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Original Article

Clinical and electrophysiological studies of botulinum toxin type A to treat hemifacial spasm complicated with auricular symptoms

Bin Peng, Hongjuan Dong, Hong Chu, Shenqi Zhang, Zuneng Lu

Department of Neurology, Renmin Hospital of Wuhan University, Wuhan University, Wuhan, Hubei, China

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Abstract: Objective: To investigate the involvement of posterior auricular muscle (PAM) and the effect of botulinum toxin type A (BTX-A) injection into PAM in patients with hemifacial spasm (HFS) complicated with auricular symptoms. Methods: Sixty-three consecutive HFS patients complicated with auricular symptoms such as tinnitus or murmur, "ticking" or a "clicking" sound and discomfort on the same side, who were referred to our department between July 2009 and January 2010, were enrolled. The diagnosis of idiopathic HFS was made clinically. The patients were largely randomized into two BTX-A treatment groups according to the order of referral. The first group included 33 cases where the injection sites were routinely located at the frontal, orbicularis oculi, zygomaticus and buccinator muscles while the other was the PAM group, which included 30 cases, where 4 units of BTX-A were additionally injected into the PAM prior to injection at other sites. A test of blink reflex was performed and the lateral spread of blink reflex to the orbicularis oris (OO) and PAM, i.e. abnormal muscle response (AMR), was recorded and the peak-peak amplitude of AMR was measured. The patients were followed up clinically and electrophysiologically for at least 4 weeks (29.47 ± 2.53 days). Results: 1) Before injection, the latencies of R1, R2, R2' were normal, there was no significant difference between uninjured and affected side; The amplitudes of R1, R2, R2' in affected side were higher. 2) After injection, there was no significant change of the R1, R2 and R2' latencies; The amplitudes of R1, R2 and R2' decreased significantly. 3) Patients reported that their auricular symptoms subsided after injection in both groups; The remission rate was 45.5% (15/33) and 76.7% (23/30) in the regular and PAM group, respectively, with a higher rate in the PAM group (χ^2 = 6.40, P = 0.011). 4) In both groups the AMR amplitude decreased significantly after injection. In the regular group, the respective OO amplitudes (μV) before and after injection were 304.00 ± 30.34 and 129.33 ± 9.59 (t = 5.820, P = 0.000), and for PAM the amplitudes were 298.00 ± 33.28 and 184.67 ± 20.21 (t = 2.818, P = 0.014); in the PAM group, the before and after injection OO amplitudes were 405.33 ± 66.71 and 116.00 ± 9.99 (t = 4.214, P = 0.001), and for PAM they were 390.00 ± 53.58 and 72.00 ± 9.67 (t = 6.011, P = 0.000), respectively. 5) PAM amplitudes in the PAM group decreased more significantly after BTX-A injection compared with those in the regular group (t = 4.237, P = 0.001). Conclusions: The treatment on HFS with local injection of BTX-A is very effective. In HFS complicated with auricular symptoms patients, electrophysiological studies are helpful for guiding treatment plans, and the auricular symptoms could be improved by BTX-A injection into the PAM in addition to the regular injection sites.

Keywords: Hemifacial spasm, botulinum toxin type A, posterior auricular muscle, blink reflex, abnormal muscle response

Introduction

Hemifacial spasm (HFS) is characterized by repetitive, involuntary contractions of some or all of the muscles supplied by the ipsilateral facial (VII) nerve. Abnormal muscle response (AMR) is an electrophysiological finding characterized by the lateral spread of the blink reflex to facial muscles other than the orbicularis oculi [1]. While microvascular decompressive procedures to treat HFS are often curative [2, 3], injection of botulinum toxin type A (BTX-A) into the affected muscles can suppress the contractions temporarily [3-6]. The routine sites of BTX-A injection are: frontalis muscle, orbicularis oculi, zygomaticus and buccinator muscles [5].

