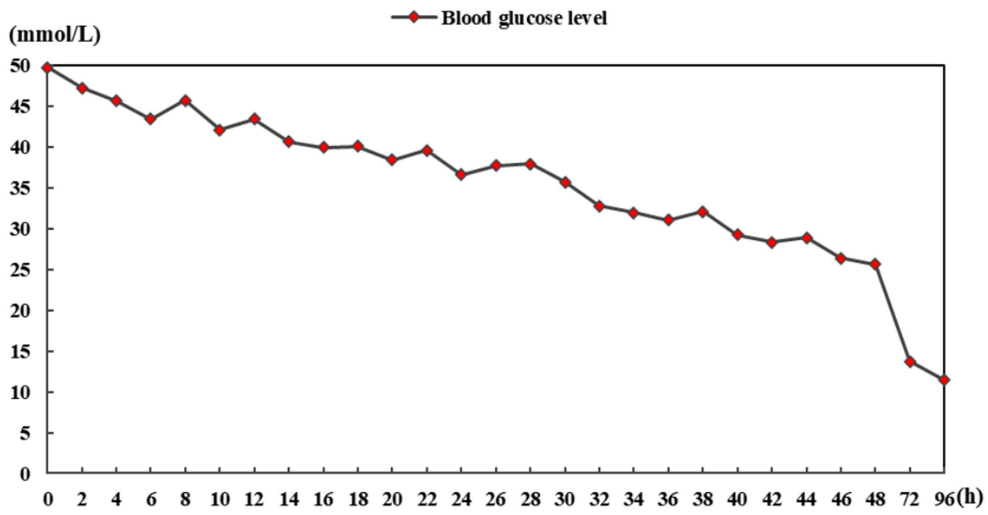

FIGURE 1
Blood glucose level chart.

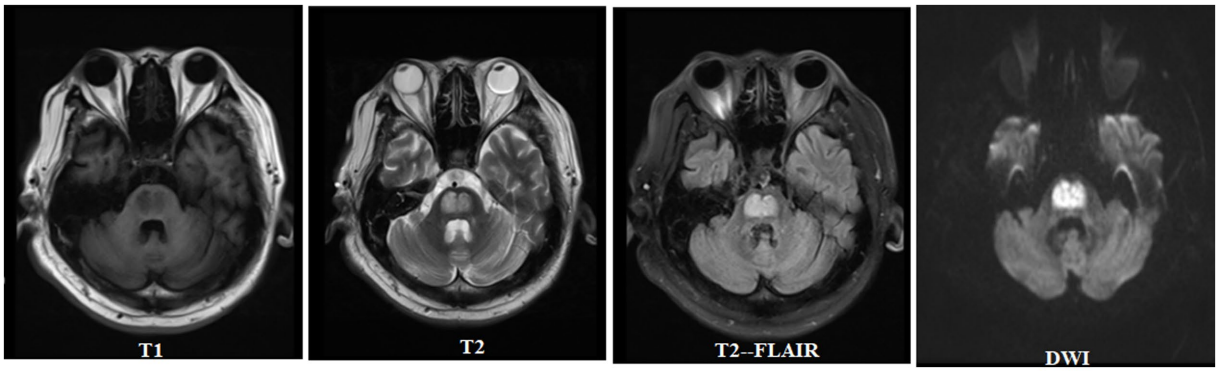

FIGURE 2
Central pontine myelinolysis in hyperglycemia.

T2-weighted MRI. The extension of T2-weighted signals can be explained by demyelination and edema (19).

Brain MRI remains the preferred diagnostic mode for CPM, and as described in the MRI results of this case, CPM may display a high signal on T2 and symmetric restricted diffusion in the pontine (10, 20). Despite reports of asymmetric lesions, pontine lesions are usually symmetrical (21). Our patient displayed the typical radiological and clinical findings of pontine myelinolysis with hyperglycemia, which is a rare phenomenon. Effective specific treatment methods have not yet been determined for the management of ODS cases. Therefore, the current treatment model includes general supportive care and treatment for potential causes, which is everything we do to treat patients. Similarly, there is no clear recommendation for the optimal timing of MRI imaging. The degree of clinical features and/or radiological changes cannot reliably determine the prognosis. The results vary from recovery to near-normal functional levels and death. More than half of ODS cases have recovered well, and the mortality rate of ODS cases has decreased over time. Even with severe neurological manifestations, patients with ODS may have a good prognosis (22).

In conclusion, the clinical case described confirmed that the hyperosmolar state inherent in hyperglycemia was a likely cause of CPM. Clinicians should consider hyperglycemia in patients with diabetes mellitus who develop CPM.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Y-JD conceived the study. H-LQ and X-YS collected the data and drafted the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Case Report
PUBLISHED 26 October 2023
DOI 10.3389/fneur.2023.1256200

OPEN ACCESS

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RECEIVED 12 July 2023
ACCEPTED 10 October 2023
PUBLISHED 26 October 2023

CITATION
Li M, Li Y, Tai L, Li H, Wang LQ, Zou YL, Feng WF, Liu Y, Liu X and He JY (2023) Cerebral venous thrombosis caused by spontaneous intracranial hypotension due to spontaneous spinal cerebrospinal fluid leakage in the high cervical region: a case report. *Front. Neurol.* 14:1256200. doi: 10.3389/fneur.2023.1256200

Cerebral venous thrombosis caused by spontaneous intracranial hypotension due to spontaneous spinal cerebrospinal fluid leakage in the high cervical region: a case report

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Spontaneous intracranial hypotension (SIH) may lead to cerebral venous thrombosis (CVT). This case report describes the diagnostic and treatment processes used for a patient with CVT caused by SIH due to spontaneous spinal cerebrospinal fluid (CSF) leakage in the high cervical region. Clinical data were collected from a 37-year-old man with an initial symptom of spontaneous posterior cervical pain. The diagnostic and treatment processes of SIH-induced CVT were described. A magnetic resonance imaging (MRI) study showed superior sagittal sinus thrombosis, and a lumbar puncture revealed a low initial CSF pressure of less than 60 mmH_2O. The patient underwent anticoagulation and fluid rehydration therapies. No abnormalities were observed in the thoracic MRI scan, but a cervical MRI scan revealed a spontaneous CSF leak. An epidural blood patch with autologous blood was performed, and symptoms completely resolved 3 days after the procedure. This report proposes a diagnostic procedure for detecting rare cases of SIH-induced CVT, thereby preventing future misdiagnoses and delayed treatment. When a patient presenting with CVT in conjunction with intracranial hypotension has no history of trauma or piercing, SIH caused by spontaneous spinal CSF leakage should be considered as a potential cause of secondary low intracranial pressure. For detection of CSF leaks at rare sites, an MRI of the whole spine rather than a localized MRI of the spine needs to be performed to avoid misdiagnosis. An epidural blood patch should be performed as soon as possible as it may shorten the length of hospitalization and improve prognosis.

KEYWORDS

cerebral venous thrombosis, epidural blood patch, low cranial pressure, spontaneous cerebrospinal fluid leak, spontaneous intracranial hypotension

Introduction

Cerebral venous thrombosis (CVT) is a rare neurological disease that may cause life-threatening complications, such as epilepsy, cerebral hemorrhage, and cerebral herniation. The incidence of CVT is approximately five cases per 1,000,000 people per year (1). The major risk factors for CVT are oral contraceptives, hereditary thrombosis, pregnancy, puerperium, and systemic diseases (e.g., tumors, autoimmune diseases, and infections).

CVT induced by spontaneous intracranial hypotension (SIH), a rare cause of CVT occurring in only 2% of SIH cases, is characterized by postural headache and a cerebrospinal fluid (CSF) pressure of less than 60 mmH_2O (2). Although the mechanisms of SIH-induced CVT are not fully understood, three hypotheses have been proposed (2): (1) Following the logic of the Monro–Kellie (3) doctrine, the loss of cerebrospinal fluid leads to compensatory dilation of veins, which slows down blood flow through the straight sinus, a complication that has been reported in some cases of CVT. (2) Through an epidural incision, CSF flows into the epidural space rather than into the venous system, resulting in increased blood viscosity in the epidural veins (2). (3) The sagging of brain tissues can pull on the parenchymal veins, leading to turbulence or stagnation of the venous blood flow. The most common focal brain injuries of SIH-induced CVT are cerebral venous infarction, cerebral hemorrhage, subarachnoid hemorrhage and focal cerebral edema, and the most common symptoms are epilepsy and limb weakness (4–6).

Spontaneous spinal CSF leakage occurs when there is a hole or tear in the membrane surrounding the dura. Dura holes or tears can cause a single localized CSF leak or multiple simultaneous leaks, either of which may lead to SIH. The annual incidence of spontaneous spinal CSF leakage is approximately four cases per 100,000 people (7). Spontaneous spinal CSF leakage is more common in middle-aged women (8). The most common clinical manifestation of spontaneous spinal CSF leakage is orthostatic headache; however, the pathogenic mechanisms remain unclear. A lack of understanding about the role of spontaneous spinal CSF leaks in SIH may lead to delayed diagnosis and treatment, thus increasing the risk of other complications, such as subdural effusion, subdural hematoma, and even life-threatening CVT.

In this case report, we present a complex case with CVT secondary to SIH caused by a spontaneous spinal CSF leak in the high cervical region.

A 37-year-old man experiencing frontal and posterior neck pain while sitting but without any inducement was admitted to the Second Hospital of Hebei Medical University 5 days after symptom onset. The pain severity became aggravated when the patient was in the sitting or standing position but was alleviated in the decubitus position. He was diagnosed with cervical spondylosis in the local hospital, but his headache became progressively worse. One day before the occurrence of left upper and lower limbs weakness and numbness, the patient had a sudden seizure and lost consciousness. There were three seizures in total, each lasting about 1 min. After emergency treatment, including sedation and seizure control, the convulsion was relieved and consciousness was recovered. Subsequently, the patient followed a continuous regimen of valproate sustained-release tablets orally (500 mg, twice daily), and no convulsion was observed.

