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Delayed lethal central nervous system toxicity induced by a low-dose intrathecal administration of bupivacaine: case report

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Spinal anesthesia by intrathecal administration of local anesthetic (LA) is a routine practice. Local anesthetic system toxicity, occurring in the central nervous system (CNS) and cardiovascular system, is a common and life-threatening adverse event of LA through a variety of routes, but is rarely encountered in spinal anesthesia when a very low dose of LA is injected into the subarachnoid space. Here, we report a case with manifestations of delayed lethal CNS toxicity after spinal anesthesia. A 55-year-old man underwent elective repair surgery for a chronic ulcer after receiving 10 mg intrathecal administration of bupivacaine. He developed nausea, agitation, paresthesia and myoclonus on the arms, legs, and trunk, as well as a gradually reduced level of consciousness one hour after intrathecal administration. He was sedated, intubated, and transferred to the intensive care unit. Both CT and MRI scans of the brain and assessments of blood showed no abnormalities. The electroencephalogram showed spike waves occurring at electrodes C3, C4, P3, P4, and T5. The patient was sedated continuously and treated with valproate. These symptoms were completely resolved in the following days without residual neurological complications. No cardiovascular complications were observed during the entire process. The delayed lethal symptoms in this case were most likely to be CNS toxicity induced by intrathecal bupivacaine administration. CNS toxicity after spinal anesthesia may be underestimated and unpredictable and should be vigilantly cared for in clinical settings.

KEYWORDS

spinal anesthesia, bupivacaine, toxicity, central nervous system, myoclonus

Introduction

Spinal anesthesia by intrathecal administration of local anesthetic (LA) is a routine practice for surgery of the lower abdomen, pelvis, or lower extremities. The most commonly adverse effects of spinal anesthesia are hypotension, respiratory paralysis, or underventilation due to the block of spinal nerves above T4, but the local anesthetic systemic toxicity (LAST) is rarely encountered in spinal anesthesia for a very low dose of LA is injected into the subarachnoid space. LAST is a common and life-threatening adverse event of LA through a variety of routes after inadvertent intravascular injection, overdose, or significant systemic absorption that plasma concentration of LA reaches a

toxic level (1). LAST can be further subdivided into central nervous system (CNS) toxicity and cardiovascular systemic toxicity. CNS toxicity occurs when LA crosses the blood-brain barrier, which leads to CNS excitation followed by CNS inhibition with potential respiratory depression and even death (2). Cardiovascular system toxicity with the symptoms of dysrhythmias and low systemic vascular resistance occurs when systemic LA concentration reaches a higher level (2). Here, we report a case with manifestations of delayed lethal CNS toxicity followed by intrathecal administration of 10 mg bupivacaine and reviewed cases with abnormal neurological symptoms after spinal anesthesia, which indicates CNS toxicity after spinal anesthesia may be underestimated and unpredictable and should be vigilantly cared for in clinical settings.

Case report

A 55-year-old man was presented for elective repair surgery for a chronic ulcer on the right foot induced by a 10-year history of type 2 diabetes mellitus. The chronic ulcer was debrided under general anesthesia uneventfully 142 days prior, and repaired with bone cement under local anesthesia uneventfully 132 days and 98 days prior, respectively. Moreover, he underwent an uneventful incision and drainage of the abscess of the ulcer under spinal anesthesia with ropivacaine three weeks prior. He had no history of drug abuse and seizures. Preoperative blood tests including liver function, renal function, and coagulation function of the patients were normal.

