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Acute Demyelinating Encephalopathy with Positive Anti-acetylcholine Receptor Antibody Possibly after Cosmetic Use of Botulinum Toxin: A Case Report and Literature Review

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Abstract

BACKGROUND: Few articles have reported the immune reaction secondary to botulinum toxin type A (BTxA) injection. To date, no data have reported BTxA-induced demyelinating encephalopathy with positive anti-acetylcholine receptor antibody (anti-AChR Ab).

CASE PRESENTATION: A 40-year-old woman developed an acute demyelinating encephalopathy 40 days after cosmetic use of low-dose BTxA injection for face lift. One week before the onset of demyelination, she manifested syndromes such as viral infection. Serum immunological examination revealed a slightly increased anti-AChR Ab IgG (0.47 g/L), quantified by an enzyme-linked immunosorbent assay. Magnetic resonance imaging (MRI) showed multiple abnormal signals perpendicular to the lateral ventricle in bilateral whiter matter.

CONCLUSIONS: This clinical profile suggests a possible pathogenic immunoreaction of BTxA infiltration and demyelinating encephalopathy. Based on the immune risk of BTxA, low-dose cosmetic use should also be considered prudently, particularly those who have potential immunologic dysfunction or history of viral infection.

Abbreviations:

BTs	- Botulinum toxins	CSF	- Cerebrospinal fluid
BTxA	- Botulinum toxin type A	OB	- Oligoclonal bands
AChR	- Acetylcholine receptor	CNS	- Central nervous system
Ab	- Antibody	AQP4	- Aquaporin-4
MRI	- Magnetic resonance imaging	MOG	- Myelin oligodendrocyte glycoprotein
DWI	- Diffusion-weighted imaging	MBP	- myelin basic protein
T2WI	- T2-weighted imaging	GFAP	- Glial fibrillary acidic protein
Gd-DTPA	- Gadolinium-diethylenetriamine pentaacetic acid	MG	- Myasthenia gravis.

CASE REPORT

BACKGROUND

Botulinum toxins (BTs) are protein toxins produced by *Clostridium botulinum* in seven serotypes (A through G, with many subtypes for each serotype (Atassi 2009). The therapeutic use of Botulinum toxin type A (BTxA) was introduced by Justinus Andreas Christian Kerner, who have recognized the effect of BTs on skeletal muscles and the parasympathetic function two centuries ago (Yiannakopoulou 2015). Subsequently, the therapeutic indications of BTxA have spread widely, such as adductor spasmodic dysphonia, oromandibular dystonia, and cervical dystonia. In 2002, cosmetic use of BTxA for glabellar wrinkle treatment was approved by the US Food and Drug Administration (Yiannakopoulou 2015).

Adverse events of BTxA injections, although rare, are often considered mild and primarily localized to adjacent muscles, such as dysphagia and eyelid ptosis (Timmermans *et al.* 2019; Bakheit 2006). Systemic reactions with no serious consequences have also been reported, for example, gastrointestinal disorders, somnolence, myasthenic reaction, and edema (Jia *et al.* 2016). Given that BTxA is inactive with 150 kDa single polypeptide chain, a few studies have reported cases with immunological reactions secondary to BTxA injection, such as allergic reaction, seropositive myasthenia gravis and peripheral nerve demyelination (Yiannakopoulou 2015). These symptoms are uncommonly observed and considered of idiosyncratic nature. To date, no data have reported BTxA-induced demyelinating encephalopathy with positive anti-acetylcholine receptor antibody (anti-AChR Ab). Here, we reported a patient with severe demyelinating encephalopathy after cosmetic injection of BTxA, aiming to arouse caution to the potential immune risk of BTxA.

CASE PRESENTATION

A 40-year-old woman was admitted to emergency room because of chest tightness and dysphagia. She was administered with BTxA injection for face lift 40 days ago. A total of Botox 50 IU (Allergan, Irvine, CA, USA) was injected into her bilateral masseter muscles. About 1 month later, she manifested nasal congestion, rhinorrhea, and malaise without fever. One week after, the patient experienced palpitation, chest tightness, suffocation, and dyspnea during sleep. These symptoms relieved only when she was sitting or walking around. The next day, she was unable to send a text message. Her condition soon aggravated with tongue numbness, alalia, chewing weakness, dribbling, bucking, and dysphagia. Her husband had to pat her back to help her swallow. These symptoms could be partially relieved after a night rest. After consultation with a neurologist, she was transferred to the neurology ward for further treatment. She had no comorbid diseases or medication history, and none of her relatives had a similar condition.