The patient had a history of upper respiratory tract infection in the seven days prior to admission, but no history of chronic disease or surgical trauma. He also had no family history of genetic diseases. The patient presented with left hemiplegia. Physical examination revealed a neck stiffness and active tendon reflex in the left. The left Babinski sign is positive.

A head magnetic resonance imaging (MRI) + diffusion weighted imaging (DWI) + magnetic resonance angiography (MRA) study showed enlargement of the pituitary gland, descent of the cerebellar tonsils and brainstem, and crowding of the posterior fossa (Figure 1C). An electroencephalogram showed increased slow wave activity. An enhanced brain MRI scan showed hemorrhagic foci in the right parietal lobe with surrounding edema (Figure 1B), filling defects of the superior sagittal sinus, cystic signal shadow under the right top cranial plate, and diffuse enhancement of the dura and pia mater (Figure 1A). Multiple filling defects at the top and back of the superior sagittal sinus (Figure 1A) were shown on a brain magnetic resonance venogram (MRV), suggesting suggesting venous sinus thrombosis venous sinus thrombosis. After admission, a lumbar puncture was performed, revealing an initial CSF pressure of less than 60 mmH_2O, indicating intracranial hypotension. The white blood cell count was 11.70×10^9/L, and the absolute value of the neutrophil was 8.50×10^9/L. The D-dimer was 0.70 μg/mL (↑). The results of a routine CSF examination were normal. Biochemical examination of the CSF showed that the protein content was 2.46 g/L (↑), and the glucose and chlorine levels were normal. The patient was treated with nadroparin calcium (anticoagulant therapy), acyclovir and foscarnet sodium (antiviral therapy), and cefoperazone sodium/sulbactam sodium (anti-infection therapy) *via* injection, as well as intravenous rehydration therapy. Symptoms of headache and left limb weakness were slightly alleviated by the treatment but did not completely resolve, and the patient was still unable to walk. Further MRI study of the cervical and thoracic vertebrae showed CSF collection at the C1-C2 level (Figure 1D), suggesting a dural CSF leak. Therefore, a percutaneous epidural blood patch was performed under the guidance of computerized tomography (CT). The headache was completely relieved 3 days after the procedure, and the patient was able to walk freely. One week after the procedure, a cervical MRI showed that the fluid collection was significantly smaller. Re-examination with an MRV showed no filling defect. Three

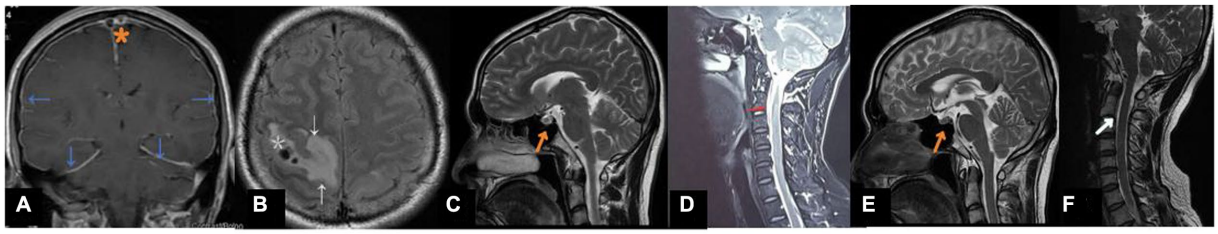

FIGURE 1
(A) Coronal T1 with contrast shows thrombus in the superior sagittal sinus and in a cortical vein at the vertex (*). Note diffuse thickening and enhancement of the dura (blue arrows). **(B)** FLAIR image showing right parietal lobe hemorrhage (*)and edema (arrow)resulting from the venous infarct. **(C)** At first resentation. Sagittal T2-weighted MRI showed full pituitary gland enlargement(arrows). **(D)** Sagittal T2-weighted MRI revealed ventral C1-C2 CSF accumulation(arrows). **(E)** 3-Month follow-up.The pituitary gland has decreased in size(arrows). **(F)** 3-Month follow-up.Sagittal T2-weighted MRI of the spine showed a significant decrease in cerebrospinal fluid collection.

months later, the pituitary gland returned to normal (Figure 1E). The spinal CSF collection was significantly reduced (Figure 1F). The patient was followed up by telephone for 4 months. At the end of the follow-up period, he reported no headache or convulsion and that his body movement had returned to normal.

Discussion and conclusions

The pathogenic mechanisms of spontaneous CSF leaks are still unclear. In some patients with a spontaneous spinal CSF leak, there may be an underlying connective tissue disorder. It is generally believed that there is a structural vulnerability point on the spinal membrane that is more susceptible to holes or tears (9). Mechanical injuries, such as trauma, may cause CSF leaks from the dura mater at the spinal level (10, 11). Generalized connective tissue disease is also considered a cause of spontaneous CSF leaks (12, 13). The common clinical manifestation of SIH induced by spontaneous spinal CSF leaks is postural headache. However, whether this headache is caused by reduced CSF volume or low intracranial pressure remains unknown. Since headache is a common symptom in patients with neurological disorders, spontaneous spinal CFS leaks are often misdiagnosed (14). Recently, Jones et al. proposed a diagnosis and treatment procedure for SIH induced by spontaneous spinal CSF leaks (15): (1) Perform cranial MRI scan + contrast. (2) If the brain MRI shows dural enhancement and downward shift of brain structures, a non-targeted epidural blood patch should be performed, followed by general treatments (i.e., bed rest and symptomatic treatment with acetaminophen, butalbital, and caffeine). (3) If the symptoms persist for 2 to 3 weeks, a plain MRI scan (without enhancement) of the spine and CT myelography should be performed. (4) If there is a localized leak, a targeted epidural fibrin patch should be performed. (5) If the symptoms persist for 2 to 3 weeks, surgical suturing should be considered for lumbar CSF leakage.

The imaging results of our patient after admission showed superior sagittal sinus thrombosis and an initial CSF pressure of lower than 60 mmH_2O. Additionally, he had a positional headache but no history of trauma or piercing, indicating SIH. Further cerebral MRI scan confirmed the diagnosis. Most spontaneous CSF leaks occur at the thoracic level (16). However, no abnormality was observed in the thoracic MRI scan of this patient. Further cervical MRI detected ventral CSF collection in the C1-C2 segment of the neck, indicating a localized CSF leak (17, 18). Performing an epidural blood patch has been shown to effectively relieve symptoms (e.g., headache) (19). Cho et al. reported that a site-directed epidural blood patch effectively alleviated symptoms in 87.1% of 56 patients, whereas a blind epidural blood patch through the epidural approach to the lumbar spine or upper chest was effective in 52% of the patients (20). In our case, a CT-guided epidural blood patch was performed, but the patient's symptoms did not completely resolve after administering an initial treatment to improve circulation, antiviral treatment, anticoagulant treatment, anti-infection therapy, and fluid replacement. Three days after the epidural blood patch procedure, symptoms completely resolved. At the end of a 4-month follow-up period, the patient reported no headache or convulsion and that his body movement had returned to normal.

When a patient has CVT in conjunction with intracranial hypotension but has no history of trauma or piercing, SIH should be considered. In cases of spontaneous spinal CSF leaks at rare sites, an MRI of the whole spine rather than a localized MRI of the spine should be performed to avoid misdiagnosis. In these patients, an epidural blood patch should be performed as soon as possible, which may shorten the length of hospitalization and improve prognosis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Hospital of Hebei Medical University. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML: Writing – original draft. YLi: Writing – review & editing. LT: Writing – review & editing. HL: Investigation, Writing – review & editing. LW: Investigation, Writing – review & editing. YZ: Validation, Writing – review & editing. WF: Data curation, Writing – review & editing. YLiu: Investigation, Writing – review & editing. XL: Resources, Writing – review & editing. JH: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Medical Science Research Project of the Health Commission of Hebei Province (20210970).

Acknowledgments

We thank all the medical staff of Neurology, Medical Video Science and Neurological Surgery who participated in the clinical diagnosis and treatment of this patient. We also thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 30 November 2023
DOI 10.3389/fneur.2023.1284098

OPEN ACCESS

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RECEIVED 27 August 2023
ACCEPTED 08 November 2023
PUBLISHED 30 November 2023

CITATION
Bhatti KS and Rajagopalan S (2023) Case report: Invasive neuromonitoring in status epilepticus induced hypoxic ischemic brain injury.
Front. Neurol. 14:1284098.
doi: 10.3389/fneur.2023.1284098

Case report: Invasive neuromonitoring in status epilepticus induced hypoxic ischemic brain injury

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Objectives: Literature on invasive neuromonitoring and bilateral decompressive craniectomies (BDC) in patients with refractory status epilepticus (RSE)-mediated hypoxic-ischemic brain injury (HIBI) is limited. Neuromonitoring can guide decision making and treatment escalation.

Methods and results: We report a case of a 17 years-old male who was admitted to our hospital's intensive care unit for RSE. HIBI was detected on neuroimaging on this patient's second day of admission after he developed central diabetes insipidus (DI). Invasive neuromonitoring revealed raised intracranial pressure (ICP) and brain hypoxia as measured by reduced brain tissue oxygen tension ($PbtO_2$). Treatments were escalated in a tiered fashion, including administration of hyperosmolar agents, analgesics, sedatives, and a neuromuscular blocking drug. Eventually, BDC was performed as a salvage therapy as a means of controlling refractory ICP crisis in the setting of diffuse cerebral edema (DCE) following HIBI.

Discussion: SE-mediated HIBI can result in refractory ICP crisis. Neuromonitoring can help identify secondary brain injury (SBI), guide treatment strategies, including surgical interventions, and may lead to better outcomes.

