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CHAPTER 5

Responsiveness to botulinum toxin type A in muscles of complex regional pain syndrome patients with tonic dystonia

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Abstract

Tonic dystonia of the limbs in complex regional pain syndrome (CRPS) is associated with considerable disability. Treatment options are scarce. Botulinum toxin (BoNT) is sometimes used, but the effect is often said to be disappointing. However, this notion stems from case reports and clinicians' opinions but has never been formally studied. We therefore investigated responsiveness to BoNT type A in CRPS patients with tonic dystonia. Tot his end, we injected the extensor digitorum brevis (EDB) muscle with BoNT-A in 17 patients with CRPS and tonic dystonia to compare the response between affected and unaffected legs. We also investigated the right legs of 17 healthy controls. Responsiveness was defined as a decrease of the amplitude of the compound muscle action potential (CMAP) of >20% from baseline two weeks after BoNT-A injection. We controlled for a temperature effect on BoNT efficacy by measuring skin temperature hourly directly above the EDB muscle in the first two weeks. CMAP amplitude decreased >20% after injection on the affected side in 16 of 17 CRPS patients, similar to the response in unaffected legs (12/13) or legs of controls (17/17). The degree of CMAP reduction was significantly smaller in patients than in controls (56.0 ± 22.3% versus 70.6 ± 14.6%; p=0.031). This may be due to a lower physical activity level and a greater difficulty to localize the EDB muscle properly in affected legs. The decrease in CMAP amplitude was not related to skin temperature. In conclusion, contrary to the prevailing opinion, BoNT-A has a normal, although perhaps slightly lower efficacy in CRPS patients with dystonia.

Introduction

Complex regional pain syndrome (CRPS) is characterized by pain in combination with sensory, autonomic, trophic and motor abnormalities. The underlying pathophysiology, though largely unknown, can be sought in three heterogeneous pathways: aberrant inflammatory mechanisms, vasomotor dysfunction, and maladaptive neuroplasticity (see [1] for review). The latter is thought to contribute to the development of a continuous abnormal tone of flexor muscles in particular, resulting in abnormal postures, i.e. tonic dystonia [2-5]. Tonic dystonia affects about 25% of patients with chronic CRPS and is associated with considerable disability [6,7]. Management of tonic dystonia in CRPS is complicated. Splints or plaster casts have been used to prevent deformity and support function but are often ineffective and may even worsen spasms. Other approaches include physical therapy and muscle relaxants, but no evidence exists to support their use [8]. Intrathecal baclofen therapy may substantially decrease the severity of dystonia, but is invasive, has a high rate of adverse events and provides no benefit in 30% of cases [4].

One other approach is the use of botulinum toxin (BoNT), which reduces muscle spasms through inhibition of achetylcholine release at the neuromuscular junction. Intriguingly, the available literature on BoNT injections in tonic dystonia in CRPS commonly reports a poor response to this treatment [6,7,9-11] although no controlled studies have been conducted. The failure to respond to BoNT contrasts with the reported efficacy of the drug in other forms of dystonia or in spasticity [12,13]. A potential explanation for this unsatisfactory effect may be sought in an impaired microcirculation in CRPS [14-16]. Impaired vasomotor function can cause cooling in the affected extremity [17,18], and a local low temperature is known to limit the capacity of BoNT to block neuromuscular synapses [19-21]. Other factors that occur in CRPS, such as inflammation and soft tissue contractures may also play a role.

The aim of this study was to compare the capacity of BoNT to block neuromuscular synapses between muscles of the affected and unaffected legs of CRPS patients with tonic dystonia and healthy controls. Additionally, we investigated the relation of skin temperature with responsiveness to BoNT.

Methods

Participants

Seventeen patients with CRPS type I and tonic dystonia in at least one leg and seventeen age- (±3 years) and sex-matched healthy controls were included. Five patients had received BoNT injections more than two years before inclusion, with an unsatisfactory or no effect. No controls had received BoNT. All patients fulfilled the International Association for the Study of Pain criteria for CRPS [22]. They were recruited from the outpatient clinic of the neurology department of the Leiden University Medical Center, which is a referral center for CRPS patients in the Netherlands. All patients who had visited our center at least once and fulfilled the inclusion criteria were contacted. The first 17 patients who consented (see sample size calculations below) were included in the study. The study was approved by the local medical ethics committee, in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Study protocol

Botulinum toxin injection and responsiveness assessment

The 'extensor digitorum brevis (EDB) test' was used to evaluate the neuromuscular blocking capacity of BoNT [23-25]. This test assesses the percentile decrease of the amplitude of the compound muscle action potential (CMAP) of the EDB muscle two weeks after BoNT injection.