The posterior auricular muscle (PAM) is supplied by a branch of the facial nerve, which can be clinically delineated by valgus traction on the ear. The PAM can be clearly seen as it forms a

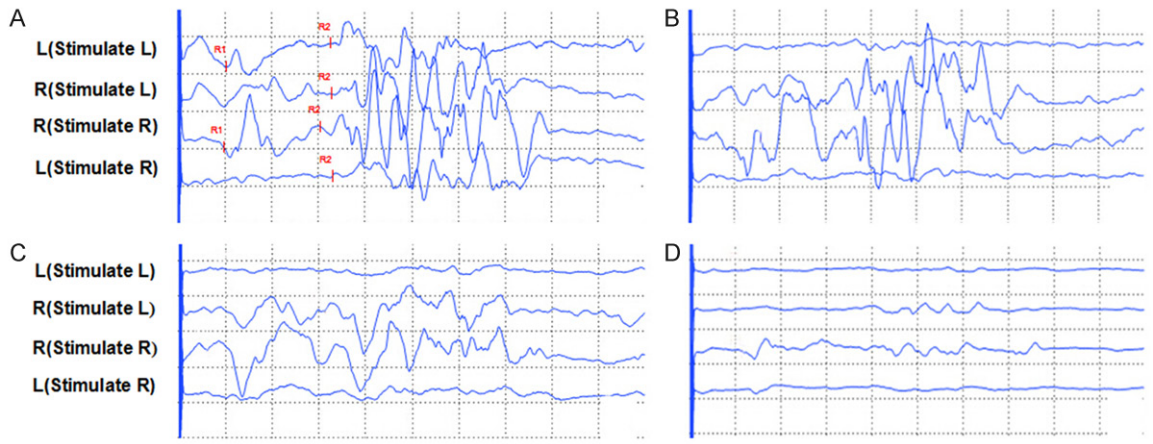

Figure 1. Electrophysiologic findings with bilateral supraorbital stimulus in a patient with right HFS. A. Blink reflex. B. AMR of the mentalis muscle. C. AMR of the PAM. D. AMR of the PAM after BTX-A injection (L, left; R, right).

ridge under the overlying skin in the sulcus of the posterior auricular region [7]. Some patients complain that the "clicking" sound they experienced was simultaneous and synchronous with facial muscle contractions [8-10]. In our routine clinical practice, we also observed a similar phenomenon, which is particularly evident at night, and can affect sleep. There have been reports suggesting that paroxysmal staccato tinnitus might be considered an auditory hyperactivity disorder of the eighth cranial nerve. Such tinnitus can be resolved or markedly improved after neurovascular compression of the eighth cranial nerve [9]. Patients presenting with auricular symptoms and showing PAM spasm activity can be thought as a candidate for botulinum toxin treatment in a case study with a small sample [8], however, suitable controls subjects for such studies are not currently available.

As such, for HFS complicated with auricular symptoms patients, in this study we aimed to compare the clinical and electrophysiological changes between regular injection sites and additional PAM injection of BTX-A, and investigate the relationship between the AMR of PAM and auricular symptoms. Information gained in this study will provide the basis for the individual injection of BTX-A to treat HFS with auricular symptoms.

Methods

Patients

Sixty-three consecutive HFS patients complicated with auricular symptoms, such as tinnitus or murmur, "ticking" or a "clicking" sound and discomfort on the same side were enrolled amongst a total of 265 cases with idiopathic HFS who were referred between July 2009 and January 2010 to the Movement Disorders Clinic in the Department of Neurology at our hospital. The auricular symptoms were simultaneous and synchronous with facial muscle contractions, and the degree varied depending on spasm severity. The diagnosis of idiopathic HFS was made clinically [3, 11]. All patients provided their written informed consent.

This study included 20 men and 43 women. The mean age was 46.3 ± 2.4 years (range: 29-73), and the mean duration of illness was 42.5 ± 3.6 months (range: 1-192). Thirty-eight patients were affected on the left side of the face, and 25 on the right side. Six patients in this group had no history of BTX-A injection, while 57 patients had a past history of injection (mean, 9 injections; range: 1-16). The patients were randomized into two groups, one group was the regular group that included 33 cases, and the second group was the PAM group, which included 30 cases. All patients showed normal CT or MRI brain scans.

Exclusion criteria were as follows: complication with other neurological disorders, or abnormal brain CT or MRI; previous ear disease and hearing loss; and heart disease or vascular disease.