KEYWORDS

invasive neuromonitoring, diffuse cerebral edema, continuous EEG monitoring, bilateral decompressive craniectomy, refractory intracranial hypertension, ICP monitoring, refractory status epilepctius, brain tissue oxygen monitoring

Introduction

Refractory status epilepticus (RSE) can rarely result in diffuse cerebral edema (DCE), which is often fatal (1) when it occurs. Increased metabolic demand of the brain along with reduced substrate delivery to the brain or inability to effectively utilize glucose and oxygen can deplete brain adenosine triphosphate (ATP), increase cerebral lactate levels, and decrease pH in the brain interstitium. Impaired cerebral autoregulation, and concomitant systemic factors such as hypotension, hypoxia from aspiration, respiratory acidosis from apnea and metabolic acidosis from seizures can compound neuronal damage that occurs in status epilepticus (SE) (2–4). Compensatory increased cerebral blood flow (CBF), especially in dysregulated brain can result in hyperperfusion-induced blood-brain barrier (BBB) disruption and worsen vasogenic edema (5). Studies have found complex molecular mechanisms of SE-induced BBB dysfunction (6, 7), summarized in Figure 1, along with other mechanisms of neuronal injury in SE.

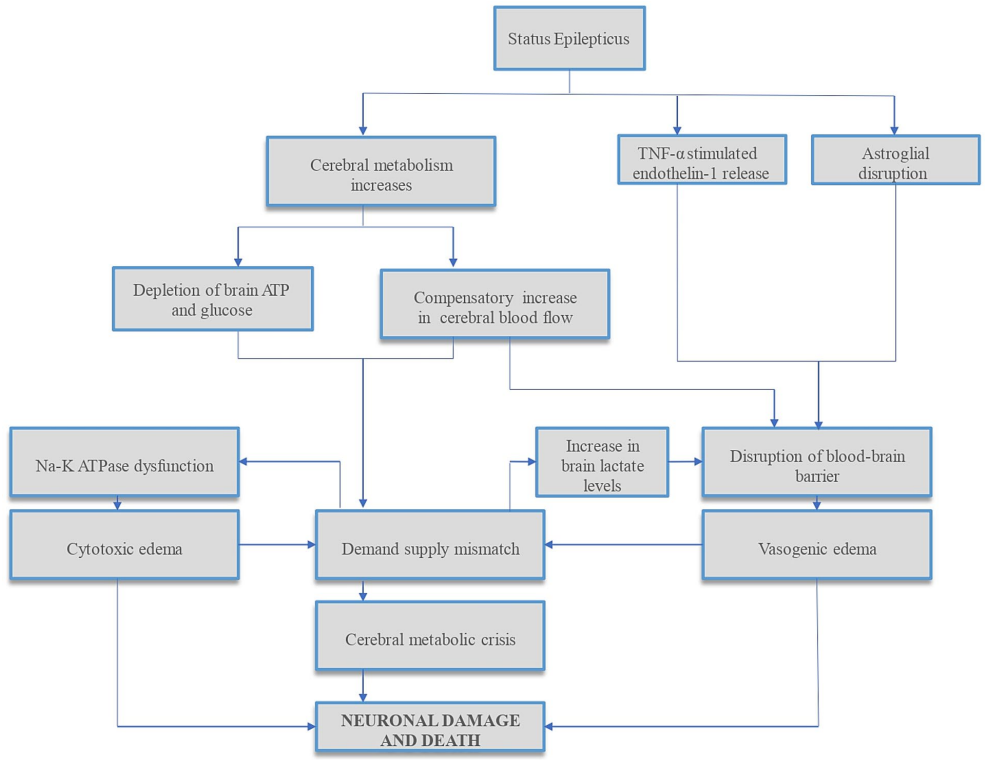

FIGURE 1
Summary of mechanisms of status epilepticus-induced neuronal injury. Status epilepticus (SE) results in disrupted glucose and oxygen delivery and/or utilization, reducing brain adenosine triphosphate (ATP) and increasing cerebral lactate levels. In addition, the increased metabolic demands during SE result in further ATP depletion, leading to sodium–potassium (Na–K) ATPase pump dysfunction and cytotoxic edema. To compensate for increased cerebral metabolic demands, cerebral blood flow (CBF) increases. This CBF increase, especially in the dysregulated brain, can cause hyperperfusion-induced blood-brain barrier (BBB) disruption and vasogenic edema, further increasing ICP. In addition, studies have found complex molecular mechanisms of SE-induced BBB dysfunction via tumor necrosis factor-alpha (TNF-α) stimulated endothelin-1 release (6) and dystrophin/α-syntrophin complex-mediated astroglial aquaporin 4 (AQP4) disruptions (7) which can compound cerebral edema and raise ICP. Both cytotoxic and vasogenic edemas can further increase the demand-supply mismatch. This cascade of events can lead to cerebral metabolic crisis and neuronal cell death. ATP, adenosine triphosphate; Na–K, sodium–potassium; TNF-α, tumor necrosis factor-alpha.

Intracranial hypertension, metabolic crisis and hypoxic-ischemic brain injury (HIBI) have been described in SE patients. However, literature is primarily focused on SE that occurs following other primary forms of acute brain injury (ABI) such as intraparenchymal hematoma, cardiac arrest, subarachnoid hemorrhage (SAH), or traumatic brain injury (TBI), which in itself may impact pathophysiology of RSE (8–11). We found limited literature on development of DCE (1) in patients with SE without other primary forms of ABI, and no literature on the use of invasive neuromonitoring (INM) to guide clinical care of these patients. We present a case report of a 17 years-old man with a history of generalized epilepsy who developed intractable intracranial hypertension secondary to RSE-induced cerebral edema and HIBI, underwent INM, cerebral physiology-targeted interventions, and ultimately bilateral decompressive craniectomies (BDC).

Case description

A 17 years-old man with a past medical history of idiopathic generalized epilepsy was brought to our tertiary care hospital after he was witnessed to become unresponsive with a blank stare. Upon arrival at the emergency room (ER), the patient was lethargic, opened eyes to minor tactile stimuli, blinked to threat, and withdrew all extremities to painful peripheral stimuli; however, he failed to follow commands or produce spontaneous speech. He was febrile with a T_{max} of 101.5 F, and although his total leukocyte count was normal, he was initiated on empiric antimicrobials. The patient's point of care glucose was 111 and his pulse oximetry reflected an oxygen saturation of 100%. The patient's fever rose suspicion for meningoencephalitis causing breakthrough seizures. Chest X ray, urinalysis, and blood cultures were included in to broaden the infectious work-up. Urine drug screen was not conducted, however the patient's family strongly denied a history of illicit drug use in the patient. The initial non-contrast head CT (NCHCT) did not reveal an acute intracranial pathology. Thereafter, the patient had three back-to-back generalized tonic-clonic seizures without returning to baseline; thus, he was given intravenous (IV) loads of lorazepam and levetiracetam. Subsequently, another clinical seizure ensued during which he was loaded with IV midazolam, intubated for airway protection, and transferred to the intensive care unit (ICU).

Propofol and midazolam infusions were initiated empirically while awaiting continuous electroencephalography (cEEG) monitoring initiation. In the interim, the patient received two additional midazolam boluses in suspicion of ongoing non-convulsive status epilepticus (NCSE). Upon initiation of cEEG, the patient was

found to have right-sided temporal lateralized periodic discharges (LPDs) followed by two clinical seizures. Serial escalation with IV anti-seizure medications (ASMs) and IV sedatives including valproate, levetiracetam, and ketamine resulted in a burst-suppression pattern on cEEG. Figure 2A depicts a detailed timeline from the patient's first seizure to the initiation of cEEG monitoring to burst-suppression.

The following afternoon, the patient developed polyuria, and serum and urine chemistries were consistent with new-onset diabetes insipidus (DI). Due to clinical suspicion of a central cause of DI, an urgent NCHCT was performed. It showed an acute diffuse loss of grey-white differentiation, consistent with DCE, a new finding compared to his initial imaging. The patient had not suffered any interval episodes of systemic hypoglycemia or hypoxia, and the patient remained afebrile. A CT venogram demonstrated patent venous outflow. A lumbar puncture was performed and yielded clear cerebrospinal fluid (CSF) with an opening pressure of 30 mmHg, nucleated cell count of 2/μL, red cell count of 148/μL, glucose of 90 mg/dL, and protein of 181 mg/dL. Infectious CSF labs were sent including bacterial/fungal cultures, and herpes simplex virus (HSV) 1/2 PCR. Since the patient's clinical presentation, with the exception of SE, were not suggestive of viral encephalitides, additional viral studies were not sent.

After a multidisciplinary discussion between the neurointensivist and the neurosurgeon, a decision was made to pursue INM to institute treatments that may reduce secondary brain injury (SBI) in a timely way. The neurosurgery team placed an intraparenchymal (IP) monitor (Raumedic Neurovent-PTO) in the right frontal lobe, consisting of an intracranial pressure (ICP) and brain tissue oxygen tension ($PbtO_2$) monitor. After the initial calibration period, $PbtO_2$ readings were 3–7 mmHg, reflecting a severely hypoxic brain. Six hours following placement of IP monitor, the ICP peaked to 50 mmHg. This was transiently abated by hyperventilation, an increase in IV propofol rate, and additional boluses of IV 20% mannitol and 23.4% sodium chloride. Treatment with hyperosmolar therapy with concomitant DI resulted in hypernatremia. Hypernatremia was managed by one-to-one replacement of urine fluid losses with isotonic fluids. Hypotonic fluids were not used to prevent overcorrection of sodium, especially in the presence of DCE and raised ICP. Clinical DI was transient, and treated with 1mcg of desmopressin. The next morning, the patient underwent a non-contrast MRI brain which showed diffuse grey matter FLAIR and DWI hyperintensities with ADC pseudonormalization reflective of edema. A slight improvement in grey-white differentiation was appreciated on this MRI in comparison to the prior NCHCT. Despite this slight radiographic improvement, the IP monitor continued to reflect persistent ICP crisis ranging between 30–60 mmHg refractory to all medical therapies, including sedatives, analgesics, hyperosmolar therapies, and neuromuscular blocking drug administration. Detailed pharmacological treatments are shown graphically, along with physiological trends of ICP, mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) in Figure 2B.