The puncture of spinal anesthesia was performed uneventfully in the L3–L4 interspace using a 25 G Quincke needle. 2 ml of 0.5% bupivacaine was injected into the subarachnoid space after obtaining cerebrospinal fluid. A good block was achieved about 5 min later. The surgery was uneventful and lasted about 50 min. No additional drugs were administered. The patient complained of nausea during transfer to the ward about 60 min after the intrathecal injection; thus, he was transferred to the post-anesthesia care unit. Finger prick blood was analyzed to detect hypoglycemia. Nausea was relieved after intravenous treatment of ondansetron 8 mg. However, about 10 min later, he became agitated and sweaty, complained of paresthesia on the skin below his neck, and developed involuntary, bilateral, asymmetrical, and arrhythmic myoclonic movements in both arms without loss of consciousness. Moreover, the heart rate, blood pressure, and arterial blood gas analysis were normal. Due to the symptoms of being sweaty and paresthesia on the skin, allergic reaction was doubted and hydrocortisone 100 mg was intravenously infused. Due to the symptoms of agitation, midazolam 5 mg was administered and dexmedetomidine was infused to sedate the patient. About 100 min after intrathecal injection, he was quickly intubated after the treatment of propofol and rocuronium for sudden blue jaundice of lips and loss of consciousness. The Glasgow coma scale was approximately 14 just before consciousness loss: eye opening was spontaneous, verbal response was responsible but a little confused, and the patient could obey commands to move his hands. The patient was transferred to the intensive care unit and a neurological doctor was consulted. Myoclonus still occurred and expanded to the legs when the muscle relaxation effect was eliminated (**Supplementary Video S1**). Both CT and MRI scans of the brain and assessments of blood showed no abnormalities. However, the electroencephalogram (EEG) showed spike waves occurring at electrodes C3, C4, P3, P4, and T5 (**Figure 1**), which showed myoclonus originated from the cortex of the parietal lobe and left temporal lobe. The patient was sedated continuously and treated with valproate. The frequency and amplitude of myoclonus decreased about 8 h after intrathecal injection. Although he still had sporadic myoclonus on postoperative day 1, he was peaceful and cooperative after stopping sedation. Therefore, he was extubated and transferred to the ward. He was discharged on postoperative day 4 without residual neurological complications. No cardiovascular complications were observed during the whole process.

Discussion

Other causes should be excluded before concluding that intrathecal bupivacaine is responsible for these delayed lethal side effects. Hypotension and underventilation are the most common adverse experiences following the administration of spinal anesthesia. However, this patient had no underventilation from intrathecal injection to the start of seizures. No hypotension occurred after intrathecal injection and even during the seizures. In addition, both the intrathecal puncture and repair surgery for chronic ulcer were performed by experienced doctors and were uneventful; no other drugs were used except for intrathecal bupivacaine; no abnormalities of CT and MRI scan of the brain and blood assessments were detected; these side effects were occurred about 1 h after intrathecal injection, relieved several hours, and completely recovered in the flowing days; the patient never underwent these symptoms before and after recovery. The total score of the Adverse Drug Reaction Probability Scale was 7 (**Supplementary Table S1**), which indicates that bupivacaine was the "probable" reason for these delayed lethal side effects.

The manifestations of CNS toxicity induced by LA include seizures, nausea, vomiting, perioral paresthesia, confusion, audio-visual disturbances, dysgeusia, agitation, or reduced level of consciousness (3). Moreover, spinal myoclonus, which originates from the spinal cord and is characterized by a non-generalized neuromuscular dysfunction restricted to a few somatic regions, was reported to be a side effect after spinal anesthesia (4–6). According to the manifestations of nausea, agitation, reduced level of consciousness, paresthesia and generalized myoclonus on arms, legs, and trunk, and spike waves in EEG, these side effects were compatible with CNS toxicity originating from the cerebral cortex induced by intrathecal bupivacaine administration.

Two pathways that lead to CNS toxicity after intrathecal administration of LA. One is that systemic absorbed LA crosses the blood-brain barrier, which usually occurs at high-dose LA administration (7). The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 ± 1.2 mg/kg with mean plasma concentration of 4.5 ± 1.7 μ/ml (8). In this case, only 10 mg of bupivacaine was used, which is far lower than its toxic