Neurological examination showed that she had bilateral facial paralysis, dysphagia, and hypotonic tetraparesis of the extremities. Tendon hyperreflexia was found in her upper limbs, with positive pathological reflection of bilateral Hoffman's sign and left Babinski's sign. No abnormal sensation was observed.

Electrophysiological study showed no abnormalities of repeat electrical nerve stimulation. No specific findings of sensation or motor conduction at bilateral facial nerve and limbs were detected. Routine blood laboratory tests and cerebrospinal fluid examination were normal. Serum antibody tests were negative for cytomegalovirus, herpes simplex virus, human immunodeficiency virus, treponema, toxoplasma, Candida albicans and cryptococcus. Slightly elevated titer of anti-AchR Abs in serum was detected (0.47 nmol/L). The cranial magnetic resonance imaging (MRI) results of the patient were presented in Figure 1. Newly developed multiple lesions perpendicular to the lateral ventricle in bilateral whiter matter were found on diffusion-weighted imaging (DWI) (Figure 1A) and T2-weighted imaging (T2WI) (Figure 1B). Patchy lesions with circular enhancement were exhibited on Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) enhancement scan (Figure 1C). Susceptibility-weighted imaging showed some of the lesions had strip-like venule images (Figure 1D). MRI of the spinal cord showed no abnormalities. cerebrospinal fluid (CSF) oligoclonal bands (OB) and demyelinating disease Abs of the central nervous system (CNS), such as aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP) Ab-IgG were not observed. On the basis of the aforementioned results, a diagnosis of acute demyelinating encephalopathy was performed. The treatment included 400 mg/kg/day of intravenous immunoglobulin (treatment 20g /day for a patient weighing 50 kg) in the course of 5 days, as well as 0.5 g of pulse methylprednisolone, which reduced by half every 3 days. One week later, her myasthenia and bulbar paralysis were controlled. Fifteen days later, she was discharged and given a tapering dose of prednisone (60 mg/day). At that time, she was able to eat, swallow, and walk normally. At 6-month follow-up, the patient has returned to normal life without muscular weakness, companying with occasional perioral numbness only.

DISCUSSION AND CONCLUSIONS

Adverse reactions after BTxA infiltration were usually considered infrequent and localized to adjacent musculature (Burguera *et al.* 2000). Common adverse symptoms, such as subclinical muscle weakness, urinary incontinence and autonomic dysfunction, were reported and primarily attributable to a distance effect in the presynaptic terminal (Yiannakopoulou 2015). However, the widespread therapeutic and cosmetic use of BTxA led to expanded safety issues. After reviewing through