Given refractory ICP crisis, following a multidisciplinary discussion, the patient underwent BDC, removal of the IP monitor and an external ventricular drain (EVD) placement. Following BDC, the patient's ICP crisis resolved and ICPs remained within the normal range. Clinical DI did not recur, and hypernatremia was attributed primarily to hyperosmolar therapy. After normal readings of ICP for 24 h, the EVD was removed, and the sedatives were weaned off. While the initial indication of burst suppression in our case was RSE, it was continued for treatment of intracranial hypertension, for a total period of 72 h. All the infectious work up, including CSF studies, resulted negative in a few days, and antimicrobials were discontinued. In the absence of pleocytosis, elevated protein in the CSF was considered to reflect non-specific neuronal inflammation in the setting of RSE and HIBI. Fever at initial presentation was attributed to RSE and being found unresponsive outside under a high-temperature weather.

The patient's ICU length of stay, complicated by aspiration pneumonia, followed by acute respiratory distress syndrome requiring venovenous (VV) extracorporeal membrane oxygenation (ECMO), was 30 days. Following extubation, 24 days from admission, the patient aroused to verbal stimuli, visually tracked people, and began following simple axial and appendicular commands. Over the next few days, his neurologic exam continued to improve as he was more persistently awake and began to respond in one to two words. At the time of discharge, after a total hospital stay of 50 days, the patient was awake, alert, oriented, mildly inattentive, produced spontaneous fluent speech, followed simple and complex commands, without any detectable cranial nerve, motor, or sensory abnormalities. A repeat MRI brain almost a month after the first MRI showed complete resolution of the previously noted radiographic abnormalities (Figure 3).

Discussion

To the best of our knowledge, this is the first case report using INM to guide management in refractory intracranial hypertension in a patient with SE-induced diffuse cerebral edema, in the absence of other primary ABI, and to survive it with a good neurologic outcome. In the setting of SE following ABI due to other primary causes such as intraparenchymal hemorrhage, cardiac arrest, SAH, and TBI, we found case reports of the use of INM showing brain hypoxia, increased ICP (8, 9, 11), hyperemia (9, 10), and cerebral metabolic crisis (9, 11). While these studies demonstrate the effects of seizures on cerebral physiology, these patients had concomitant primary ABI as a cause of seizures, therefore many of the physiological changes were attributable to their primary ABI rather than effects of seizures alone.

Sedatives were titrated to achieve burst suppression to treat RSE, as supported per guidelines (12), however optimal intensity and duration of sedation, as well as goals of seizure or burst suppression remain to be determined. A recent study showed that suppressing rhythmic and periodic EEG activity for at least 48 h in HIBI patients did not alter neurological outcome (13), however this cannot be extrapolated to other types of ABI, including secondary HIBI from RSE rather than cardiac arrest. Addition of ketamine to propofol and midazolam infusions have shown reduced seizure burden and increased seizure termination in RSE and super refractory status epilepticus (SRSE) in both adult and pediatric populations (14, 15).

New-onset DI raised the clinical suspicion of intracranial hypertension. Prompt institution of INM confirmed intracranial hypertension and brain hypoxia, enabling timely escalation of medical treatments and, ultimately, BDC, preventing transtentorial herniation and death.

Hyperosmolar therapy was instituted to reduce ICP. Mannitol and hypertonic saline reduce ICP by way of fluid shift from intracellular to the extracellular space. In addition, mannitol promotes osmotic diuresis and alters blood viscosity (16). Sedatives and analgesics were

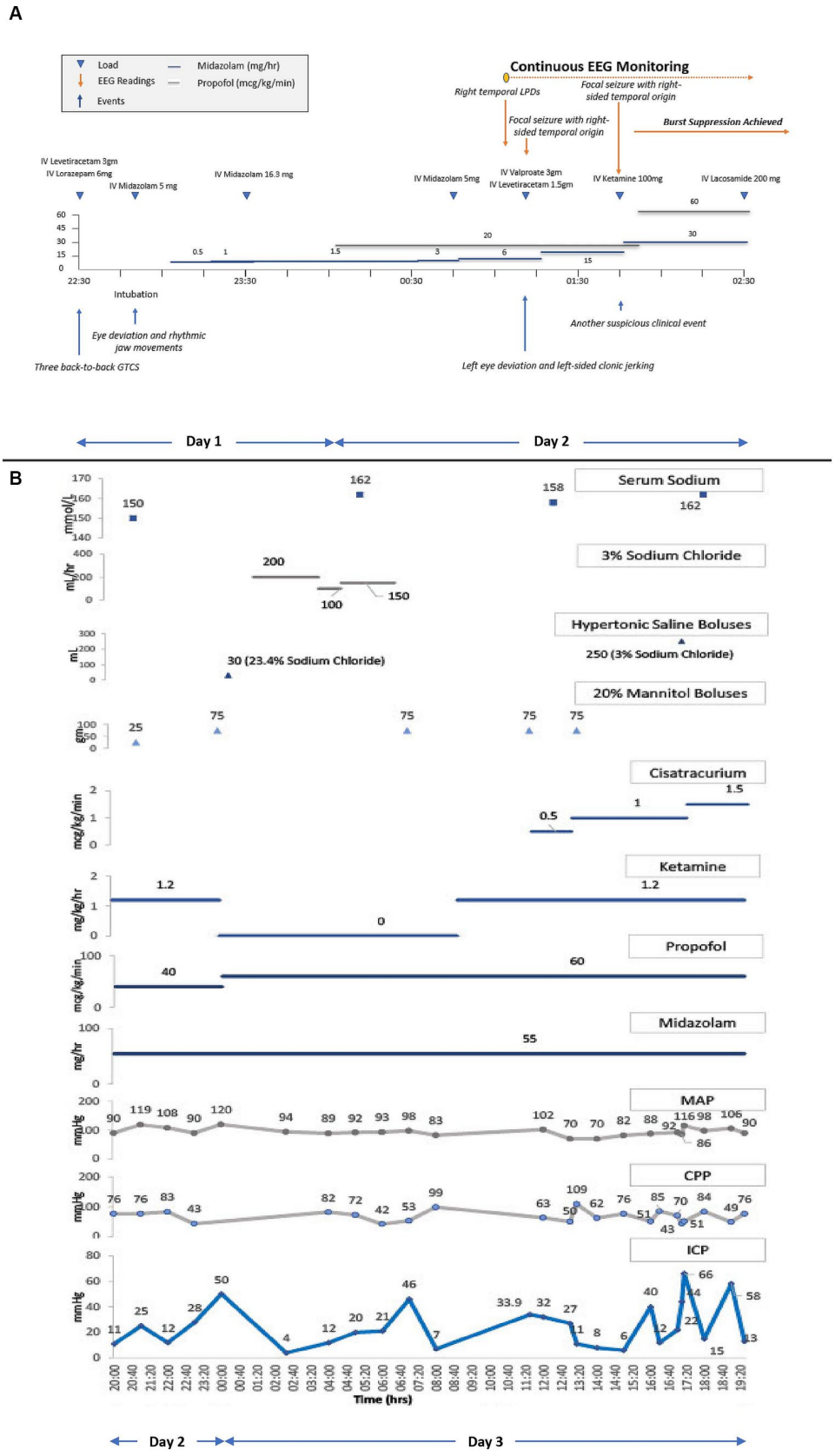

FIGURE 2
(A) Refractory status epilepticus treatment timeline. cEEG, continuous electroencephalography. Shows a detailed timeline from the patient's first seizure to the initiation of cEEG monitoring to burst-suppression. Triangles connotate boluses or loads, and lines connotate continuous infusions. The patient received loads of IV levetiracetam, IV lorazepam, and IV midazolam, and underwent endotracheal intubation for airway protection. Following

(Continued)

FIGURE 2 (Continued)
intubation, IV midazolam and IV propofol infusions were initiated and up-titrated for suspicion of ongoing non-convulsive status epilepticus (NCSE). Upon initiation of cEEG monitoring, right temporal lateralized periodic discharges (LPDs) and right temporal focal seizures were seen, prompting an increase in the rate of midazolam infusion with additional IV loads of valproate, levetiracetam, and ketamine, to achieve burst suppression. **(B)** ICP, CPP, MAP, and serum sodium trends along with the titration of sedatives, hyperosmolar therapies, and neuromuscular blocker infusions. ICP, intracranial pressure; CPP, cerebral perfusion pressure; MAP, mean arterial pressure. Triangles connotate boluses, and lines connotate continuous infusions. ICP monitoring was initiated on the second day of hospitalization after the onset of clinical DI and radiographic diffuse cerebral edema. Propofol, versed, and ketamine infusions were already running to maintain burst suppression for RSE. The initial ICP readings between 25–28 mmHg were treated with a mannitol bolus. A subsequent ICP peak of 50 mmHg was treated with hyperventilation, an increase in the propofol infusion rate, a mannitol and hypertonic saline bolus, followed by a hypertonic saline infusion. Ketamine infusion was discontinued due to a concern of possibly contributing to intracranial hypertension, but after multidisciplinary rounds on the next day, it was restarted. Shortly thereafter, the patient's ICP went up to 46 mmHg, for which the patient received another mannitol bolus which resulted in a transient ICP reduction before another ICP crisis to 32–34 mmHg. These subsequent ICP surges were treated with two mannitol boluses in conjunction with the initiation and rapid up-titration of cisatracurium infusion. ICP was transiently reduced, but became sustained at 40–70 mm Hg, despite an increase in the rate of cisatracurium, a hypertonic saline bolus, and continuation of all previous therapies.