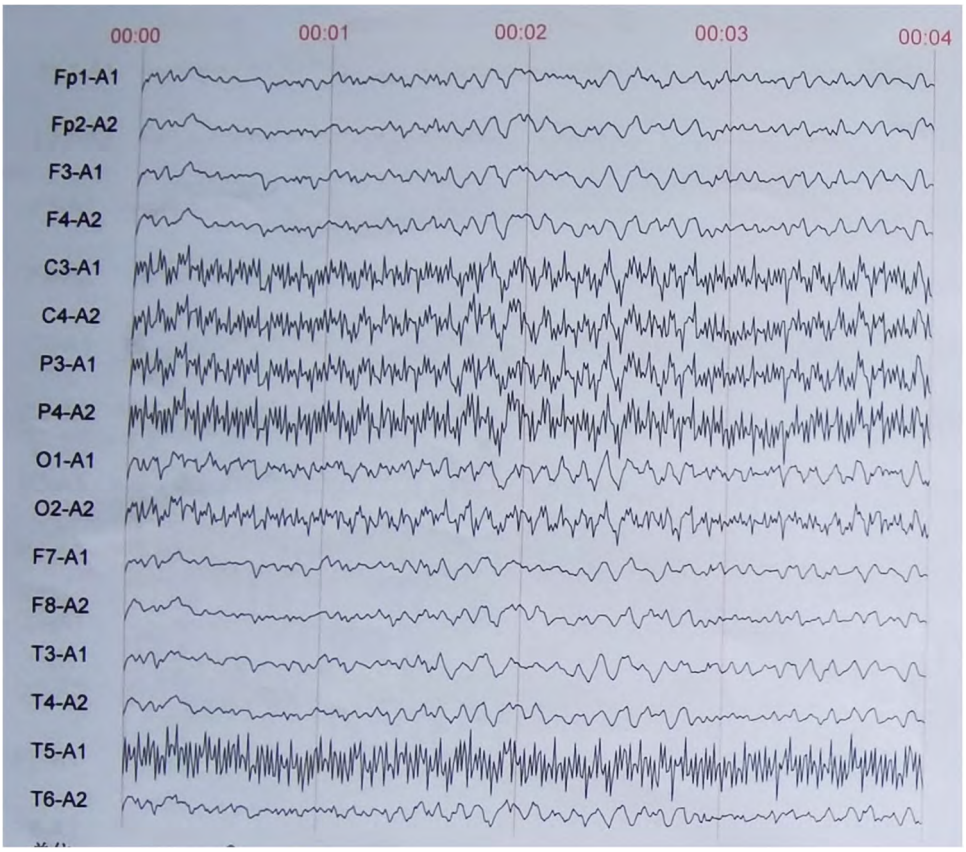

FIGURE 1
Representative electroencephalogram of this case after the onset of myoclonus.

dose; thus, we believe this pathway is impossible. The other is that the drug in the cerebrospinal fluid cephalic diffused to the cerebral cortex then leads to neuron excitation (7). In this case, even if the dose of LA is low, it can affect the activity of neurons. Therefore, we speculate cephalic diffusion is the reason for CNS toxicity induced by intrathecal LA administration.

Based on the theory of LA cephalic diffusion after intrathecal administration, CNS toxicity should be not rare. We reviewed the published literature and found that 30 publications (1, 2, 4–6, 9–33) involving 31 patients and two cats had generalized tonic-clonic seizures or myoclonus after spinal anesthesia (**Table 1**), which is a symptom of LA-induced CNS toxicity. Although these myoclonus or generalized tonic-clonic seizures were considered to originate from the spinal cord (4–6), it could not be excluded that these side effects originated from the cerebral since the EEG assessment was absent in about 71% of the cases (**Table 2**) and abnormal EEGs were detected in two cases (2, 12). Moreover, these neurological symptoms presented in patients of different ages and genders, with or without neurological diseases, and different types of surgeries; they occurred quickly or slowly from several hours to one day after spinal anesthesia; and 64% of them were mild and resolved quickly and spontaneously (**Table 2**). Thus, CNS toxicity after spinal anesthesia is unpredictable and may be ignored in clinical settings, and underestimated. In addition, 46.7% of parturients underwent involuntary arm shaking or shivering soon after spinal anesthesia during cesarean delivery while they didn't feel cold (34), which has some similarity with myoclonus indicates that involuntary arm shaking may be a CNS toxicity induced by LA. Taken together, the rare complication of CNS toxicity induced by intrathecal LA administration may not be rare.

