

Case Report

Adverse neurological events following botulinum toxin type A: A case series of post-injection seizures and paralysis

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ABSTRACT

Within the field of rehabilitation and aesthetic medicine, botulinum neurotoxin (BoNT), particularly type A (BoNT-A), has gained significant popularity for its unique muscle-relaxing properties including muscular spasticity and reducing wrinkles. Nevertheless, its widespread use is accompanied by the inherent risk of poisoning. This report presents two distinct patterns of neurological adverse events observed across three patients involving BoNT-A. In the first pattern, Patients 1 and 2, who had cerebral infarction and cerebral hemorrhage, respectively, both developed seizures after BoNT-A injection in the context of multiple seizure risk factors, but with no definitive causal link between BoNT-A and seizures. In the second pattern, Patient 3, a healthy woman, developed severe generalized muscular weakness after receiving BoNT-A injection for cosmetic purposes. Based on a comprehensive review of the patients' clinical manifestations, auxiliary examinations, and rehabilitation treatments, this report underscores the importance of prompt recognition, accurate diagnosis, and timely intervention to improve patient outcomes and prevent complications such as seizures.

1. Introduction

Botulinum neurotoxin (BoNT) is a neurotoxin produced by *Clostridium botulinum* and consists of seven serotypes (BoNT type A through G). BoNT type A (BoNT-A) blocks the presynaptic release of acetylcholine (ACh) at the neuromuscular junction, thereby inhibiting nerve impulse transmission and resulting in muscular flaccidity (Hamid et al., 2014). Owing to this characteristic, BoNT-A has been widely used in rehabilitation and cosmetology (Wilkenfeld et al., 2013). In rehabilitation, BoNT-A is commonly administered to control spasticity following central nervous system (CNS) injuries such as stroke or traumatic brain injury (Facciorusso et al., 2024). It is also effective in treating spasmodic torticollis (also known as cervical dystonia) by reducing involuntary muscle contractions in the neck (Simpson et al., 2016). Besides, BoNT-A has been shown to alleviate neuropathic pain, including conditions such as postherpetic neuralgia and trigeminal neuralgia (Val et al., 2023). In cosmetology, it is used to relax overactive facial muscles, thereby smoothing wrinkles and slimming the face. Nevertheless, its widespread

use necessitates vigilance for dose-dependent peripheral neuromuscular adverse events and potential central nervous system complications in susceptible individuals. It is critical to note that BoNT-A formulations from different manufacturers are not interchangeable, owing to differences in bacterial strains, purification processes, complexing proteins, and unit-specific potency. Clinicians must adhere to product-specific dosing guidelines and avoid extrapolating doses across different brands. Herein, we describe two distinct neurological complications of BoNT-A: two stroke patients who developed seizures (probable central nervous system adverse events) following BoNT-A treatment for muscle spasms, and one patient who developed probable iatrogenic botulism (peripheral neuromuscular toxicity) following a cosmetic BoNT-A injection.

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2. Case presentation

2.1. Seizures

2.1.1. Case 1

2.1.1.1. Clinical background. A 63-year-old female suddenly developed right limb immobility, aphasia, and cognitive impairment on April 17, 2023. Diffusion-weighted imaging (DWI) of the brain revealed an acute cerebral infarction in the left frontal lobe and centrum semiovale (Fig. 1A). She received thrombolytic therapy along with neuroprotective treatment. Upon transfer to the Department of Rehabilitation Medicine at Xijing Hospital on July 9, 2023, the patient continued to experience right-sided hemiplegia. The 7-item Generalized Anxiety Disorder questionnaire (GAD-7) score was six. Electrical stimulation, repetitive transcranial magnetic stimulation (rTMS), and physical therapy were administered to improve her motor, cognitive, and swallowing functions. Medications for neuroprotection, enhancement of cerebral circulation, and plaque stabilization were also administered. No baseline EEG was performed prior to BoNT-A injection, as there was no clinical indication given the absence of prior seizure history.