Electrophysiological studies

For electrophysiological studies, the subjects lay supine on a bed with their eyes gently

Table 1. The general condition of the regular group and the PAM group

	Cases (number)	Male/Female	Age	Duration (year)	History of injection	Left/Right
The regular group	33	11/22	45.8 ± 2.6	3.9 ± 0.6	8	20/13
The PAM group	30	9/21	46.9 ± 1.4	3.6 ± 0.5	10	18/12
P	1.57	1.235	0.077	0.171	1.107	0.874

closed. The simplest method to obtain the blink reflex is by stimulating the supraorbital nerve with a cathode placed on the supraorbital notch and the anode 2-3 cm away along the course of the supraorbital nerve. Recordings were obtained from the orbicularis oculi of both sides with surface electrodes, with the active electrode placed in the middle of the lower eyelid and the reference electrode located 2-3 cm laterally [12]. The AMR recordings were made from the orbicularis oris muscles and posterior auricular muscles following stimulation of both sides of the supraorbital nerve (**Figure 1**). Peak-peak amplitude was measured.

BTX-A injection

BTX-A (a Chinese formulation, Hengli, Lanzhou Institute of Biological Products) was reconstituted into sterile, preservative-free 0.9% saline solution and injected within 4 h of reconstitution. About 100 U BTX-A were diluted in 2.5 ml of saline solution to yield toxin at a concentration of 40 U/ml. Injections were performed subcutaneously according to standardized procedures. The dose varied according to the severity of the patient's spasm. In the regular group, routine sites of injection were used [5], while in the PAM group, an additional 4 units of BTX-A were injected into the PAM area, excepting the routine sites of injection.

Follow-up

Both therapeutic effect (by the patients' report) and the electrophysiological studies were re-evaluated at least 4 weeks later (mean 29.47 ± 2.53 days).

Statistical analyses

Statistical analyses were made with SPSS 13.0 software. The measurement data were expressed as mean ± SD, and the χ^2 test was used in a rate test. The analysis of treatment response was performed by means of a *t* test to compare the mean of continuous variables of the sample between the different treatments. A paired *t* test analysis was used to compare before and after treatment. The test was considered significant when the *P* value was < 0.05.

Results

Patient age and illness duration

There was no significant difference in age (t = 1.910, P = 0.077) and illness duration (t = 1.442, P = 0.171) between the regular group and the PAM group (**Table 1**).

Facial spasm

Regarding facial spasm, there was no significant difference in remission rate (χ^2 = 0.006, P = 0.54) between the regular group and the PAM group.

The average latency of improvement of facial spasm after the injection was 5 days, with a maximal benefit occurring 1-2 weeks following the injection. The response was rated according to a 0 to 4 "peak effect" scale [13] (0: no effect and 4: marked improvement in severity and function). Sixty patients had a good response (peak effect ≥ 2) after injection, 3 had minimal or no effect (peak effect ≤ 1). The most common side effects were temporary facial weakness, lid weakness and ptosis. All the side effects were transient, reversible, and rarely disabling.

Auricular symptoms

The patients reported that their auricular symptoms subsided after injection in both groups, with a remission rate of 45.5% (15/33) in the regular group and 76.7% (23/30) in the PAM group, which showed a higher remission rate (χ^2 = 6.40, P = 0.011).

Electrophysiologic findings

The changes of BR in 63 cases were recorded before injection (**Table 2**), and 42 cases were recorded after injection (**Table 3**). No AMR activity was recorded in the orbicularis oris

Table 2. Blink reflex of 63 patients before injection

	Latency (ms)			Wave amplitude (uV)		
	R1	R2	R2'	R1	R2	R2'
Uninjured side	10.19 ± 0.14	31.82 ± 1.01	30.07 ± 1.13	117.14 ± 10.02	56.43 ± 4.64	92.86 ± 10.76
Affected side	10.41 ± 0.22	29.99 ± 1.18	30.09 ± 1.15	165.71 ± 17.84	227.14 ± 37.98	181.07 ± 35.45
P	1.082	1.357	1.13	0.025	0.032	0.042