Although CNS toxicity after spinal anesthesia is unpredictable, our literature review found that (**Table 2**) it mainly occurred in female patients (75%), patients with ages between 18 and 65 years (65%), and bupivacaine administration (84%). The potential for CNS toxicity correlates with the potency of LA. Potent lipid-soluble agents such as bupivacaine can cause CNS toxicity at lower doses than less potent agents, such as levobupivacaine and ropivacaine (2). Shiratori et al. (35) found that 70% of patients had neurological symptoms after spinal and epidural anesthesia with bupivacaine. Moreover, our case underwent an uneventful incision and drainage of the abscess under spinal anesthesia with ropivacaine three weeks ago. These data indicate that intrathecal administration of bupivacaine has a high risk of CNS toxicity even if a very low dose was used.

Although 64% of the CNS toxicity induced by intrathecal LA administration was mild and resolved quickly and spontaneously, 13% of cases (2, 23, 24, 30) were severe and needed medical interventions to avoid hypoxia as presented in our case (**Table 2**).

TABLE 1 The characteristics of the published cases with myoclonus after spinal anesthesia.

Study	Age	Gender	Medical history	Type of surgery	Type of anesthesia	Side effects	Ab-normal EEG	Treatment	Prognosis
Cenani (33)	UC	UC (cat)	UC	UC	B, M	Myoclonus	UC	UC	UC
McFadzean and Holopherne-Doran (27)	UC	UC (cat)	UC	UC	B, M	Myoclonus, hypersensitivity of the tail	UC	UC	UC
Vanmarcke et al. (2)	76 years	Female	Hysterectomy, supraventricular tachycardia	Total hip arthroplasty	Hyperbaric B 15 mg, S 2.5 μg	Myoclonus of the lower extremities followed by generalized tonic-clonic seizures 1 h after intrathecal injection	Yes	Sedation, intubation, valproate	Resolved completely 6 days after stopping sedation
Pradhan and Robson (5)	44 years	Female	Two previous caesarean section	Elective caesarean section	Hyperbaric B 13 mg, F 15 μg, M 100 μg	Mild myoclonus of the right upper limb 1 h after intrathecal injection, followed by increased frequency and amplitude of myoclonus spreading to both upper limbs and trunk	No	UC	Resolved completely by 48 h
Patel and Verma (32)	35 years	Female	UC	Cesarean section	B	Myoclonus followed by generalized tonic-clonic seizures	UC	UC	UC
Sieffien et al. (6)	64 years	Female	Diabetes mellitus, restless legs syndrome	Total hip arthroplasty	Isobaric B 10 mg	Bilateral myoclonus of the upper limbs and torso about 210 min after intrathecal injection, which persisted 90 min	UC	Sedation, muscle relaxant	Resolved completely
Shaikh et al. (31)	68 years	Female	Hepatitis C positive	Removal of infected a femur implant	Hyperbaric B 15 mg	Moderate to severe pain in non-operated leg about 140 min after intrathecal injection, myoclonus about 20 min after pain onset	UC	Magnesium sulphate, lidocaine	Resolved completely after drug infusion
Jacob et al. (1)	80 years	Female	UC	Surgical treatment of leg bones fracture	Levobupivacaine	A tonic-clonic seizure with sphincter incontinence soon after intrathecal injection	No	No	Resolved completely
Silva et al. (30)	67 years	Female	No	Hip replacement surgery	B 10 mg	Unbearable pain in legs and perineum and bilateral myoclonus in the lower limbs 7 min after intrathecal injection	No	Sedation, muscle relaxant, intubation	Resolved completely at POD1
Tajima et al. (29)	33 years	Female	UC	Emergency caesarean section	Hyperbaric B	Myoclonus of the upper limbs 76 min after intrathecal injection	UC	No	Ceased 4 h after intrathecal injection
Shiratori et al. (28)	33 years	Female	No	Elective cesarean section	Hyperbaric B 13 mg	Myoclonus about 130 min after intrathecal injection, which gradually increased in frequency and magnitude	UC	No	Disappeared 5 h after intrathecal injection
Kösem and Kılınç (26)	36 years	Female	No	Surgery for left leg varices	Hyperbaric B 15 mg	Myoclonus of right leg about 1 h after intrathecal injection, which persisted 5 h	UC	No	Resolved completely
Nakamoto et al. (25)	35 years	Female	No	Elective cesarean section	Hyperbaric B 12.5 mg, F 15 μg	Myoclonus in both upper extremities about 1 h after intrathecal injection	UC	Sedation	Stopped after midazolam treatment
Lev et al. (4)	28 years	Female	No	Elective cesarean section	Hyperbaric B 8 mg, M 0.15 mg	Myoclonus of the arms, legs, and trunk 2 h after intrathecal injection	No	Clonazepam, muscle relaxant	Resolved after 72 h with a very mild proximal right leg weakness