2.1.1.2. Botulinum neurotoxin injection and seizures. The patient exhibited a significant increase in flexor muscle tone in the right upper limb, with the Modified Ashworth Scale (MAS) score of 1+. Then, BoNT-A treatment was administered to reduce muscle tone in the right upper limb. A total of 200 units of BoNT-A (HengLi, China) was dissolved in 4 ml of saline and injected into the biceps brachii and brachioradialis muscles in 12 separate doses under ultrasound guidance—a dose substantially below the 800 units maximum demonstrated safe in single-session treatment (Francisco et al., 2021). Ultrasound guidance was employed to ensure precise intramuscular delivery, thereby minimizing

systemic absorption and reducing the risk of unintended vascular or systemic spread (Llorente Peris et al., 2025). A seizure occurred 2 h following the procedure without prior seizure history, characterized by loss of consciousness, clenched teeth, and foaming at the mouth, with extremity twitching. Emergency interventions were promptly initiated, including oxygen inhalation, electroencephalography (EEG) monitoring, and intravenous administration of 10 mg diazepam. The epileptic seizure episode lasted for 3 min.

2.1.1.3. Continuous scalp EEG monitoring. Continuous EEG monitoring was conducted for 6 h during the inpatient period following the seizure. No further seizures occurred during this time. Most of the EEG activity was not associated with epileptiform discharges and either showed minimal changes or irregular left central theta waves (Fig. 1B). These non-specific findings do not support BoNT-A-induced epileptogenesis.

2.1.2. Case 2

2.1.2.1. Clinical background. A 54-year-old male suddenly experienced vomiting of gastric contents, accompanied by right limb weakness, loss of speech, and urinary incontinence on May 28, 2023. The head CT scan revealed a 60 ml hemorrhage in the left cerebral hemisphere. He underwent craniectomy and hematoma evacuation under general anesthesia in the Department of Neurosurgery.

By July 22, 2023, when the patient was transferred to the Department of Rehabilitation Medicine at Xijing Hospital, he remained unable to speak and had poor auditory comprehension, limited mobility of the right extremities, and was unable to stand, walk, or perform daily self-care. He also experienced anxiety during hospitalization, with a GAD-7 score of seven. The follow-up fluid-attenuated inversion recovery (FLAIR) scan indicated a subacute late-stage hemorrhage in the left basal ganglia, lateral ventricle, and centrum semiovale, along with local