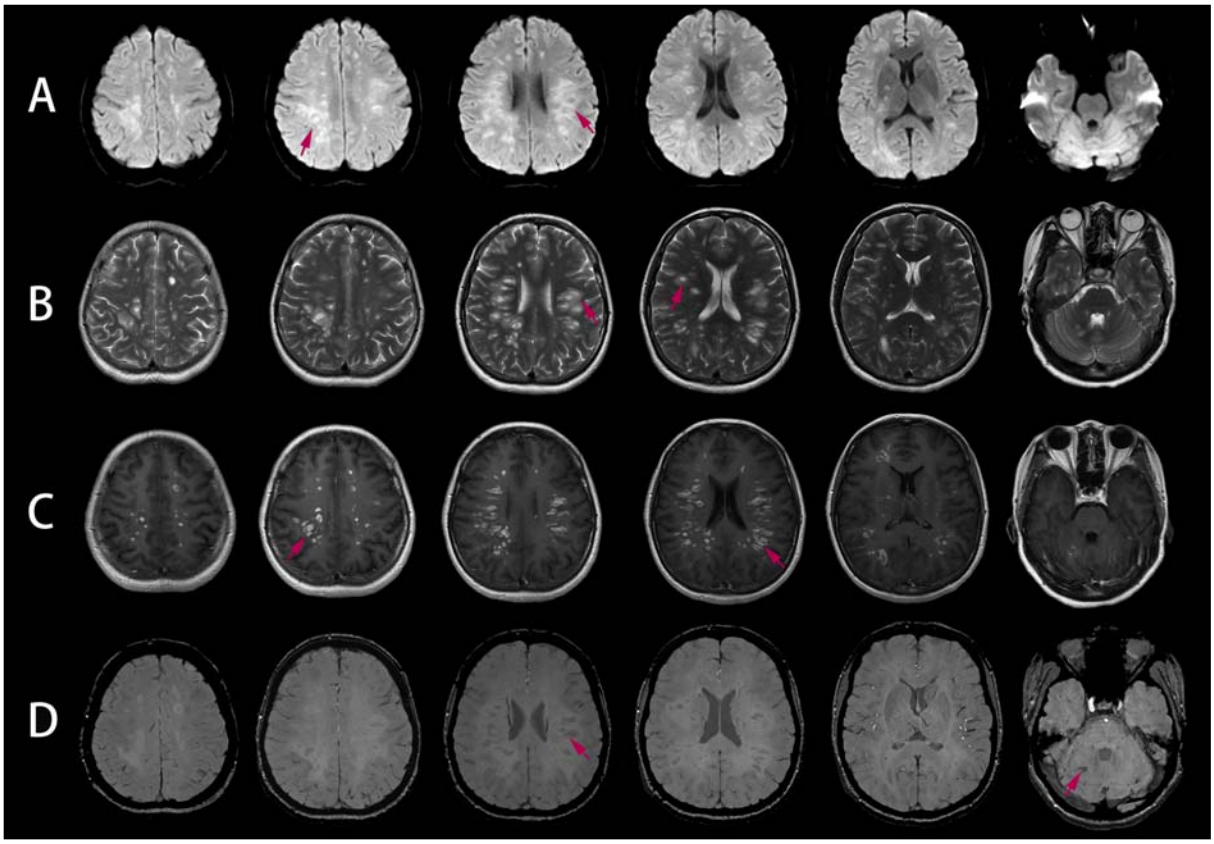

Fig. 1. Cranial MRI showed multiple abnormal signals perpendicular to the lateral ventricle in bilateral whiter matter. The examples of corresponding lesions were indicated with red arrows. A: Diffusion-weighted imaging showed newly developed lesions. B: The patchy lesions displayed high signal intensity on T2-weighted imaging (T2WI) in the center of bilateral semioval, paraventricular and right cerebellar hemisphere, some of which showed 'fried-egg sign'. C: Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) enhancement scan showed patchy lesions with circular enhancement. D: Susceptibility-weighted imaging showed some of the lesions had strip-like venule images.

PubMed, China Knowledge Network and Wangfang Medical database search from 1982 to 2021, a few cases have provided clinical profile that is compatible with immune-mediated adverse events after BTs infiltration. As listed in listed in Table 1, these articles included 5 reports on 7 cases published in English (Haug *et al.* 1990; Sheean GL *et al.* 1995; LeWitt & Trosch 1997; Burguera *et al.* 2000; Mezaki & Sakai 2005), 1 case in French (Ahbib *et al.* 2006), 1 case in Japanese (Onoue *et al.* 2004) and 2 cases in Chinese (Zhang 2008; Zhao 2010). Nevertheless, no literature has reported the demyelinating encephalopathy after BTxA infiltration. As known, acute demyelinating encephalopathy is marked by infiltration of myelin-specific T cells that attack the protective myelin sheath surrounding nerve axons in the central neuron system. For this case, the suggested hypotheses were listed as follows.

(1) Similar to BTs - related clostridial neurotoxin tetanus toxin, BTs retrogradely transported to central nervous system and cause centrally mediated effects such as demyelination (Montecucco *et al.* 1996). Previous experimental studies in rodents have proved that BTs receptors exist in the CNS, and a small amount of BTs can cross the blood-brain barrier (Yiannakopoulou 2015; Currà & Berardelli 2009). The specific mechanism of BTs central action might be retrograde transport, transcytosis, or both (Currà & Berardelli 2009). However, since rodents bear little neurologic resemblance to humans, whether the experimental findings on BTs in animals can be generalized to humans remained controversial. Besides, as lacking of reported deleterious central effects in human clinical practice, the doses of BTs that spreads retrogradely when injected in the muscles is also a question.

(2) Immune response after blood-brain barrier disruption. BTs is an immunogenic protein capable of inducing the formation of IgG-neutralizing Abs (Krampfl *et al.* 2003). Anti-AchR Abs were considered highly specific for myasthenia gravis (MG) because they are not detected in healthy individuals and are rarely seen in patients with other autoimmune or neuromuscular disorders (Meriggioli & Sanders 2012). However, elevated anti-AChR Abs has been reported as long-term adverse event of BTs injections in about 10% of subjects with repeated dose of more than 300 units (Matarasso 2001; Tang *et al.* 2018). Increased anti-AChR Abs have also been found presenting in patients with systemic lupus, rheumatoid arthritis (Lefvert & Bjorkholm 1987;

Tab. 1. Literature review of immune-mediated adverse events after BT infiltration (cases in reports).