Prior to the study, two pilot studies were conducted to detect which method of assessing EDB CMAP amplitude had the best reproducibility. First, we tested 15 healthy volunteers (5 men; age 26.8±5.1 years) twice with a two-week interval. Two localization methods and three different electrode sizes were tested: small (S): 1.0 cm diameter, medium (M): 2.65x2.9cm, and large (L): 6.0x10.0 cm. In the palpation method (PM), the small electrode was placed on the skin where the EDB muscle belly was felt best; the anatomically based (AB) method placed the electrodes along a line which was drawn from the inferior part of the lateral malleolus to the protuberance of the first metatarsophalangeal joint (Figure 5.1). The longer side of the electrode was placed perpendicular to this line at the level the EDB muscle belly was felt. A 2 mm hole in the center of the electrode ensured accurate placement on the line. The method with the smallest coefficient of variation (CV; standard deviation expressed as

a percentage of the mean) for CMAP amplitude was the AB-L technique (amplitude 2.6±1.0 mV, CV 10.0±6.8%). Values for the PM were 6.0±2.3 mV with a CV of 16.7±11.1%; for the AB-S method they were 5.3±2.0 mV with a CV of 16.3±11.9% and for the AB-M they were 4.9±1.8 mV with a CV of 11.2±14.5%. As expected the large electrodes lowered CMAP amplitudes [26-28], so we compromised between amplitude and reproducibility aims and used the AB-M combination for the BoNT-study. The method was further optimized in 12 healthy volunteers (3 men; age 26.7±2.3 years) who were tested twice with a one-week interval. In this group, after having recorded a baseline CMAP with the AB-M technique, the locations of recording electrode and stimulation site on the volar aspect of the ankle were marked on a transparent plastic foil, together with vein topography and other skin characteristics (e.g. naevi, scars). This foil was used in the follow-up measurement to further improve reproducibility of electrode placement. This method resulted in mean amplitudes of 5.6±1.8 mV for the first test and 5.3±1.6 mV for the second test. The absolute difference between each subject's two measurements was calculated. When expressed as a percentage of the first measurement, the mean value was 9.1±5.3%. We used the mean plus two SD to arrive at a threshold percentage of 19.6%: percentile changes larger than this threshold, rounded to 20%, will be due to chance in only about 2.5% of cases. This threshold was used to define responsiveness to BoNT as a CMAP amplitude decrease >20% and nonresponsiveness as a decrease ≤20%. Because other cut-off values have been used in previous studies, we additionally checked the number of non-responsive muscles using thresholds of 30, 40 and 50%.

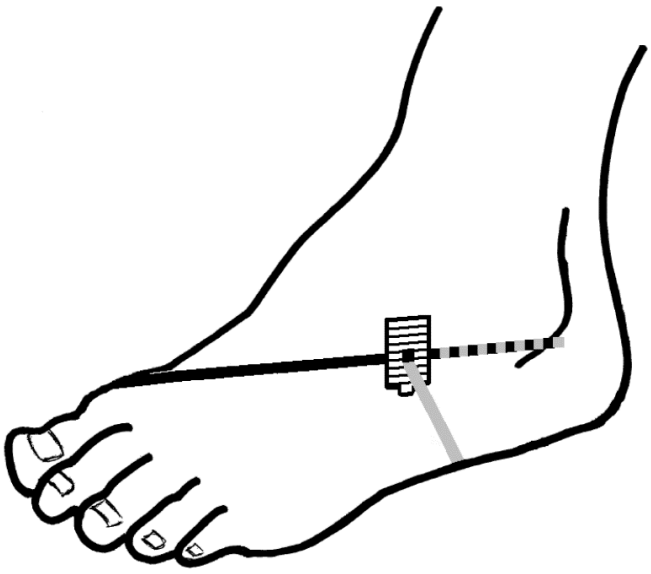
In the pilot studies as well as in the BoNT-study, hot water baths were used to warm the feet before measuring CMAPs while heat lamps were used during measurements to assure that skin temperatures of the feet remained between 32-34°C. When patients were unable to extend the toes of their affected extremity, the distances from the lateral foot side and bottom of lateral malleolus to the drawn line of the unaffected foot were used to determine the proper placement of the EDB electrode at the affected side. After electrode removal, twenty units of BoNT type A (onabotulinumtoxin-A/Botox® Allergan, Irvine, USA; diluted with normal saline to a concentration of 50 U/ml) were injected under needle-guidance in the EDB muscles. We injected one foot in healthy controls and patients in whom both legs were affected. In CRPS patients with one affected leg, we injected both legs to allow conclusions about whether a potentially observed lack of effect would be attributable to a local (i.e., CRPS-related) or systemic (e.g., myogenic) cause. A dose of 20 units of BoNT-A is considered sufficient to achieve maximal CMAP amplitude reduction in the

EDB muscle [24]. To ensure that relative changes in CMAP amplitude could be measured accurately, the initial negative peak CMAP amplitude had to be ≥2.0 mV; if not, that side was excluded from analysis. We also performed follow-up measurements 7 and 35 days after injection so as not to miss a possible larger effect of BoNT-A at a time different from two weeks. All measurements were carried out by the first author. Records of previous tests were not available at the follow-up measurements.

Temperature measurements

Skin temperature was assessed with 'iButtons' (type DS1922L, Maxim, San Jose, CA, USA). These are small wireless devices to record temperature over long periods. They were placed over the EDB muscle on both feet and temperature was measured hourly during the first two weeks of the study.