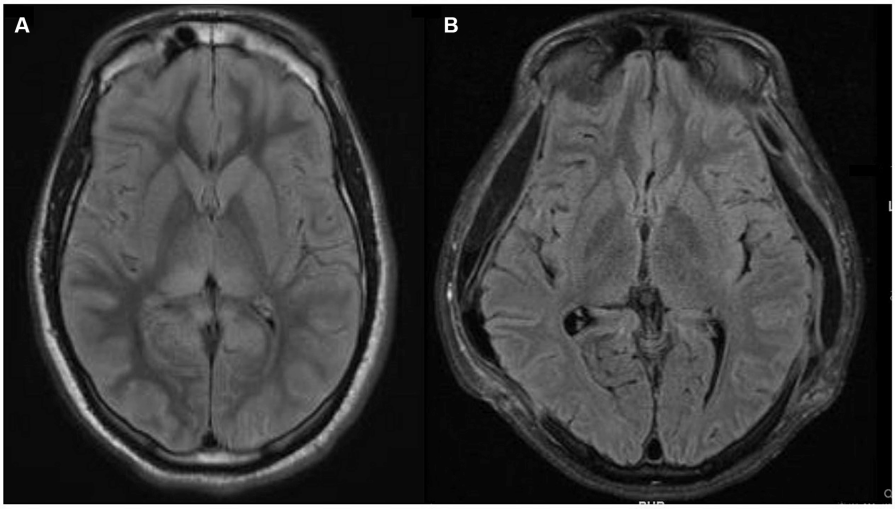

FIGURE 3
Magnetic resonance imaging (MRI) brain fluid-attenuated inversion recovery (FLAIR) sequences. **(A)** MRI brain FLAIR sequence that demonstrates bright T2/FLAIR signal, suggesting diffuse grey matter edema which could indicate hypoxic-ischemic brain injury. **(B)** Repeat MRI brain FLAIR sequence a month later, showing near complete resolution of prior abnormalities and expected extra-cranial herniation of brain through the craniectomy sites.

initially used to treat seizures, pain and anxiety, but these doses were titrated up to reduce the cerebral metabolic rate of oxygen ($CMRO_2$) during periods of intracranial hypertension. Reduction in $CMRO_2$ reduces the cerebral metabolic demand in the setting of demand-supply mismatch during SE, which is crucial in preventing further neuronal damage during periods of metabolic crisis. The reduction in $CMRO_2$ also leads to concurrent decreases in CBF, cerebral blood volume, and ultimately ICP (17, 18). In this case, ketamine was continued alongside propofol and midazolam for sedation, based on recent studies dispelling concerns of elevated ICP associated with ketamine use (19). Notably, a retrospective study in the pediatric severe TBI population suggested that ketamine might aid in reducing ICP during ICP crisis (20). A MAP augmentation challenge was performed to identify if ICP crisis was perfusion-limiting, i.e., oligemic or perfusion-driven, i.e., hyperemic and suggested a mixed picture, typical of heterogenous injury (21). As ICPs remained refractory of treatment with sedatives and hyperosmolar therapy, cisatracurium, a neuromuscular blocking agent (NBMA), was introduced to further reduce $CMRO_2$ by promoting ventricular synchrony and preventing ICP peaks from coughing, suctioning, motion, pain, or shivering (22), however, there is a dose-dependent association with increased neuromuscular weakness and morbidity (23).

IP monitor removal during BDC was followed by an EVD placement for continued ICP monitoring and to allow therapeutic lowering of ICP via CSF diversion, which may have helped to reduce ICP further. The two most commonly used techniques to measure ICP, with good correlation, are the fluid-coupled EVD and strain-gauge or fiberoptic-based IP monitors. One may be preferentially chosen based on the need for CSF drainage, interest in regional cerebral physiology, need for continuous ICP measurements or feasibility. In this case, the decision to place an EVD was based on both the option of therapeutic ICP lowering and clinical feasibility (24).

Although literature explores the use of BDC in TBI (25), SAH (26) and cerebral venous sinus thrombosis (27), we found no literature on BDC for DCE and medically refractory intracranial hypertension in HIBI, and particularly SE-induced HIBI. In this report, we describe the first case report of a patient where BDC was utilized as a means of controlling refractory elevated ICP in the setting of DCE following SE-induced HIBI. The rationale for instituting BDC as a salvage therapy is rooted in Monroe Kellie doctrine, as the removal of the "rigid" cranial vault allows cerebral expansion extracranially, resulting

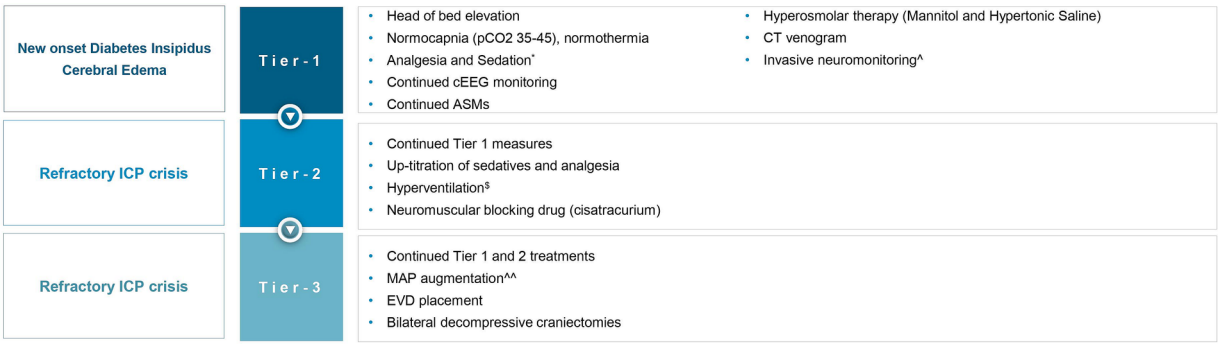

FIGURE 4
Invasive neuromonitoring-guided treatment for refractory intracranial hypertension and brain hypoxia. ICP, intracranial pressure; pCO_2, partial pressure of carbon dioxide; cEEG, continuous electroencephalography; ASMs, anti-seizure medications; MAP, mean arterial pressure; EVD, external ventricular drain. *The patient was already on propofol, midazolam, and ketamine, before the onset of global hypoxic brain injury, for status epilepticus, now up-titrated to treat ICP crisis. $Briefly targeting hypocapnia. ^Using an intraparenchymal monitor (Raumedic Neurovent-PTO). ^^To identify if ICP elevation was perfusion-limiting (oligemic) or driven (hyperemic).

in reduced ICP and improved cerebral perfusion. Pentobarbital coma was not offered as the patient was already in burst suppression with the other management strategies, and given the diffuse nature of cerebral edema, increasing the intensity of burst suppression further was not expected to address the intracranial hypertension and brain hypoxia further. A multidisciplinary consensus was achieved that maximal intensity of medical therapies was offered in this case prior to the decision of pursuing BDC. Unilateral decompressive hemicraniectomy (DHC) was felt to be an inadequate therapeutic option given the diffuse nature of cerebral edema demonstrated on neuroimaging. Given paucity of data in this particular clinical situation, a detailed and informed conversation explaining risks and benefits was conducted with the patient's family, who elected to proceed with BDC. Our physiology-based algorithm using INM (Figure 4) data, drove a tiered approach for refractory intracranial hypertension and brain hypoxia in the setting of severe cerebral edema and HIBI following SE. Based on radiographic cerebral edema alone without INM, it is unlikely that this intensity of treatments would have been offered, and death from cerebral herniation may have been a realistic outcome. In this case, treatment was escalated to the highest tier, requiring BDC as a salvage therapy, which was effective at both reducing ICP immediately, and preventing death. Though ultimately whether treatments modified the course of SBI is unknown, we believe the tiered medical management limiting prolonged periods of intracranial hypertension and brain hypoxia, and expeditious decision to proceed with BDC once it was evident that intracranial hypertension was becoming refractory to medical therapies not only prevented this patient's death, but may have also limited neuronal loss and contributed to the patient's excellent eventual neurologic recovery.

Limitations of this report include the loss of continuous data capture, especially $PbtO_2$ recordings due to manual data entry into the electronic medical record, given the retrospective nature of this case report. Data loss also limited measurement of markers of cerebral autoregulation, such as cerebral pressure and oxygen reactivity indices. Our intensive care unit is not equipped to perform cerebral microdialysis, so while this data may have added further information, this was not performed.

In conclusion, our case report implores intensivists to consider the use of invasive neuromonitoring to guide management in patients who suffer HIBI secondary to SE and to consider BDC as a salvage treatment option in cases with refractory intracranial hypertension and brain hypoxia.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the patient's legal guardian/next of kin. Written informed consent was obtained from the participant/patient(s) legal guardian/next of kin for the publication of this case report.

Author contributions

KB: Data curation, Writing – original draft. SR: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 21 March 2024
DOI 10.3389/fneur.2024.1308462

OPEN ACCESS

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RECEIVED 06 October 2023
ACCEPTED 24 January 2024
PUBLISHED 21 March 2024

CITATION
Engrand N, Salardaine Q, Desilles J-P, Echard C, Bourdillon P, Williams M and Baille G (2024) Case report: Simultaneous measurement of intracranial pressure and lumbar intrathecal pressure during epidural patch therapy for treating spontaneous intracranial hypotension syndrome. Spontaneous intracranial hypotension or spontaneous intraspinal hypovolume? *Front. Neurol.* 15:1308462.
doi: 10.3389/fneur.2024.1308462

Case report: Simultaneous measurement of intracranial pressure and lumbar intrathecal pressure during epidural patch therapy for treating spontaneous intracranial hypotension syndrome. Spontaneous intracranial hypotension or spontaneous intraspinal hypovolume?

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Objectives: Spontaneous intracranial hypotension (SIH) is frequently complicated by subacute subdural hematoma (SDH) and more rarely by bilateral thalamic ischemia. Here, we report a case of SIH-related SDH treated with three epidural patches (EPs), with follow-up of the intracranial pressure and lumbar intrathecal pressure.

Methods: A 46-year-old man presented bilateral thalamic ischemia, then a growing SDH. After failure of urgent surgical evacuation, he underwent three saline EPs, two dynamic myelography examinations and one digital subtraction angiography–phlebography examination. However, because of no dural tear and no obstacle to the venous drainage of the vein of Galen, no therapeutic procedure was available, and the patient died.

Results: The case exhibited a progressive increase in the transmission of lumbar intrathecal pressure to intracranial pressure during the three EPs. The EPs may have successfully treated the SIH, but the patient did not recover consciousness because of irreversible damage to both thalami.

Conclusion: Clinicians should be aware of the bilateral thalamic ischemia picture that may be the presenting sign of SIH. Moreover, the key problem in the pathophysiology of SIH seems to be intraspinal and intracranial volumes rather than pressures. Therefore, intracranial hypotension syndrome might actually be an intraspinal hypovolume syndrome.