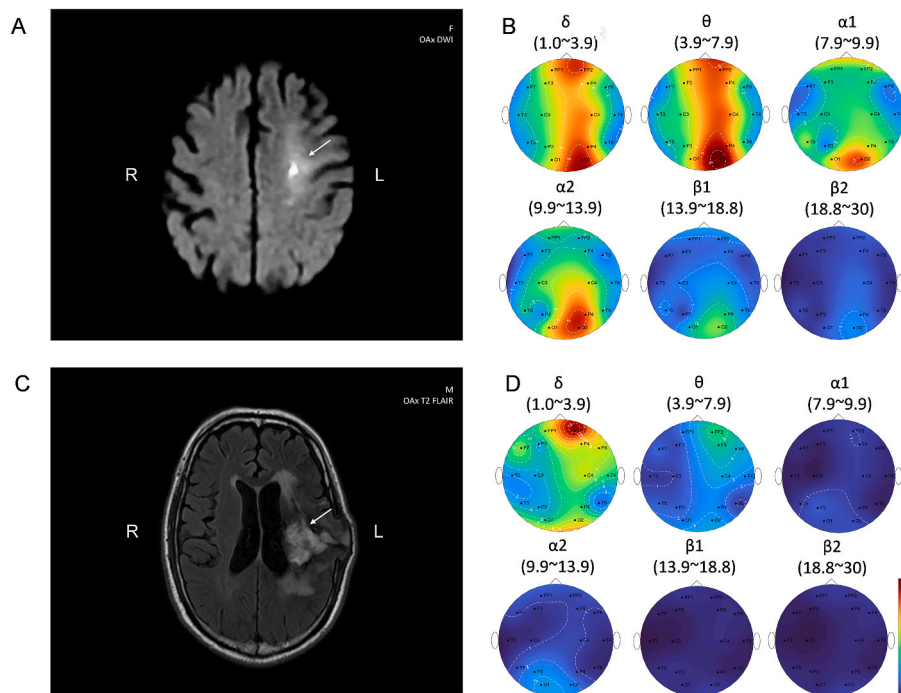


Fig. 1. Neuroimaging and continuous scalp EEG monitoring of two cases. (a) Case 1: DWI scanning indicated cerebral infarction in the left frontal lobe and centrum semiovale (white arrow). F, female; OAx, oblique axial view; DWI, diffusion-weighted imaging; (b) Case 1: Six hours of continuous EEG monitoring were recorded during inpatient after seizures. No further seizure began during 6 h EEG monitoring. Most were not associated with epileptiform activity and showed non-specific background slowing (irregular left central theta waves).; (c) Case 2: FLAIR scanning indicated subacute late-stage hemorrhage in the left basal ganglia, lateral ventricle, and centrum semiovale (white arrow). M, male; OAx: oblique axial view; FLAIR, fluid-attenuated inversion recovery; (d) Case 2: Six hours of continuous EEG monitoring were recorded during inpatient after seizures. No further seizure began during 6 h EEG monitoring. Most were not associated with epileptiform activity and showed non-specific background slowing (irregular left central theta waves).

encephalocele (Fig. 1C). Medications were administered to improve cerebral circulation, and comprehensive physical therapy was provided to promote the recovery of right limb function, as well as cognitive and speech functions. As with Case 1, no baseline EEG was performed.

2.1.2.2. Botulinum neurotoxin injection and seizures. Despite comprehensive rehabilitation, the patient continued to exhibit significantly increased muscle tone in the right lower extremity, particularly in the muscle groups responsible for ankle inversion, with the MAS score of 1+. This resulted in marked ankle inversion during walking, further impairing gait control. Therefore, BoNT-A treatment was administered to reduce muscle tone in the right lower extremity. A total of 300 units of BoNT-A (HengLi, China) was dissolved in 6 ml of saline and injected into the tibialis posterior, soleus, and gastrocnemius muscles in 18 separate doses under ultrasound guidance. Similarly, a seizure occurred 24 h post-procedure without prior seizure history, characterized by extremity twitching, upward eye movement, and vomiting of gastric contents. Emergency oxygen inhalation, EEG monitoring, and intravenous injection of 10 mg diazepam were promptly initiated. The epileptic seizure episode lasted for 4 min.

2.1.2.3. Continuous scalp EEG monitoring. Continuous EEG monitoring was conducted for 6 h during the inpatient period following the seizures. No further seizures occurred during this time. Most recorded activity was not associated with epileptiform discharges and showed minimal changes or irregular left central theta waves (Fig. 1D). Such non-specific patterns do not substantiate a direct epileptogenic role for BoNT-A in this clinical context.

2.2. Botulism

2.2.1. Case 3

2.2.1.1. Clinical background. A 48-year-old female received BoNT-A injections into the mandibular (25 units per side), trapezius (50 units per side), and inner upper arm muscles (50 units per side) at a cosmetic hospital, with a total dose of 250 units (HengLi, China) dissolved in 5 ml of saline. She subsequently developed clinical features consistent with probable iatrogenic botulism, characterized by decreased chewing strength three days post-injection. Nine days post-injection, her symptoms worsened significantly, including body pain, difficulty swallowing, coughing while drinking water, dyspnea, slurred speech, reduced neck mobility, and limb weakness, though she was still able to walk independently. Considering the possibility of allergic reactions and potential thyroid crisis, as well as severe infections or inflammations, she received initial treatment with 5 mg of intravenous dexamethasone and oral amoxicillin for 2 day at the cosmetic hospital, but her symptoms did not improve. She was then referred to our outpatient department and prescribed 120 mg of pyridostigmine bromide twice daily, but this treatment was discontinued due to abdominal pain and diarrhea. Neither metabolic support, nutritional therapy, nor symptomatic treatment proved effective. As a result, she was admitted to our department for further hospitalization. Definitive confirmation by botulinum toxin assay was not obtained due to limited laboratory availability and delayed presentation beyond the diagnostic window.

