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BRIEF COMMUNICATION

Botulinum toxin treatment for hypersalivation in anti-NMDA receptor encephalitis

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Abstract

Hypersalivation is one of the intractable symptoms of anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. While anticholinergic medications partially improve the hypersalivation, they can aggravate the autonomic dysfunctions associated with anti-NMDAR encephalitis. Thus, we investigated the efficacy and safety of botulinum toxin type A injection on hypersalivation refractory to anticholinergics in six patients with anti-NMDAR encephalitis. Hypersalivation was well-controlled without remarkable adverse reaction over 16 weeks after botulinum toxin type A, although two patients were reinjected at 12 weeks due to reaggravation of hypersalivation. Our findings suggest that botulinum toxin type A might be a better choice than anticholinergics for management of hypersalivation in patients with anti-NMDAR encephalitis.

Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune synaptic disorder caused by autoantibodies directed against GluN1 subunit of the anti-NMDAR, resulting in psychosis, loss of consciousness, memory deficits, seizure, speech problems, dyskinesia, autonomic dysfunction, and central hypoventilation.[1–4] By the first-line immunotherapy (steroids, immunoglobulins, or plasma exchange) and second-line immunotherapy (rituximab or cyclophosphamide), about 80% of patients with anti-NMDAR encephalitis recovers favorably to be able to look after own affairs without assistance.[5] However, 7% of the patients still die due to complications such as autonomic dysfunction, pneumonia, hypoventilation, rhabdomyolysis, or status epilepticus.[5–7]

Hypersalivation is one of the main autonomic dysfunctions in anti-NMDAR encephalitis where its prevalence was estimated between 4 and 18%.[1,3] Patients with anti-NMDAR encephalitis can show excessive production of saliva, the inability to retain saliva within the mouth, and profound drooling, thus sometimes requiring constant suction of saliva. It may complicate aspiration pneumonia and volume depletion in severe cases.[8] While anticholinergic medications partially improve the hypersalivation, they can aggravate the autonomic dysfunctions, including paralytic ileus, orthostatic hypotension, and heart rate variability.[9]

Accordingly, effective and safe therapeutics to control the hypersalivation are critically necessary.

Botulinum toxin type A (BTXA) is a neurotoxin that can reduce saliva secretion by blocking the release of acetylcholine at the neuroglandular junction of salivary gland.[10] Evidence indicates that BTXA is an effective and safe treatment for hypersalivation related to several neurological disorders including Parkinson's disease,[11] amyotrophic lateral sclersois,[12] and cerebral palsy.[13] If this works without remarkable adverse effects in anti-NMDAR encephalitis setting, it could be a great option to replace anticholinergic drugs and would prevent aspiration events. Thus, we evaluated the efficacy and safety of BTXA injection on hypersalivation due to anti-NMDAR encephalitis.

Methods

Patients

We have operated a prospective cohort for anti-NMDAR encephalitis since June 1, 2012, and the current study is an analysis of the data-set. The patients with anti-NMDAR encephalitis were included who were treated with BTXA injection due to disabling hypersalivation from Sep 30, 2016, when the first injection of BTXA was performed, until Mar 1, 2017. Anti-NMDAR encephalitis was diagnosed according to clinical presentation and the detection of NMDAR autoantibodies in the serum or cerebrospinal fluid using rat brain section and cell-based immunocytochemistry kit (Euroimmune Ag, Germany), as described previously.[6,14] The study protocol was approved by the Seoul National University Hospital Institutional Review Board and followed to the principles of the Declaration of Helsinki.

BTXA injection and outcome evaluation

For each patient, 2 mL of normal saline was used to dilute 100 units of BTXA (Botox®, Allergan, Irvine, CA).[11] Using a 25-gauge needle under ultrasonography guidance, 30 units was injected into each parotid gland and 20 units into each submandibular gland, totaling 100 units per patient. The effect of BTXA on hypersalivation was measured using Drooling Severity and Frequency Scale before injection and at 1, 4, 8, 12, and 16 weeks after injection. Adverse effects following BTXA injection were evaluated using a review of medical records. The patients were reinjected on week 12 if the Drooling Severity and Frequency Scale had deteriorated.

Drooling severity and frequency scale

The Drooling Severity and Frequency Scale was used to evaluate the severity and frequency of hypersalivation. The severity and frequency scales were categorized into 5-level domains (1 = never drools; 2 = only lips wet; 3 = lips and chin wet; 4 = clothing soiled; and 5 = clothing, hands and tray moist wet) and 4-level domains (1 = never drools; 2 = occasional drooling-not every day; 3 = frequent drooling-every day; and 4 = constant drooling), respectively.

Results

Clinical features and demographics

Among 36 patients with anti-NMDAR encephalitis enrolled in our cohort registry, 12 (33.3%) experienced hypersalivation. However, the treatment of BTXA was initiated since Sep 2016, and thus, six patients were included in this study. Table 1 shows the result of clinical features and demographics of the patients. The median age was 24.5 years (range, 17–58 years), and five were women. All patients had semi-comatose mentality with tracheostomy and feeding tube.