Table 3. Blink reflex of 42 patients before and after injection

	Latency (ms)			Wave amplitude (uV)		
	R1	R2	R2'	R1	R2	R2'
Before injection	10.41 ± 0.22	29.99 ± 1.18	30.09 ± 1.15	165.71 ± 17.84	227.14 ± 37.98	181.07 ± 35.45
After injection	10.60 ± 0.16	30.87 ± 0.48	30.65 ± 0.52	62.14 ± 6.31	56.43 ± 4.64	52.14 ± 5.26
P	0.573	0.491	0.986	0.000	0.001	0.004

Table 4. Comparison of AMR amplitude (μV) before and after BTX-A injection

	Regular group	PAM group	*t*	*P*
OO amplitude				
Before injection	304.00 ± 30.34 (31)	405.33 ± 66.71 (29)	1.886	0.080
After injection	129.33 ± 9.59 (22)	116.00 ± 9.99 (20)	1.127	0.269
t/P	5.820/0.000	4.214/0.001		
PAM amplitude				
Before injection	298.00 ± 33.28 (31)	390.00 ± 53.58 (29)	1.425	0.175
After injection	184.67 ± 20.21 (22)	72.00 ± 9.67 (20)	4.237	0.001
t/P	2.818/0.014	6.011/0.000		

The figures in parentheses represent the number of cases. AMR = abnormal muscle response; OO = orbicularis oris; BTX-A = botulinum toxin type A.

muscle or PAM on the contralateral side. AMR of the PAM was recorded synchronously with the other facial muscles on the symptomatic side in all but 3 patients (2 in the regular group and 1 in the PAM group). These 3 patients were not included in the statistical analyses. The latencies of R1, R2 and R2' did not differ between uninjured sides and affected sides. The amplitudes of R1, R2 and R2' in affected side were higher (**Figure 1**). The AMR amplitude of the orbicularis oris muscle and PAM on the spasm side decreased significantly after injection in both groups. PAM amplitudes in the PAM group decreased more significantly compared to those in the regular group (**Table 4**).

Discussion

Spontaneous recovery in HFS is extremely rare. Treatment options are aimed at reducing or stopping muscular twitches, and include medications (e.g. carbamazepine, baclofen and benzodiazepine, which have limited efficacy), botulinum neurotoxin injections, neurosurgery, and more recently, doxorubicin chemomyectomy [4]. Microvascular decompression surgery, a highly invasive procedure, is considered to be an effective treatment option to medical therapy, but is still not widely used or accepted, especially in China. Botulinum neurotoxin injection may also be considered as a treatment option for HFS (Level C) [14], but the evidence supporting its use in HFS is suboptimal. BTX can be an effective treatment that has a low incidence of immunogenicity after long-term use [15]. However, no studies have compared botulinum neurotoxin with other major treatment alternatives, including oral pharmacologic and surgical therapies [14].

The pathophysiological mechanisms underlying the abnormal activity in HFS are ectopic generation of discharges, ephaptic transmission, and lateral spread of excitation between facial axons [1]. The characteristic EMG (electromyography) findings of HFS are paroxysmal activity of the motor units of all facial innervated muscles, synkinetic co-activation and lateral spread of reflex activity. In HFS, paroxysmal muscle activity consists of rapid, irregular, synchronous clonic bursts or long lasting EMG discharges in lower and upper facial muscles [1, 6]. The PAM is supplied by the posterior auricular branch of

the facial nerve, which is found immediately distal to the stylomastoid foramen. In normal subjects, EMG activity can be recorded in the PAM during lateral gaze, a phenomenon that is also called the oculoauricular phenomenon. None of the normal subjects showed any spontaneous activity in the PAM [16].