2.2.1.2. Physical examination after admission. The patient was conscious but appeared fatigued, with a painful expression and difficulty speaking smoothly when answering questions. In addition, her sense of smell was diminished. Physical examination revealed weak eyelid elevation, reduced bite force, difficulty swallowing, and weak neck and shoulder shrug. Muscle strength and tone in the limbs were decreased, and tendon reflexes in the extremities were diminished. No pathological signs or meningeal irritation were observed.

2.2.1.3. Laboratory testing. There were no abnormalities in the blood routine, markers of myocardial injury, thyroid function, cardiovascular and cerebrovascular disease, preoperative infection, inflammatory markers, hemagglutination, myocardial enzyme profile, blood glucose, electrolytes, or liver and kidney function.

2.2.1.4. Auxiliary examination. The single-fiber electromyography (SFEMG) performed prior to hospital admission revealed increased jitter in the extensor digitorum communis, along with an increment in amplitude during high-frequency repetitive nerve stimulation (RNS). After admission, the patient exhibited moderate restrictive ventilatory dysfunction and a severe reduction in respiratory muscle strength. No significant abnormalities were found in the pulmonary, musculoskeletal, or brain DWI/magnetic resonance angiography (MRA). The results of the functional assessment and electromyography (EMG) examination after admission are presented in Table 1. It should be noted that EMG amplitude changes observed in this study are nonspecific. Serum and stool toxin assays were not performed; thus, laboratory confirmation of botulinum toxin was unavailable.

2.2.1.5. Treatment. Upon admission, the patient was started on a nasogastric feeding regimen and continuous oxygen therapy. Medications, including mecobalamin, galantamine, etc., were administered to improve circulation and nourish the nerves and muscles. Electrotherapy was provided to enhance neuromuscular function. An intensive rehabilitation program was implemented, including daily training for speech, lower limb rehabilitation with robotic assistance, hand function exercises, and other activities to improve daily communication, limb mobility, coordination, and balance. Specific parameters and details of the main therapeutic modality are summarized in Table 2.

2.2.1.6. Discharge status. After approximately one month of hospitalization, the patient's condition improved substantially. Respiratory muscle strength significantly increased, along with notable progress in swallowing and speech functions. Furthermore, there was a significant recovery in limb motor function, walking gait, and balance. The condition of motor nerve conduction has improved. As a result, the functional assessment score at discharge was considerably higher than at admission. The specific changes in functional scores are detailed in Table 1 for reference and further understanding.

3. Discussion

The case series provides a new clinical demonstration of the diverse neurological adverse events of BoNT-A associated complications. The presented cases in this study highlight the complex pharmacodynamics of BoNT-A. They also underscore the importance of understanding both the therapeutic benefits and the potential risks associated with BoNT-A use.

3.1. Post-stroke seizure risk and causality analysis

In the first two cases, patients without a prior history of seizures experienced seizures following BoNT-A injection, though causality is uncertain. While the manufacturer confirmed the batch's quality, it is noteworthy that the current product labeling for HengLi BoNT-A acknowledges post-marketing reports of new or recurrent seizures, primarily in patients with predisposing factors, despite the absence of large-scale, dose-escalation safety studies specific to this product. Epileptic seizures are a phenomenon of the CNS, caused by abnormal excitation of the cerebral cortex or brain, which manifests as abnormal muscle activity. Following upper-motor-neuron injury, denervated muscle commonly shows extrajunctional ACh-receptor up-regulation and increased membrane excitability (Balch et al., 2021).

Han ZA et al. attempted to alleviate pain by subcutaneously injecting

Table 1
Functional assessment and EMG results of case 3.