Despite the best effort with careful nursing such as frequent suction and gauze packing, our patients showed uncontrollable hypersalivation. Anticholinergic drugs including trihexyphenidyl (1.5–6 mg/day) and glycopyrrolate (0.2–0.6 mg/day) were tried to control it before BTXA injection, but the drooling severity and frequency scores were, respectively, 5 and 4 in patient 1, 4, 5, and 6. In addition, patient 2 and 3 could not use anticholinergics continuously because aggravation of ileus and low blood pressure, although their drooling scores were improved transiently (in both the patients, severity: 5 → 4, and frequency: 4 → 3).

The effect and safety of BTXA injection

At baseline, median drooling severity and frequency scores were 5 and 4, respectively. In all patients, the drooling severity and frequency scores showed a decrease at 1, 4, 8, 12, and 16 weeks after BTXA injection than the baselines values (Fig. 1). Patient 2 and 3 were reinjected with BTXA on 12 weeks because hypersalivation was reemerged 8 weeks. Their drooling severity and frequency scores were improved again until 16 weeks without any side effect. Hypersalivation of patient 4 was fully recovered 12 weeks after BTX injection with improvement of the encephalitis when the ovarian teratoma was removed. None of the patients occurred suspicious adverse effects after BTXA injection over follow-up period.

Discussion

We examined the efficacy and safety of BTXA injection in six patients with anti-NMDA receptor encephalitis who

Table 1. Clinical features of the patients with anti-NMDA receptor encephalitis.

Patient	1	2	3	4	5	6
Age	17	20	28	24	25	58
Gender	F	F	F	F	F	M
Clinical manifestations						
Psychiatric symptoms	√	√	√	√	√	√
Seizure	√	√	√	√	√	√
Dyskinesia	√	√	√		√	√
Memory disturbance			√			
Speech problem	√	√	√			√
Central hypoventilation	√	√				
Decreased mentality	√	√	√			√
Autonomic instability	√	√	√	√	√	√
List of autonomic dysfunction						
Hypersalivation	√	√	√	√	√	√
Paralytic ileus	√	√	√			√
Orthostatic hypotension		√	√			
Heart rate variability	√		√			√
Bladder dysfunction	√					
Immunotherapy	Steroid IVIG Rituximab Tocilizumab	Steroid IVIG PP Rituximab Tocilizumab	Steroid IVIG Rituximab Tocilizumab CTX Proleukin	Steroid IVIG Rituximab	IVIG Rituximab Tocilizumab Proleukin MMF	Steroid IVIG Rituximab Tocilizumab Bortezomib
mRS changes (initial→16 weeks)	5→5	5→5	5→5	5→3	4→4	5→5
Drooling control medication	G	T,G	T,G	T	T,G	G
Ovarian teratoma		√	√		√	
CSF	27 WBC	167 WBC	EP	90 WBC	130 WBC	12 WBC, EP
MRI	Left hippocampus T2 HSI	Diffuse leptomeningeal enhancement	Bilateral hippocampi T2 HSI	Normal	Normal	Normal
EEG	Continuous slowing	Generalized ictal discharge	Generalized rhythmic slowing	Continuous slowing	Continuous slowing	Generalized rhythmic slowing

PP, plasmapheresis; CTX, cyclophosphamide; MMF, mycophenolate mofetil; mRS, modified Rankin Scale; T, trihexyphenidyl; G, glycopyrrolate; CSF, cerebrospinal fluid; EP, elevated CSF protein; MRI, magnetic resonance imaging; HSI, high signal intensity; EEG, electroencephalography

suffered from very severe hypersalivation. Our results showed that hypersalivation was well-controlled without remarkable adverse reaction over 16 weeks after BTXA. Although two patients were reinjected at 12 weeks due to aggravation of hypersalivation, this finding indicates that repetitive use of BTXA is also effective and safe for hypersalivation in anti-NMDA receptor encephalitis.

Within the first 4 weeks of symptom onset, more than 40% of the patients with anti-NMDAR encephalitis experience autonomic symptoms including hyperthermia, tachycardia, hypersalivation, bradycardia, hypertension, and hypotension.[1,3,5] Although hypersalivation is one of the main autonomic dysfunctions in anti-NMDAR encephalitis, there has been no clear consensus regarding which treatment is better for controlling hypersalivation. In general, therapeutic strategy for hypersalivation aims to reduce salivation rather than to completely eliminate it.[15] Pharmacological agents such as anticholinergic drugs are preferentially considered to be treatment option for hypersalivation.[16] However, the use of anticholinergic drugs is limited due to adverse reactions in some patients.[17] In particular, their unwanted effects can aggravate autonomic dysfunction related to anti-NMDAR encephalitis, which may be seriously dangerous. In this study, two patients discontinued anticholinergics because of aggravation of paralytic ileus, and four had very severe hypersalivation despite the use of anticholinergic drugs. In these patients, treatment with BTXA was remarkably effective and safe for hypersalivation. These findings strongly suggest that BTXA can be regarded as the treatment of choice for hypersalivation in