In our study, the AMR of PAM and orbicularis oris was recorded synchronously with the other facial muscles on the symptomatic side in most patients, but no AMR was observed on the uninjured side, which demonstrates that PAM and the orbicularis oris muscle also show synkinetic co-activation together with other facial innervated muscles during voluntary movements or by spontaneous blinking in HFS cases. The patients reported that their auricular symptoms subsided after injection in both groups, with remission rates of 45.5% (15/33) and 76.7% (23/30) in the regular and PAM groups, respectively; a higher rate was seen in the PAM group. PAM amplitudes in the PAM group decreased more significantly compared with those in the regular group (**Table 4**), indicating that PAM likely contributes to the generation of auricular symptoms or at least enhances the severity of auricular symptoms. Accordingly, we suggest that BTX-A be applied to the PAM in HFS patients who develop discomfort around the ear and tinnitus on the symptomatic side. However, the capacity of BTX-A to block acetylcholine release at neuromuscular junctions can result in muscle paralysis without relief of vascular compression of the nerve, and in turn the AMR persists.

In accordance with the prevailing hypothesis, idiopathic HFS could be considered as a consequence of chronic subclinical facial nerve damage [17-19]. This peripheral movement disorder is most frequently attributed to compression of the facial nerve at the root exit zone (REZ) by an ectopic anatomical or pathological structure that results in “ephaptic transmission”. This theory is supported by the fact that the nerve is encircled at its root exit zone, and by the clinical improvement seen following surgical decompression [18, 20, 21]. Consistent with this hypothesis, patients improve after surgical intervention at the posterior fossa. However, there are other etiologies that should be considered in the differential diagnosis. HFS can be associated with lesions involving the brain stem, subcortical areas, and even the cortex [11].

Previous work suggested that HFS often initially involves the orbicularis oculi muscle, and then gradually spreads to other facial muscles, with the effects exaggerated by the trigeminal-facial nerve reflex. After BTX-A injection into the orbicularis oculi, the spasms in this muscle lessen significantly, and the excitability of orbicularis oris neurons concomitantly are reduced [22]. Our findings show that after BTX-A injection that is confined to the orbicularis oculi muscle in HFS patients in the regular group, the auricular symptoms were relieved and the AMR amplitude of the orbicularis oris and PAM (non-injection site) was reduced (**Table 4**). These results are consistent with the hypothesis that in HFS, skin or muscle afferent signals volley via the trigeminal nerve to enhance the excitability of facial nerve motoneurons. Amelioration of HFS by a trigeminal nerve block indicates that the increased excitability of facial motoneurons in HFS may be modulated by decreasing afferent inputs [23]. The current findings support that after a standard treatment plan the auricular symptoms were relieved in some patients.

The mechanism by which tinnitus is generated in some patients with HFS is unknown. Tinnitus has many causes, making determination of the exact cause difficult. As such, there are other possible explanations for the relief of auricular symptoms seen here. It is conceivable that one cause of tinnitus-the contraction of the tensor tympani or stapedius muscles [24]- is responsible for the “clicking” sound that is simultaneous and synchronous with facial muscle contractions [2, 3]. Some patients report that their auricular symptoms subsided even when they were given a standard treatment plan. We suspect this symptom resolution is associated with the lessening or disappearance of spasms in the tensor tympani or stapedius muscles, or could be due to neuromuscular effects that are distant from the site of botulinum neurotoxin injection [25]. There have been several case reports of HFS occurring in patients who reported attacks that are usually long-lasting (10-20 s) and involve loud, monaural tinnitus with a staccato character (e.g., clattering or a sound like a machine gun). The attacks were spontaneous, but could also be provoked by certain

head positions or exposure to loud sounds. Such symptoms could be relieved by low doses of carbamazepine [26]. Furthermore, auricular symptoms were not relieved or did not disappear in all patients after BTX was applied to the PAM. Based on the results obtained here, the reason for the persistence of the auricular symptoms in some cases is unclear.

In addition, there are no reliable data, at least from this study, on the prevalence of this syndrome. The auricular symptoms were improved to a greater degree after BTX-A injection into the PAM as well as at regular injection sites. Thus, electrophysiological studies could provide additional information on pathophysiology that could inform therapeutic decisions.

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Disclosure of conflict of interest

None.

Abbreviations

BTX-A, Botulinum toxin type A; PAM, Posterior auricular muscle; HFS, Hemifacial spasm; BR, Blink reflex; OO, Orbicularis oris; AMR, Abnormal muscle response; EMG, electromyography.

Address correspondence to: Zu-Neng Lu, Department of Neurology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China. E-mail: lzn196480@126.com

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