10.3389/fneur.2024.1308462

KEYWORDS

subacute subdural hematoma, spontaneous intracranial hypotension, epidural patch, bithalamic ischemia, case report

Introduction

Spontaneous intracranial hypotension (SIH) is frequently complicated by subacute subdural hematoma (SDH) (1–4) and more rarely bilateral thalamic ischemia (5–8). The management of this condition is poorly codified and is often based on surgical evacuation of the SDH. However, this therapeutic approach remains controversial because of the paradoxical nature of removing the intracranial volume in the context of pre-existing hypotension. Consequently, a growing number of authors now recommend treating SIH-related SDH with a blood patch, targeted to a possible dural tear or not (1, 4, 8–12). The management of rare bilateral thalamic strokes is even less known.

Here, we present a case of SIH complicated by SDH, with follow-up of the intracranial pressure (ICP) and lumbar intrathecal pressure (LITP) during the etiological therapeutic management (epidural patches [EPs]). The case allows for further understanding treatment.

Case report

A 40-50 year-old patient with no known medical condition other than chronic alcoholism and no usual treatment was referred to the stroke unit for severe aphasia. The patient was slightly isolated socially, and next-of-kin interrogations revealed orthostatic headache and walking disturbance for 4 months. The initial examination revealed delirium, aphasia, and spastic hypertonia of all four limbs. Pulse oxygen saturation and blood glucose level were normal. Immediate brain MRI highlighted bilateral thalamic diffusion and FLAIR hypersignals, with apparent diffusion coefficient hyposignals, associated with thin, chronic, right convexity SDH (Figure 1A). Arterial 3D time-of-flight sequences did not show arterial amputations consistent with ischemic stroke (Figure 1B), and no cerebral venous (sinus) thrombosis was evidenced.

Biological work-up revealed HIV infection associated with lymphopenia, with no associated infections. SARS-CoV-2 PCR results for a nasal swab were negative. Four days after hospital admission, the patient became comatose (Glasgow coma score 6). An urgent brain CT scan revealed an acute bleed inside the chronic right-convexity SDH (13 mm total thickness) causing a subfalcine herniation without associated uncal herniation (Figures 1E,F). After intubation, the patient underwent surgery for evacuation of the SDH. During the surgery, the brain did not re-expand to the dura, and venous bleeding was observed (bridging veins). An intracranial pressure sensor was implanted for monitoring (Pressio®2, Sophysa, Orsay France). During the next days, despite the cessation of sedation on day one (D1) and extubation on D5 postoperatively, the patient did not recover contact with the environment (Glasgow coma score 10), exhibiting fluctuating eye opening and severe spastic tetraparesis. A review of the MRI (Figures 1C,D) and the ICP measurements confirmed the diagnosis of severe SIH. A spinal MRI revealed cervico-arthrosis causing posterior spinal cord compression at C6-C7 with a mild centromedullary T2-weighted hypersignal but no apparent dural tear. Electroencephalography did not reveal epileptic activity or toxic or metabolic encephalopathy. Biological investigations ruled out the differential diagnoses: viral and bacterial meningo-encephalitis, auto-immune encephalitis, hyperammonemia, toxic encephalitis, and vitamin B1 deficiency. Although immunophenotyping revealed a CD4 lymphocyte count of 4/mm3 with a viral load of 5 log, the diagnosis of HIV-specific encephalitis was not retained because of the unfavorable radiological picture. No opportunistic infections were found. A summary of the biological investigations is in Supplementary Table 1. Figure 2 shows a timeline of diagnostic and therapeutic procedures. Intensive care unit follow-up was uneventful, with satisfactory airway control by the patient, although two nosocomial infections occurred (ventilator-associated pneumonia and bacteremia), which were resolved with antibiotics. SIH treatment initially consisted of the Trendelenburg position, with a moderate effect on ICP (values from 0 to 5 mmHg vs. −3 to 0 mmHg in the semi-seated position), but with no substantial effect on consciousness. Then, three saline EPs were performed, on D13, D20 and D36. Each procedure included an initial measurement of LITP at L3-L4 with a lumbar puncture needle and tubing fitted with a pressure transducer, to verify that it was low and to perform the various intrathecal tests for etiologic purposes. The EPs consisted of three 20-ml syringe injections into the epidural space at L2-L3 while measuring LITP and ICP (Figure 3). Saline injection was preferred to blood injection because of the high HIV viremia. The first lumbar puncture was very difficult, with the need to suck with the syringe to obtain less than 1 mL of cerebrospinal fluid (CSF) (hence, no laboratory analysis could be performed), whereas the following punctures were considered "easy" (allowing for laboratory analysis).

Because of the persistence of the patient's lack of communication and low ICP (continuously ≤5 mmHg), two dynamic myelography examinations were performed on D25 and D48 to search for a dural tear that could have been surgically repaired (Supplementary Figures 1A,B). However, no extra-thecal CSF leak was found. During the first dynamic myelography, ICP immediately and transiently increased from 2 to 80 mmHg, and the optic nerve sheath diameters measured on ultrasonography immediately dilated from 6.4 to 7.7 mm (Supplementary Figures 1C,D). Finally, in view of the bilateral thalamic ischemia and the sharp angle between the vein of Galen and the straight sinus on a D35 phlebography–CT scan (measured at 12°, Supplementary Figures 1E,F), digital subtraction angiography–phlebography was performed on D55 to search for an obstacle to the venous drainage. However, venous flow was normal, and no therapeutic procedure could be performed.

Abbreviations: SIH, spontaneous intracranial hypotension; ICP, intracranial pressure; LITP, lumbar intrathecal pressure; EP, epidural patch; ONSD, optic nerve sheath diameter; SDH, chronic subdural hematoma.

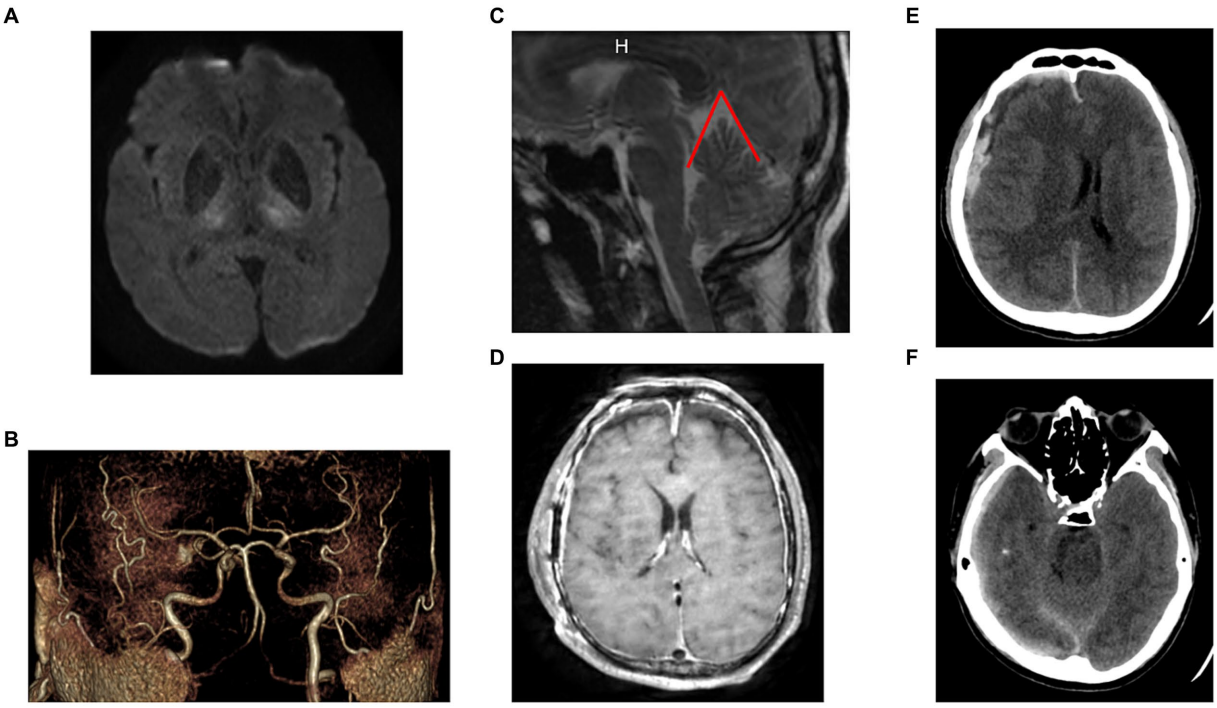

FIGURE 1
Initial imaging. **(A)** Initial [day 4 (D4)] MRI (axial diffusion b2000 sequence): bilateral thalamic ischemia. **(B)** Initial (D4) MRI (3D arterial time-of-flight image): no arterial amputation favoring ischemic stroke. **(C)** Initial (D4) MRI (sagittal view of a T2-weighted sequence): evidence of posterior sagging of the brain and brainstem, with closure of the angle between the protuberance and the diencephalon, verticalization of the cerebellar tent, herniation of the cerebellar amygdala, favoring the SIH diagnosis. The angle between the vein of Galen and the right sinus was measured at 52° (angle marked in red). **(D)** D17 MRI (axial T1-weighted sequence): significant and diffuse pachymeningeal enhancement after contrast agent injection and markedly distended dural venous sinuses, favoring the SIH diagnosis. **(E)** D0 CT-scan (no contrast agent). Evidence of a 13-mm-thick heterogenous subdural collection in the right convexity with significant midline deviation. **(F)** D0 CT-scan: No uncal herniation, favoring no intracranial hypertension (SDH, subacute subdural hematoma; SIH, spontaneous intracranial hypotension; D0: day of neurosurgical evacuation of the SDH).

Unfortunately, 2 months after the aphasia onset, the patient remained in a minimally conscious state and died after active therapy was discontinued on D72.