No.	Author (yr)	Age/Gender	Symptoms
1	Haug (1990) [7]	63/M	Polyradiculoneuritis
2	Sheean (1995) [8]	36/F	Brachial neuritis
		55/F	Neuralgic amyotrophy
3	LeWitt (1997) [9]	69/F	Persistent and localized rash at injection site
		50/F	Localized anaphylactic reaction
5	Burguera (2000) [6]	40/M	Polyradiculoneuritis
6	Onoue (2004) [12]	68/M	Polyradiculoneuritis
7	Mezaki (2005) [10]	73/F	Generalized skin rash
8	Ahbib (2006) [11]	57/F	Sarcoidal granulomas
10	Zhang (2008) [13]	37/F	Anaphylactic shock
11	Zhao (2010) [14]	64/M	Allergic reaction (facial swelling, dyspnea and diarrhea)

F: female; M: male.

Meriggioli & Sanders 2012), as well as neuromyelitis optica (McKeon *et al.* 2009; Leite *et al.* 2012). In this case, the coexistence of demyelinating encephalopathy and positive anti-AchR Ab is very rare. Inspired by animal studies which have proved that BTs receptors exist in the CNS, a possible explanation is when the blood–brain barrier was damaged by viral infection (Currà & Berardelli 2009), the BTs-induced Abs may enter the CNS and attack myelinated nerve of the white matter, thereby leading to demyelinating encephalopathy. However, the detailed pathogenesis of demyelinating encephalopathy combined elevated anti-AchR Ab remained elusive and needed more studies.

(3) Crossed antigen produced by pathological factors, such as infections, which acted on both AChR at the neuro-muscular junction and sphingomyelin in the CNS. Pathogens with certain pathogenic elements similar to specific proteins can induce immune crossreactivity via molecular mimicry (Cao *et al.* 2019), thus lead to autoimmune attacks and presentations of both demyelinating encephalopathy and myasthenia symptom. For example, previous studies found the AChR-specific Ab from MG patients also cross-reacts with herpes simplex virus; an epitope on the type I glycoprotein of the virus shares significant structural homology to the host receptor (Schwimmbeck *et al.* 1989; Ercolini & Miller 2005). Another intriguing study identified a homologous T cell epitope in *H. influenzae* that was shown to be protective upon pre-immunization in an experimental rat model of MG (Im *et al.* 2002). Although these findings demonstrate that molecular mimicry is a feasible theory explaining the link between anti-AchR Abs and demyelinating encephalopathy, the search continues for direct evidence to support this phenomenon in human disease.

In conclusion, physicians should pay attention to the uncommon complications during BTs injection. Although the causal relationship is not firmly established between idiosyncratic reaction of demyelinating encephalopathy and BTs-induced anti-AchR Abs, the special case raised a caution on BTxA cosmetic infiltration, particularly those who have risk factors or recent history of viral infection. Furthermore, a rational period of observation time should be reserved to minimize complications. Physicians should respond properly and timely in a suspicious situation with medical methods to prevent adverse events after injection. Fortunately, the patient in this case recovered well as most acute autoimmune diseases caused by vaccination. Early recognition and proper management are vital for a better prognosis.

DECLARATIONS

Ethics approval and consent to participate

Informed consent was obtained from the patient to publish this case, and approval for this study was provided by the Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University.

Consent to publish

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

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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REFERENCES