(*Continued*)

TABLE 1 Continued

Study	Age	Gender	Medical history	Type of surgery	Type of anesthesia	Side effects	Ab-normal EEG	Treatment	Prognosis
Kim et al. (24)	27 years	Female	Hepatitis B carrier	Emergency cesarean section	B 8 mg	Generalized tonic-clonic seizures 3 min after delivery, which followed by loss of consciousness and apnea	No	Intubation	Resolved after several hours
Abrão et al. (23)	63 years	Male	No	Transurethral resection of the prostate	B 15 mg	Myoclonus of the lower limbs and significant agitation soon after intrathecal injection	UC	Sedation, intubation	Resolved completely on POD3
Zamidei et al. (22)	77 years	Female	No	Hip replacement	Isobaric B 12 mg	Sudden myoclonus of the arms, legs, and trunk on POD1	No	Valproate, clonazepam	Disappeared completely on POD4
Lee et al. (21)	35 years	Female	No	Surgical treatment of peroneal tendonitis	Hyperbaric B 9 mg	Myoclonus of both legs and arm about 100 min after intrathecal injection	UC	Sedation	Disappeared completely 4 h after its onset
Bamgbade et al. (19)	90 years	Male	Cardiac failure, ischemic heart disease	Prostatectomy	Hyperbaric B 10 mg	Right leg myoclonus during the attempt at lithotomy positioning soon after intrathecal injection	UC	An epidural dose of 10 ml of 0.25% bupivacaine	Resolved 10 min after epidural treatment
Bamgbade et al. (19)	64 years	Female	Coronary artery disease, diabetes mellitus	Ureterotomy	Hyperbaric B 10 mg	Lower-limb myoclonus 1 h after intrathecal injection, which lasted less than 3 min	UC	No	Resolved completely
Bamgbade et al. (19)	53 years	Female	Hypertension, rheumatoid arthritis	Pelvic surgery	Hyperbaric B 12.5 mg, M 300 mg	Lower-limb myoclonus about 90 min after intrathecal injection, which lasted 1 h	UC	Sedation	Resolved completely
Bamgbade et al. (19)	67 years	Male	Diabetes, peripheral neuropathy, obesity, asthma	Refashioning of a left below-knee amputation stump	Hyperbaric B 12.5 mg, M 300 mg	Myoclonus in the absent amputated limb about 1 h after intrathecal injection	UC	Sedation	Resolved completely
Galante (20)	73 years	Male	A serious urinary tract infection with multiresistant Escherichia Coli.	Transurethral resection of the prostate	Hyperbaric B 13 mg, F 20 μg	Generalized tonic-clonic seizure with transient loss of consciousness 20 min before the end of the procedure, which persisted 65 min	UC	Sedation	Disappeared completely
Alfa and Bamgbade (15)	53 years	Female	Hypertension, hyperlipidemia, rheumatoid arthritis	Surgical repair of cystocoele and uterine prolapse	Hyperbaric B 12.5 mg, M 300 mg	Myoclonus of both lower limbs 3 h after intrathecal injection, followed by increased amplitude and frequency of the myoclonus, which persisted about 2 h	UC	Sedation	Resolved completely
Lin et al. (18)	UC	UC	UC	Excision of a Baker's cyst	Hypobaric B 12.5 mg	Myoclonus in the lower legs 1 h after intrathecal injection, followed by gradually increased amplitude and frequency of the myoclonus, which persisted about 50 min	UC	Sedation	Resolved completely
Kim et al. (16)	18 years	Male	UC	Varicocelectomy	Hyperbaric B 14 mg	Myoclonus on upper extremities 90 min after intrathecal injection, which sustained about 1 month	UC	Anti-convulsants, muscle relaxant	Resolved completely
Lee et al. (17)	45 years	Female	UC	UC	Hyperbaric B 12 mg	Myoclonus on lower extremities 2 h after intrathecal injection	UC	Sedation	Resolved completely
Batra et al. (14)	45 days	Male	No	Bilateral inguinal hernia repair	B 2 mg, F 2.5 μg	Myoclonus on left thigh and arm soon after intrathecal injection, which persisted 4 min	No	No	Resolved spontaneously