Functional assessment	Admission score	Discharge score
MBI(score)	42	74
BBS(score)	31, some balance ability, can walk with assistance	46, good balance function, can walk independently
FAC(grade)	14, moderate anxiety	11, moderate anxiety
PHQ-9(score)	18, major depression	13, significant depressive symptoms
mFMA-M(score)	left upper limb: 52; right upper limb: 52; left lower limb: 33; right lower limb: 34	left upper limb: 59; right upper limb: 59; left lower limb: 33; right lower limb: 34
mFMA-B(score)	8, impaired	10, impaired
NIHSS(score)	9	5
MASA(score)	77	98
WST(grade)	V, obvious swallowing dysfunction	I, normal
mFDA(score)	20, mild impairment	26, mild impairment
EMG(amplitude, mV)	Radial nerve <i>forearm</i> L: 4.8↓, R: 5.2↓ <i>radial groove</i> L: 4.7↓, R: 5.3↓ Musculocutaneous nerve <i>supraclavicular fossa</i> L: 3.9↓, R: 5.3↓ Axillary nerve <i>supraclavicular fossa</i> L: 4.7↓, R: 7.3↓ Accessory nerve <i>sternocleidomastoid</i> L: 1.0↓, R: 0.7↓ Suprascapular nerve <i>sternocleidomastoid</i> L: 1.6↓, R: 1.5↓	L: 6.4, R: 5.1↓ L: 6.3, R: 5.3↓ L: 4.9↓, R: 5.5↓ L: 7.3↓, R: 7.3↓ L: 1.4↓, R: 1.7↓ L: 1.8↓, R: 1.2↓

Abbreviation: MBI: modified barthel index; BBS: berg balance scale; FAC: functional ambulation category scale; GAD-7: 7-item generalized anxiety disorder questionnaire; PHQ-9: patient health questionnaire-9; mFMA-M: modified Fugl-Meyer assessment of motor function; mFMA-B: modified Fugl-Meyer assessment of balance function; NIHSS: national institute of health stroke scale; MASA: modified mann assessment of swallowing ability; WST: water swallowing test; mFDA: modified frenchay dysarthria assessment; EMG: electromyography; L: left; R: right.

Table 2
The main therapeutic regimen.

Type	Name	Dosage	Frequency	Function
General Treatment	Nasogastric feeding			
	Continuous oxygen inhalation			
Drugs	Idebenone	30 mg	thrice daily	improve circulation and eliminate blood stasis
	<i>Ginkgo biloba</i> extract	20 ml	twice daily	
	Mecobalamin	0.5 mg	three times daily	neural nourishment
	Acetylcysteine nebulization	3 ml	twice daily	improve respiratory tract function
	Betahistine	30 mg	twice daily	alleviate vertigo symptoms
	Galantamine	2 ml	once daily	enhance muscular strength
Physical Therapy	Intermediate frequency Electrotherapy		once daily	improve skeletal muscle contraction
	Low-frequency electrotherapy		once daily	excite neuromuscular function
	rTMS	affected side, 10 Hz at 1400 pulses	once daily	enhance motor function
	Electronic biofeedback therapy		once daily	regulate body functions

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

BoNT-A into the painful area of neuropathic pain patients after spinal cord injury. Surprisingly, three patients reported spasticity symptoms in the treated area after the injection (Han et al., 2016). Feyissa AM et al. concluded that stroke is the cause of about 10% of all epilepsy and 55% of newly diagnosed seizures among the elderly (Feyissa et al., 2019). Using the SeLECT prognostic model for post-stroke late seizures (Galovic et al., 2018), the calculated risks were 11% for Case 1 and 18% for Case 2. Besides, structured causality assessment using the Naranjo algorithm and WHO-UMC criteria yielded scores of “possible” for both cases (Naranjo et al., 1981; Uppsala Monitoring Centre). It is worth noting that the patient received neuroprotective treatment and medications aimed at enhancing cerebral circulation and stabilizing plaques. The potential of drugs such as donepezil to provoke seizures or alter seizure thresholds cannot be overlooked (Ha et al., 2022). The patient also underwent electrical stimulation and repetitive transcranial magnetic stimulation (rTMS), both of which have the potential to alter cerebral excitability (Terney et al., 2008). In the present cases, the onset of seizures occurred 2 hours and 15 minutes after rTMS (2 hours after BoNT-A) in the first patient, and approximately 22 hours after the last rTMS session (24 hours after BoNT-A) in the second patient. The close temporal relationship between the seizure episodes and the recent