Discussion

This case report is the first to describe simultaneous ICP and LITP measurements during EP therapy for SIH. SIH is defined by CSF opening pressure ≤ 60 mm H_2O (3). In most cases, SIH leads to mild symptoms (typically orthostatic headaches), with good outcome. However, spontaneous SDH is a common complication of SIH (up to 20–45%), due to rupture of bridging veins between the dura and surface of the brain, and can be frequently recurrent (1–3, 9). In the present case, the diagnosis of bilateral thalamic arterial infarct was first considered, but lesions encountered in such cases involve more the anterior and lateral parts of the thalamus supplied by the paramedian thalamic artery (13). Bilateral thalamic lesions are a rare radiological feature of SIH and could be linked to a closing angle between the vein of Galen and the straight sinus compromising the venous drainage of thalami and resulting in vasogenic edema (5–8). In addition, a narrower angle between the vein of Galen and the straight sinus was found associated with poor response to an epidural blood-patch (50 ± 16° vs. 67 ± 26°) (14). This angle could even close if the blood patch were ineffective.

In our case, the first or second EP may have treated the SIH, which would explain why subsequent etiologic investigations did not reveal a dural tear or venous obstruction. However, the patient would not have recovered consciousness because of the irreversible damage to both thalami caused by the venous ischemia. The progressive increase in transmission of LITP to ICP observed during the three EPs argues for this hypothesis. The absence of pressure transmission from the lumbar to the cranial compartment during the first epidural injections (Figures 3A,B) revealed an abnormally high compliance of the spinal compartment. Then, the superposition of pressure peaks between the two compartments during the last injections (Figure 3C) revealed that compliances had normalized and were balanced between the two compartments. Variations in intraspinal and intracranial volumes rather than pressures probably determined the respective compliances and symptoms of SIH, as previously reported (15). The hypothesis of this sequence is all the more likely because the first lumbar puncture was difficult due to lack of pressure in the intrathecal space, whereas dynamic myelography, after the leak had probably been sealed, resulted in immediate dilation of the optic nerve sheath diameters.

A recent article reported two cases of ICP measurement during successful blood EP treatment of SIH complicated by SDH (16). Similarly, epidural injections led to an increase in ICP, but this was treated in turn by opening the previously placed intracranial subdural drains. Another study also showed that treating SIH with blood EP led to an increase in optic nerve sheath diameters (which indirectly reflects ICP) and even suggested that this increase was a marker of treatment efficacy (17).

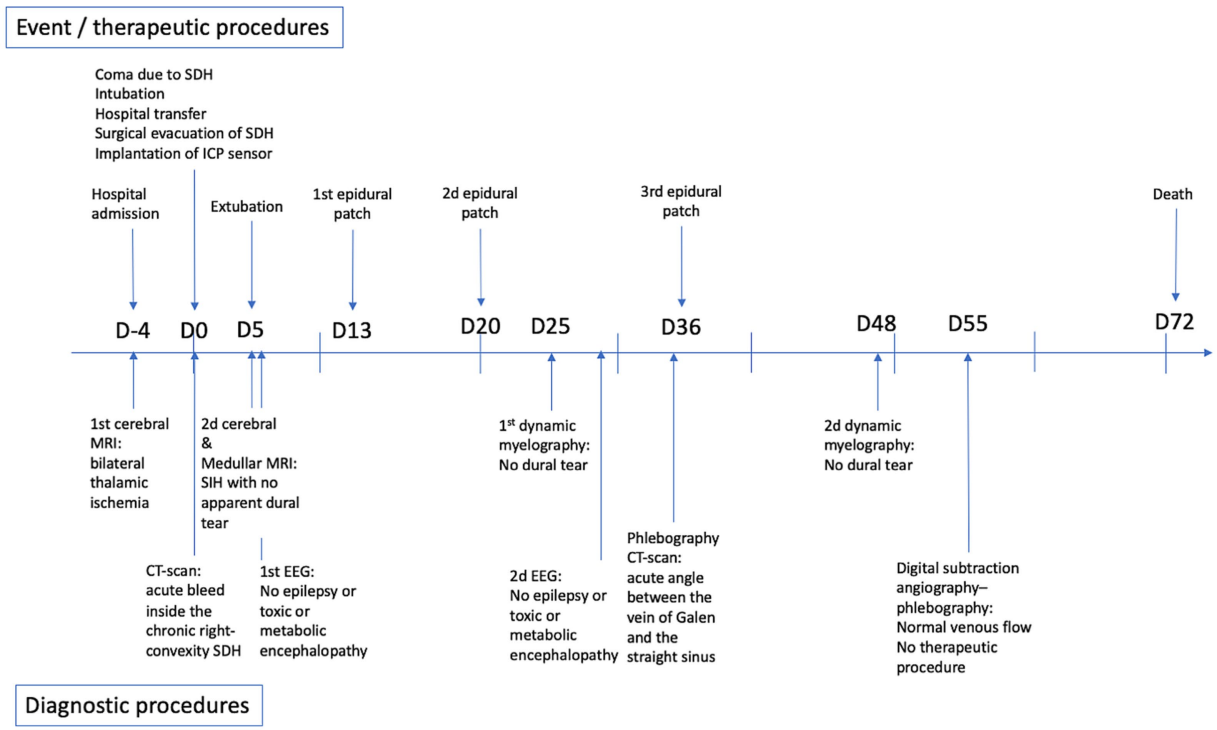

FIGURE 2
Timeline of diagnostic and therapeutic procedures.

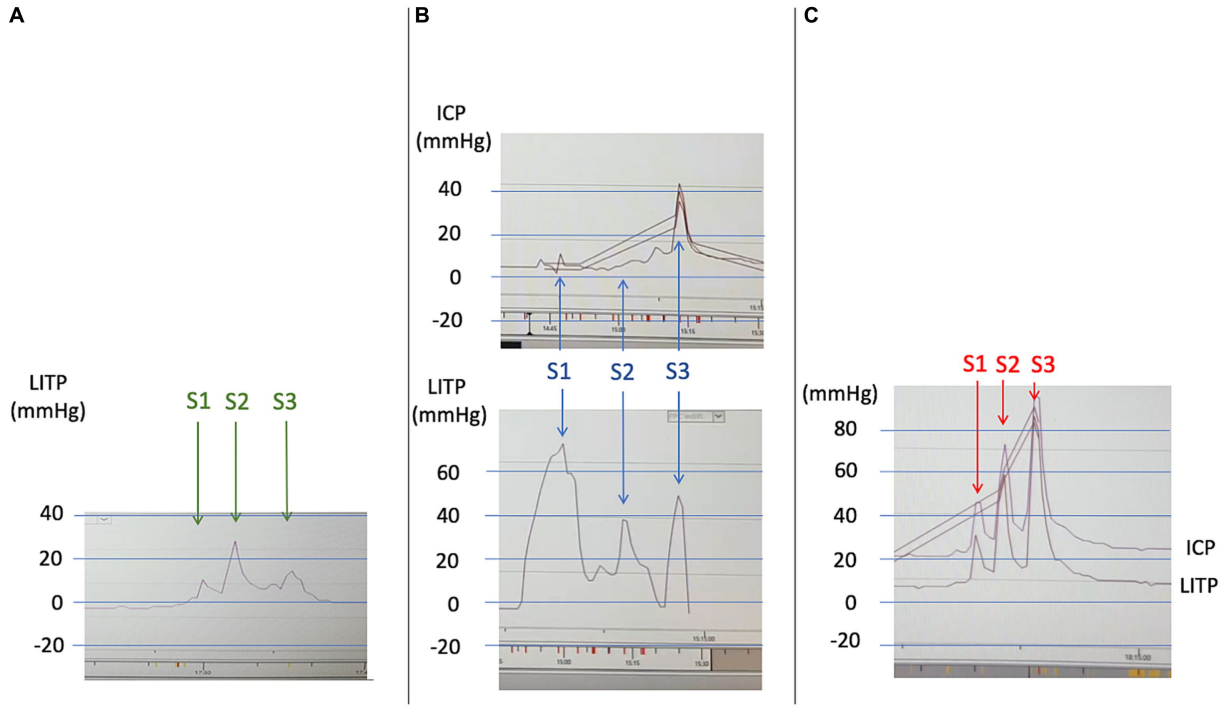

FIGURE 3
LITP and ICP curves during the three saline epidural patches (identical scales). Each procedure included an initial measurement of LITP at L3-L4. The epidural patch treatment involved three 20-ml syringe injections into the epidural space at L2-L3 (marked by arrows and annotated S1, S2, S3). **(A)** First epidural patch (D13). Three epidural injections of 20-mL volume led to a moderate increase in LITP (max 25mmHg), with no increase in ICP (curve not recorded). **(B)** Second epidural patch (D20). Three epidural injections of 20-mL volume led to a transient but significant increase in LITP (max 75mmHg), with an increase in ICP only during the third injection (max 45mmHg). **(C)** Third epidural patch (D36). Three epidural injections of 20-mL volume resulted in a major and strictly parallel increase in LITP and ICP during all three injections (max 85mmHg). Thus, the three epidural patches led to a progressive increase in LITP and ICP as well as transmission from LITP to ICP. This phenomenon probably indicates that the intraspinal and intracranial compliances became lower, even if the pressures themselves remained low (apart from their transient increase during the injections). Hence, volume deficit of the intraspinal compartment was probably filled by the first epidural injections and the dural tear was treated (LITP, lumbar intrathecal pressure; ICP, intracranial pressure).