(*Continued*)

TABLE 1 Continued

Study	Age	Gender	Medical history	Type of surgery	Type of anesthesia	Side effects	Ab-normal EEG	Treatment	Prognosis
Celik et al. (13)	56 years	Female	UC	UC	Hyperbaric B 15 mg	Bilateral myoclonus on the lower extremities 2 h after intrathecal injection, which persisted about 1 h	UC	No	Stopped completely
Chen et al. (9)	36 years	Male	UC	Ureteroscopic lithotomy	Tetracaine 18 mg	Episodic seizure soon after intrathecal injection	UC	UC	UC
Watanabe et al. (12)	81 years	Male	No	Bilateral ureterostomy	Isobaric dibucaine 3.6 mg	Periodic left plantar flexion after intrathecal injection, which persisted 70 min	Yes	No	Resolved spontaneously
Nadkarni and Tondare (11)	45 years	Female	No	Abdominal hysterectomy	5% lidocaine 1.5 ml	Bilateral myoclonus of the abdomen, low back, thighs, and legs about 2 h after intrathecal injection	UC	Sedation	Resolved completely
Fox et al. (10)	57 years	Female	Nephrectomy	Ureterostomy	Tetracaine 14 mg	Slight twitching around the right knee 5 h after surgery, followed by strong myoclonus on the thigh and knee, which persisted several hours	UC	Sedation	Resolved completely

UC, unclear; B, bupivacaine; S, sufentanil; F, fentanyl; M, morphine; EEG, electroencephalogram; POD, postoperative day.

TABLE 2 Summary of the published cases with myoclonus after spinal anesthesia.

Heading	Subgroup	Number (%)	Heading	Subgroup	Number (%)
Age	≥65 years	9 (29)	Gender	Female	22 (71)
	≥18 years and <65 years	20 (65)		Male	8 (23)
	<18 years	1 (3)		Unclear	1 (3)
	Unclear	1 (3)	Preoperative neurological diseases	Yes	2 (6)
Type of surgery	Cesarean	7 (23)		No	21 (68)
	Urinary	7 (23)		Unclear	8 (26)
	Abdominal	5 (16)	Abnormal EEG	Yes	2 (6)
	Orthopedic	7 (23)		No	7 (23)
	Others	3 (10)		Unclear	22 (71)
	Unclear	2 (6)	Time of neurological symptom	Quick	8 (23)
Local anesthetic	Bupivacaine	26 (84)		Delayed	22 (71)
	Levobupivacaine	1 (3)		Unclear	1 (3)
	Ropivacaine	0 (0)	Degree of myoclonus	Mild	20 (64)
	Lidocaine	1 (3)		Moderate	4 (13)
	Tetracaine	2 (6)		Severe	4 (13)
	Dibucaine	1 (3)		Unclear	3 (10)

EEG, electroencephalogram. Quick myoclonus was categorized as those occurred within 10 min or described as soon after intrathecal injection. Delayed myoclonus was categorized as those occurred more than 30 min after intrathecal injection.

Importantly, the time of the CNS toxicity development after spinal anesthesia was delayed (occurred more than 30 min after intrathecal injection) in 71% of cases (Table 2). Therefore, CNS toxicity following spinal anesthesia can be fatal and delayed, which should be sustained care even if the patient leaves the operation room.

Conclusion

Intrathecal administration of a low-dose LA, especially bupivacaine, can result in delayed, lethal, and unpredictable CNS toxicity, which may be underestimated and should be vigilantly cared for in clinical settings.

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

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin 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

WS: Conceptualization, Writing – original draft. HZ: Conceptualization, Writing – original draft. XL: Writing – original draft, Data curation. CY: Data curation, Writing – original draft. YZ: Writing – original draft, Formal Analysis. YL: Conceptualization, Writing – review & editing. BC: Conceptualization, Writing – review & editing, Funding acquisition.

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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/fanes.2023.1298806/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Representative symptom of myoclonus in this case.

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