neuromodulatory interventions, together with the absence of any documented seizure history, supports a more plausible association with the neurostimulation rather than botulinum toxin administration alone. Additionally, patients' emotions and mental state may also serve as triggers for seizures. Brown RJ et al. noted that psychogenic non-epileptic seizures (PNES) are commonly observed in patients with neuropathological conditions, often associated with significant distress and disability (Brown et al., 2016). Moreover, anxiety, present in both patients (GAD-7 scores: 6 and 7), may have further lowered seizure threshold (Hamid et al., 2014). Therefore, given the presence of multiple recognized seizure risk factors including recent stroke, concomitant neuroactive medications, neurostimulation therapies, and anxiety—offers more robust explanatory mechanisms for the observed seizures, which most likely represent coincidental events. Although BoNT-A was administered shortly before the events, it does not cross the blood-brain barrier and has no known pro-convulsive pharmacological activity. Thus, the injection of BoNT-A is more likely to serve as a potential nonspecific physiological stressor rather than a definitive cause. Nevertheless, it is crucial to take these factors into account during the BoNT-A evaluation process. Close monitoring and the establishment of post-injection emergency measures for seizure management should be

standard practice when administering BoNT-A.

3.2. Cosmetic BoNT-A and systemic neuromuscular toxicity

In contrast, the third case presents a different mechanism, where the patient developed severe generalized muscular weakness due to the depletion of Ach at the neuromuscular junction. The patient having no signs of myasthenia before the injection and not taking any medications that could damage the neuromuscular junction, she still experienced flaccid paralysis along with symptoms such as dysphagia, dyspnea, dysarthria, and limb weakness. Once BoNT-A enters the bloodstream, it is efficiently transported to peripheral cholinergic nerve terminals (Humeau et al., 2000), which can result in cranial nerve paralysis syndrome (Rao et al., 2017). Since the U.S. Food and Drug Administration approved BoNT-A for medical cosmetic use in 2002, it has become a widely used treatment for wrinkle reduction and facial contour enhancement. An observational study reported 86 cases of cosmetic botulinum neurotoxin overdose (Bai et al., 2018), with patients exhibiting a range of symptoms. Various physical and chemical factors can influence the stability and potency of BoNT-A. In this case, the active ingredient of BoNT-A (HengLi, China) for injection is produced from the highly toxigenic Hall strain of *Clostridium botulinum* type A. The excipients are sucrose, dextran, and gelatin. The potency labels of different botulinum neurotoxin brands are not directly comparable due to differences in bacterial strains, purification processes, and complexing proteins, which can make determining the appropriate therapeutic dosage more challenging (Dressler et al., 2021). In addition, it should be noted that the operation was carried out by an external organization, and there was no available operation record, image guidance document or operator's detailed information, so the specific technical factors (dilution, injection depth and injection volume) related to systemic diffusion in theory could not be clarified retrospectively in this case.