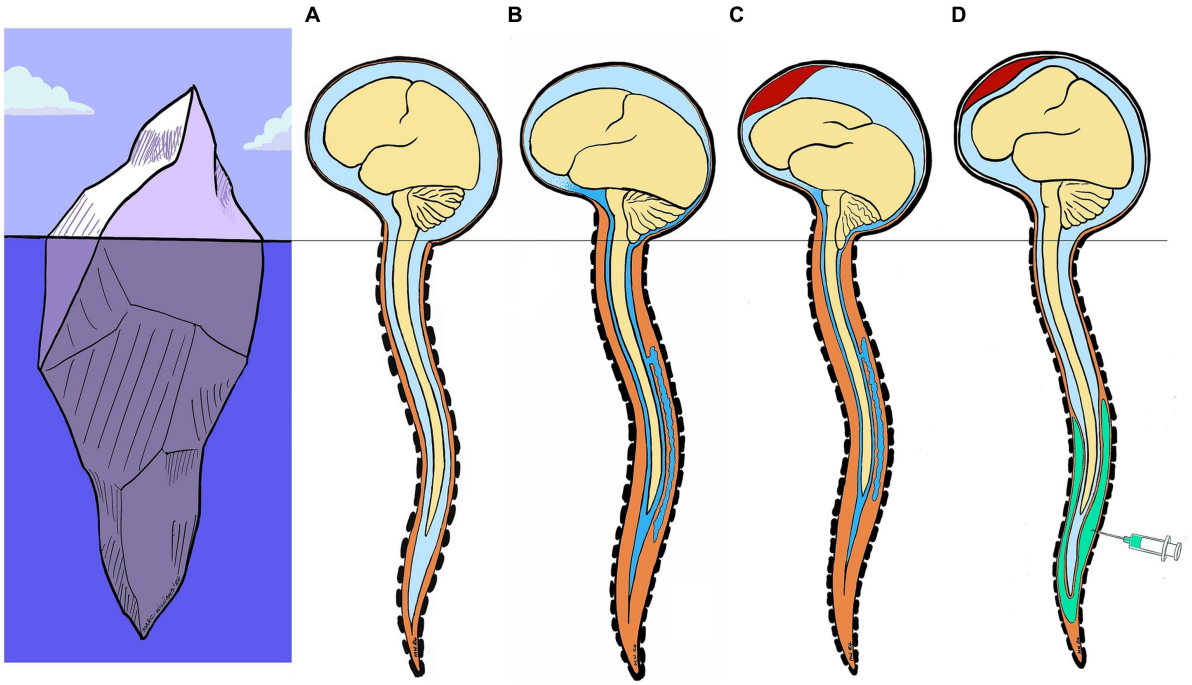

FIGURE 4
Model of SIH pathophysiology and epidural patch action. Iceberg analogy: the melting of the glacier (brain) on the surface (base of skull) follows a previous underwater event (spinal cord) **(A)** Normally, the brain is suspended in its CSF pool **(B)** In the event of SIH, the CSF pool empties and the brain tilts backward onto the skull base. **(C)** Subdural hematoma is a common complication of SIH, due to rupture of bridging veins between dura and surface of the brain. **(D)** SIH treatment with an EP seems to act by 1) interrupting the process of spinal transdural siphoning (extradural pressure becoming greater than subarachnoid pressure; the pressure effect), and 2) refilling the fluid volume deficit in the entire intraspinal compartment (the volume effect). Injecting a volume of fluid into the spinal epidural space flushes CSF from the perimedullary subarachnoid compartment into the continuous periencephalic subarachnoid compartment, thus restoring the brain's floating pool and enabling the brain to tilt forward again. (CSF, cerebrospinal fluid; SIH, spontaneous intracranial hypotension; EP, epidural patch).

To synthesize our pathophysiological hypothesis, one must first remember that normally, the brain is suspended in its CSF pool. In the event of SIH, the pool empties and the brain tilts backward onto the skull base (Figure 4). SIH treatment with an EP seems to act by (1) interrupting the process of spinal transdural siphoning (extradural pressure becoming greater than subarachnoid pressure; the pressure effect), rather than by anatomically sealing a breach (18), and (2) refilling the fluid volume deficit in the entire intrarachid compartment (also known as the "spinal" compartment, which includes the intradural and the epidural space; the volume effect). Thus, injecting a volume of fluid into the spinal epidural space flushes CSF from the perimedullary subarachnoid compartment into the continuous periencephalic subarachnoid compartment, thereby restoring the brain's floating pool and enabling the brain to tilt forward again (Figure 4). This is followed by a significant transient increase in ICP lasting from a few seconds to a few minutes, shown by the ICP curves (Figure 3), as previously reported (16, 18). In fact, this is what anesthetists unknowingly do when treating a post-peridural dural breach with a blood patch, stopping the injection just as the headache appears. Thus, headache probably indicates that CSF has shifted from the spinal compartment into the cranial compartment, hence leading to transient intracranial hypertension. This hypothesis would also explain why the EP can be effective regardless of the spinal injection level (4, 10–12) and the nature of the fluid, blood or saline (18, 19).

We suggest an algorithm for the investigation and therapeutic management of SDH with SIH (Supplementary Figure 2): the therapeutic and etiological strategy would be progressively more invasive, starting with an initial assessment using MRI sequences of the skull and spine, followed by non-targeted lumbar EPs, which may be repeated once or twice, and finally, in the event of failure, dynamic myelography in search of a persistent extensive tear, with surgical repair if necessary, but with no indication for surgical removal of subacute SDH except in the event of coma with uncus herniation.

Our case report has three main limitations. First, a peri-medullary breach was not definitively established, but the diagnosis of SIH was not in doubt (clinical history, MRI findings, ICP and LITP always low). Second, the narrowing of the cervical canal at C6-C7 could have affected pressure transmission between the lumbar sac and cranium. However, the narrowing of the cervical canal was limited to its posterior part, and the two dynamic myelograms showed no slowing of contrast agent diffusion toward the rostral level. In any case, the transmission between the two pressure measurements could have been hindered, with an underestimation rather than an overestimation of the effect we have documented. Third, other associated conditions could explain the bithalamic lesions and the lack of conscious recovery. Although acute Wernicke's encephalopathy, osmotic demyelination or cerebral venous sinus thrombosis do not seem to be involved

given the overall clinical, biological and radiological picture, cerebral lymphoma or encephalitis (HIV, West Nile virus, Japanese encephalitis or tick-borne encephalitis) were not formally ruled out. Nevertheless, the diagnosis of SIH and the evolution of ICP and LITP curves remain relevant, illustrating the pathophysiology of this syndrome.

In conclusion, clinicians should be aware of the bilateral thalamic ischemia picture that may be the presenting sign of a SIH. Also, the spinal compartment has an established central role in the pathophysiology of SIH, but the key problem may be intraspinal and intracranial volumes rather than pressures. Therefore, intracranial hypotension syndrome could actually be intraspinal hypovolume syndrome.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because the patient has died. The deceased patient's next of kin did not object to publication of the case study after the information had been provided.

Author contributions

NE: Investigation, Writing – original draft, Conceptualization, Data curation, Formal analysis, Validation. QS: Data curation, Investigation, Writing – original draft, Writing – review & editing. J-PD: Investigation, Writing – review & editing. CE: Writing – review & editing, Writing – original draft. PB: Writing – review & editing. GB: Writing – review & editing, Investigation, Writing – original draft. MW: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank Laura Smales for English proofreading.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1308462/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Subsequent imaging. **(A)** First dynamic myelography (D25). No extra-thecal CSF leak found. **(B)** CT-scan myelography (D25). The patient was transferred for CT immediately after the dynamic myelography was performed, without further contrast injection into the intrathecal space. No extra-thecal CSF leak was found. **(C)** Left ONSD just before dynamic myelography. ONSD was already moderately dilated by SIH to 6.4 mm (normal £ 5.8 mm). Transcranial Doppler ultrasonography findings were normal on both sides (not shown). **(D)** Left ONSD during dynamic myelography. ICP increased from 2 to 80 mmHg for a few seconds, then returned to a normal value within 5 min. ONSD dilation was further increased to 7.7 mm by intrathecal injection. The ONSD remained high, with maximal values in the following days. Only the left side is shown, but the same pattern was observed on the right side. **(E)** Phlebography–CT scan (D36). An excessively closed angle between the vein of Galen and the right sinus: 12° (angle marked in red). **(F)** Digital subtraction angiography–phlebography (D55). The excessively closed angle between the vein of Galen and the right sinus was confirmed. Nevertheless, venous flow was normal, and no therapeutic procedure could be performed. (CSF, cerebrospinal fluid; ONDS, optic nerve sheath diameter).

SUPPLEMENTARY FIGURE 2
Proposed algorithm for the investigation and therapeutic management of SDH with SIH:
The therapeutic and etiological strategy is increasingly invasive:
- initial evaluation by skull and spine MRI sequences
- non-targeted lumbar epidural patches, possibly with saline, which may be repeated once or twice
- in case of failure, dynamic myelography to search for a persistent extensive tear, with surgical repair if present.
No indication for surgical removal of a subacute SDH except in cases of coma with uncus herniation.
This algorithm follows logically from our observations (previous and current clinical notes) but still needs to be the subject of larger prospective studies.
(SDH, subacute subdural hematoma; SIH, spontaneous intracranial hypotension)

SUPPLEMENTARY TABLE 1
Main laboratory data.

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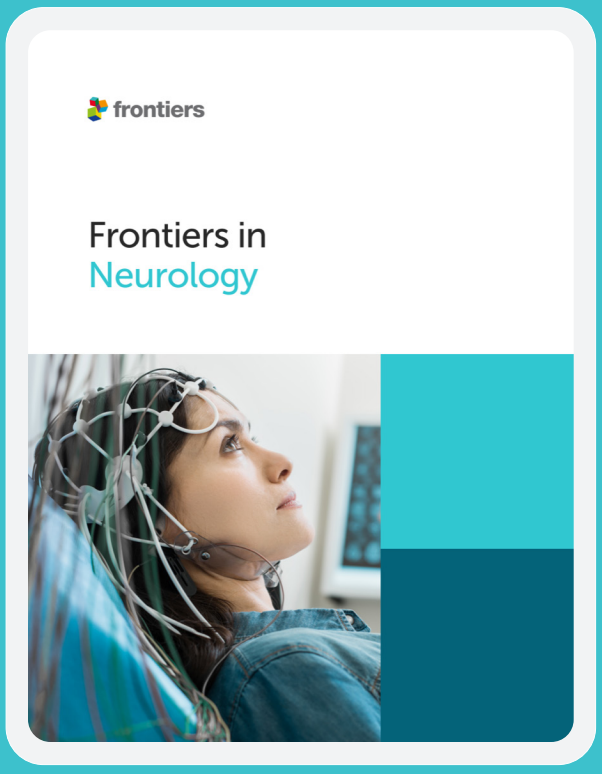

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