1 Ahbib S, Lachapelle JM, Marot L (2006) Sarcoidal granulomas following injections of botulic toxin A (Botox) for corrections of wrinkles (in French). Ann Dermatol Venereol. **133**(1): 43–45.
2 Atassi MZ (2009) Immune recognition of BoNTs A and B: how anti-toxin antibodies that bind to the heavy chain obstruct toxin action. Toxicon. **54**(5): 600–613.
3 Bakheit AM (2006) The possible adverse effects of intramuscular botulinum toxin injections and their management. Curr Drug Saf. **1**(3): 271–279.
4 Burguera JA, Villaroya T, Lopez-Alemany M (2000) Polyradiculoneuritis after botulinum toxin therapy for cervical dystonia. Clin Neuropharmacol. **23**(4): 226–228.
5 Cao Y, Gui M, Ji S, Bu B (2019) Guillain-Barre syndrome associated with myasthenia gravis: Three cases report and a literature review. Medicine (Baltimore). **98**(47): e18104.
6 Currà A, Berardelli A (2009) Do the unintended actions of botulinum toxin at distant sites have clinical implications? Neurology. **72**(12): 1095-1099.
7 Ercolini AM, Miller SD (2005) Role of immunologic cross-reactivity in neurological diseases. Neurol Res. **27**(7): 726–733.
8 Haug BA, Dressler D, Prange HW (1990) Polyradiculoneuritis following botulinum toxin therapy. J Neurol. **237**(1): 62–63.
9 Im SH, Barchan D, Feferman T, Raveh L, Souroujon MC, Fuchs S (2002) Protective molecular mimicry in experimental myasthenia gravis. J Neuroimmunol. **126**(1–2): 99–106.
10 Jia Z, Lu H, Yang X, Jin X, Wu R, Zhao J et al. (2016) Adverse Events of Botulinum Toxin Type A in Facial Rejuvenation: A Systematic Review and Meta-Analysis. Aesthetic Plast Surg. **40**(5): 769–777.
11 Krampfl K, Mohammadi B, Buchwald B, Jahn K, Dengler R, Toyka KV et al. (2003) IgG from patients with Guillain-Barre syndrome interact with nicotinic acetylcholine receptor channels. Muscle Nerve. **27**(4): 435–441.
12 Lefvert AK, Bjorkholm M (1987) Antibodies against the acetylcholine receptor in hematologic disorders: implications for the development of myasthenia gravis after bone marrow grafting. N Engl J Med. **317**(3): 170.
13 Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, Sato D et al. (2012) Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. Neurology. **78**(20): 1601–1607.
14 LeWitt PA, Trosch RM (1997) Idiosyncratic adverse reactions to intramuscular botulinum toxin type A injection. Mov Disord. **12**(6): 1064–1067.
15 Matarasso SL (2001) Update on the aesthetic uses botulinum-A neurotoxin in facial rejuvenation. Curr Probl Dermatol. **13**: 46–53.
16 McKeon A, Lennon VA, Jacob A, Matiello M, Lucchinetti CF, Kale N et al. (2009) Coexistence of myasthenia gravis and serological markers of neurological autoimmunity in neuromyelitis optica. Muscle Nerve. **39**(1): 87–90.
17 Meriggioli MN, Sanders DB (2012) Muscle autoantibodies in myasthenia gravis: beyond diagnosis? Expert Rev Clin Immunol. **8**(5): 427–438.
18 Mezaki T, Sakai R (2005) Botulinum toxin and skin rash reaction. Mov Disord. **20**(6): 770.
19 Montecucco C, Schiavo G, Rossetto O (1996) The mechanism of action of tetanus and botulinum neurotoxins. Arch Toxicol Suppl. **18**: 342–354.
20 Onoue H, Matsunobu A, Nagaishi A, Yukitake M, Kuroda Y (2004) A case report of acute polyradiculoneuritis developing after multiple injections of botulinum toxin for cervical dystonia (in Japanese). Rinsho Shinkeigaku. **44**(1): 20–24.
21 Schwimmbeck PL, Dyrberg T, Drachman DB, Oldstone MB (1989) Molecular mimicry and myasthenia gravis. An autoantigenic site of the acetylcholine receptor alpha-subunit that has biologic activity and reacts immunochemically with herpes simplex virus. J Clin Invest. **84**(4): 1174–1180.
22 Sheean GL, Murray NMF, Marsden CD (1995) Pain and remote weakness in limbs injected with botulinum toxin A for writer's cramp. Lancet. **346**: 154–156.
23 Tang M, Li W, Liu P, He F, Ji F, Meng F (2018) Blepharospasm with elevated anti-acetylcholine receptor antibody titer. Arq Neuropsiquiatr. **76**(8): 522–526.
24 Timmermans G, Depierreux F, Wang F, Hansen I, Maquet P (2019) Cosmetic Injection of Botulinum Toxin Unmasking Subclinical Myasthenia Gravis: A Case Report and Literature Review. Case Rep Neurol. **11**(2): 244–251.
25 Yiannakopoulou E (2015) Serious and long-term adverse events associated with the therapeutic and cosmetic use of botulinum toxin. Pharmacology. **95**(1–2): 65–69.
26 Zhang H (2008) Allergic reaction caused by botulinum toxin A injection: a case report (in Chinese). Chin J Misdiagnosis. **8**(36): 8963–8963.
27 Zhao YX (2010) Anaphylaxis produced by local injection of botulinum toxin A (in Chinese). Adverse Drug Reactions J. **12**(5): 360–361.