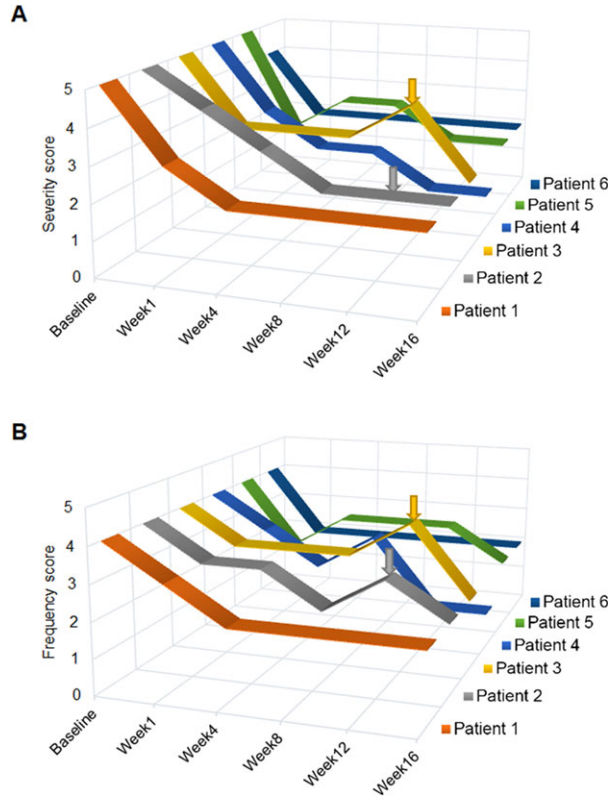

Figure 1. Individual response on hypersalivation to botulinum toxin A at baseline, 1-, 4-, 8-, 12- and 16-week follow-up. Hypersalivation was assessed using the Drooling Severity (A) and Frequency Scale (B). The severity and frequency scales were categorized into 5-level domains (1 = never drools; 2 = only lips wet; 3 = lips and chin wet; 4 = clothing soiled; 5 = clothing, hands and tray moist wet) and 4-level domains (1 = never drools; 2 = occasional drooling-not every day; 3 = frequent drooling-every day; 4 = constant drooling), respectively. Arrows indicate reinjection of botulinum toxin A at 12-week follow-up.

patients with anti-NMDAR encephalitis. While oromandibular dyskinesia of anti-NMDAR encephalitis results lip and tongue injuries in some patients, BTXA can control oromandibular dystonia.[18] It is feasible to try BTXA to control the oromandibular dyskinesia of anti-NMDAR encephalitis in future researches.

Hypersalivation in two patients were aggravated between 8 and 12 weeks after BTXA injection, whereas it was well-controlled over 16 weeks in other four patients. Considering that the effect of BTX in the treatment of hypersalivation generally lasts about 2–4 months,[19,20] our finding suggests that duration of BTXA effect in hypersalivation due to anti-NMDA receptor encephalitis is similar to that due to other neurological disorders. However, despite these results, its duration in anti-NMDA receptor encephalitis still remains unclear because hypersalivation is significantly affected by disease activity. This is well described by patient 4 whose hypersalivation was fully recovered after removal of ovarian teratoma.

A recent meta-analysis from eight randomized placebo-controlled trials of BTX injection in other diseases showed that common side effects included increased saliva thickness (3.9%), dysphagia (3.3%), xerostomia (3.3%), and pneumonia (2.2%).[21] Although our patients did not experience any adverse reaction related to BTXA, dysphagia could not be evaluated due to tube feeding resulting from decreased mentality. However, patients with anti-NMDAR encephalitis recover slowly from comatose mentality after their autonomic functions stabilize and the effect of BTXA goes away.[2] This suggests that worsening of dysphagia is not critical as a side effect of BTXA in patients with anti-NMDAR encephalitis.

The current study has potential limitations. It was a single center study involving a small number of patients, and the indication of BTXA was based on the clinicians' decision. Nevertheless, the current study demonstrated, for the first time, the effect and safety of BTXA injections into the submandibular and parotid glands under ultrasound guidance on hypersalivation in patients with anti-NMDAR encephalitis. A larger prospective study with a long-term follow-up needs to be further investigated.

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Author Contribution

JS Jun contributed to the initial conception and design, collected data, and wrote the first draft of the manuscript. HG Seo injected the botulinum toxin and wrote the manuscript. ST Lee contributed to the initial conception and design, interpreted the results, revised the manuscript, and supervised all aspects of the study. K Chu and SK Lee reviewed previous studies and organized experimental plans.

Conflict of Interest

No conflicting relationship exists for the authors.

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