Over the course of approximately one month under our care (Table 2), the third patient showed significant improvements in both limb and speech function. Nonetheless, it is essential to note that the lack of timely and effective detoxification treatment during the early stages of the patient's presentation likely contributed to a prolonged and potentially slower recovery process. However, given the absence of controlled data and variable individual response to antitoxin, whether earlier administration would have altered the recovery timeline in this specific case remains uncertain. The initial empirical use of dexamethasone and amoxicillin, prompted by the patient's history of hyperthyroidism and glomerulonephritis, and considering the patient's severe clinical symptoms, was inappropriate for iatrogenic botulism. Neither glucocorticoids nor beta-lactam antibiotics can neutralize botulinum toxin. Additionally, glucocorticoids may even mask early cranial nerve signs. Botulinum antiserum is currently the only specific treatment for botulism (Pohanka et al., 2020). In China, the botulinum antiserum is centrally managed, with a stringent application and approval process, which can be cumbersome. This underscores the importance of early identification of the toxic agent and its sequelae. Given the non-specific clinical manifestations of botulism and the potential for patients to conceal their injection history, clinicians must remain highly vigilant and conduct thorough inquiries to minimize missed or misdiagnoses. Notably, the serological positive rate for BoNT is often low due to metabolic factors, which can lead to false-negative results (Thirunavukkarasu et al., 2018). Although routine laboratory tests for botulism are often normal, brain imaging and chest X-rays can help exclude other conditions, such as brainstem stroke, lung cancer, or paraneoplastic syndrome. Electrophysiological diagnostic studies, including RNS, SFEMG, and nerve conduction studies (NCSs), can further aid in determining the underlying etiology of the symptoms (Rao et al., 2021). In this case, the initial diagnosis of probable botulism was primarily based on characteristic clinical manifestations and the results of SFEMG and RNS. The EMG findings of reduced amplitude were nonspecific (Table 1). Although subsequent comprehensive laboratory

tests, ruling out other diagnoses, the absence of definitive botulinum toxin assay remains a limitation. This highlights the critical importance of pursuing early laboratory confirmation in similar clinical presentations, while acknowledging that clinical assessment remains paramount when toxin assays are unavailable.

Several limitations should be considered when interpreting these findings. The absence of serum toxin assay in all three cases represents a critical diagnostic gap. Thus, the diagnosis of iatrogenic botulism in Case 3 remains presumptive based on clinical and electrophysiological criteria alone. The EEG recordings in Cases 1 and 2 demonstrated only nonspecific changes, which cannot substantiate a definitive causal relationship with BoNT-A administration. Moreover, non-specific EEG changes without baseline recordings, and multiple confounding factors in seizure cases precluding definitive causality. Long-term follow-up revealed differing outcomes: Case 1 and Case 3 remained seizure-free after discharge, while Case 2 experienced three generalized tonic-clonic seizures following levetiracetam discontinuation, suggesting an underlying seizure predisposition in this individual. Given these methodological constraints, the generalizability of our observations to broader populations may be limited. Besides, given the small sample size of the present series and the apparent rarity of adverse events such as seizures, future multicenter prospective registries or systematic analyses of pharmacovigilance databases with long-term follow-up are warranted. Such efforts will help clarify the true incidence, identify potential risk factors, and refine management strategies for BoNT-A-associated neurological complications.

Collectively, the three present cases illustrate a spectrum of neurological complications observed following BoNT-A administration. These observations highlight the critical importance of mechanism-based differential diagnosis when neurological symptoms emerge after BoNT-A use, and the need for comprehensive pre-injection evaluations, including a thorough assessment of the patient's medical history, potential risk factors (e.g., pre-existing neurological conditions, concurrent medications), and emotional state. In summary, while iatrogenic botulism is relatively rare in clinical practice, its non-specific clinical manifestations require heightened awareness among clinicians. Early recognition, careful history-taking, and timely antitoxin treatment are crucial for preventing disease progression and avoiding serious complications. These cases demonstrate that heightened diagnostic awareness, rather than modified dosing alone, is essential for safe BoNT-A administration across diverse patient populations.

CRedit authorship contribution statement

Qiaozhen Li: Writing – original draft, Visualization, Investigation, Data curation. **Chunqiu Dai:** Writing – original draft, Visualization, Investigation, Data curation. **Hongbin Wang:** Resources. **Feng Feng:** Resources. **Xiao Xi:** Writing – review & editing, Conceptualization. **Hong Wang:** Resources. **Hua Yuan:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Xiaolong Sun:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Availability of data

The datasets used and analyzed during the study are available from the corresponding author upon reasonable request.

Consent for publication

The patients have provided written informed consent and approved for publication.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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