Figure 5.1. Schematic illustration of the active electrode placement. Distances from electrode center to lateral foot side (grey line, from electrode center perpendicular to lateral foot side) and to the lateral malleolus (striped grey line) obtained from the unaffected side were used for localization of the active electrode on the affected side if patients could not extend their middle toes.



Statistical analysis

Sample size

Based on clinical experience we expected that at least half of the CRPS patients would not respond to BoNT-A while at most 10% of controls would be nonresponders. In controls nonresponsiveness to BoNT is likely to be due to failure of the delivery method, not to any putative resistance of neuromuscular synapses to BoNT. Assuming nonresponse levels of 10% (controls) and 50% (patients), with β=0.8 and α=0.05, a population of 17 patients and 17 controls would be sufficient to detect a statistical significant difference between groups.

Data analysis

Fisher's exact test was used to compare the number of nonresponders between groups (CRPS patients' affected or unaffected side versus controls), while McNemar's test was used to compare responsiveness to BoNT-A between the affected and unaffected extremities of patients. Data on percentile CMAP reductions at weeks 1, 2 and 5 were normally distributed after ^{10}log transformation. Percentile CMAP reductions at week 2 were compared between groups with the t-test for independent samples (CRPS patients' affected or unaffected side versus controls) or the t-test for dependent samples (CRPS patients' affected versus unaffected side). Changes over time (week 1, 2 and 5) within sides (affected, unaffected or controls) were analyzed with repeated measures ANOVA. Pearson's correlation coefficient was used to examine the relation between skin temperature and CMAP amplitude reduction. Significance was set at the 0.05 level. All analyses were performed with IBM® SPSS® Statistics 20.0 (IBM Corp., Armonk NY, USA).

Results

Age- and sex had been matched and hence did not differ between groups: both groups included two male participants. Mean±SD age of CRPS patients was 41.9±12.5 and 42.0±11.6 years for controls. Mean±SD disease duration was 11.8±7.0 years. Mean±SD numerical rating scale pain score was 6.6±2.4. Clinical characteristics of individual patients are summarized in Table 5.1 (p.98). In three patients both legs were affected; in these cases only the most affected leg was examined. These patients were excluded from analyses in which affected and unaffected sides were

compared. As the CMAP baseline amplitude of the unaffected side was below 2.0 mV in one other patient, information on BoNT-A responsiveness of the unaffected sides was available from 13 CRPS patients. Mean CMAP amplitude values per group over time are shown in Table 5.2.

Table 5.2. CMAP amplitudes (mV) over time, shown as mean (SD)

	Affected side CRPS patients (n=17)	Unaffected side CRPS patients (n=13)	Controls (n=17)
Baseline	3.5 (1.3)	4.7 (1.6)	4.6 (1.3)
Week 1	1.6 (0.7)	1.9 (0.8)	1.3 (0.7)
Week 2	1.4 (0.7)	1.8 (1.0)	1.3 (0.7)
Week 5	1.6 (0.8)	2.0 (1.1)	1.5 (0.7)

Inspection revealed the largest effect of BoNT-A two weeks after injection in line with expectation. The following analyses focus on the decrease in CMAP amplitude at week 2 as compared to baseline. All but one patient showed a CMAP amplitude decrease of >20% after BoNT injection in the EDB on the affected side after two weeks. The numbers of responding and non-responding sides of patients and controls are shown in Table 5.3. They did not differ significantly between affected and unaffected sides in patients, nor between patients' affected sides and controls, nor between patients' unaffected sides and controls. There were also no differences between groups when responsiveness was based on 30, 40 or 50% thresholds.

Table 5.3. Number of responding sides of CRPS patients and controls for different responsiveness thresholds

CMAP amplitude decrease at week 2	Affected side CRPS patients (n=17)	Unaffected side CRPS patients (n=13)	Controls (n=17)	P-value*: Affected vs unaffected CRPS	P-value#: Affected CRPS vs controls	P-value#: Unaffected CRPS vs controls
> 20%	16	12	17	1.00	1.00	0.433
> 30%	15	11	17	1.00	0.485	0.179
> 40%	14	10	16	1.00	0.601	0.290
> 50%	12	9	16	1.00	0.175	0.138

* McNemar's test; # Fisher's exact test.

As the qualitative conventional way to evaluate responsiveness may fail to detect small quantitative differences, we compared percentile CMAP amplitude reductions between groups two weeks after injection (Figure 5.2). The CMAP amplitude decrease was significantly smaller in patients' affected sides than in controls (56.0±22.3% versus 70.6±14.6%; p=0.031). There were no significant differences between affected and unaffected sides in CRPS patients, nor between the unaffected side of patients and controls. All patients who had received BoNT injections in the past showed a >50% decrease of CMAP amplitude at week 2. The percentile decrease in CMAP amplitude did not differ significantly between weeks 1, 2 and 5 in patients' affected or unaffected legs. The amplitude decrease in controls was smaller at week 5 (67.1 ± 12.9%) than at week 1 (71.3±13.7%; p=0.026) and 2 (70.6±14.6%; p=0.003).

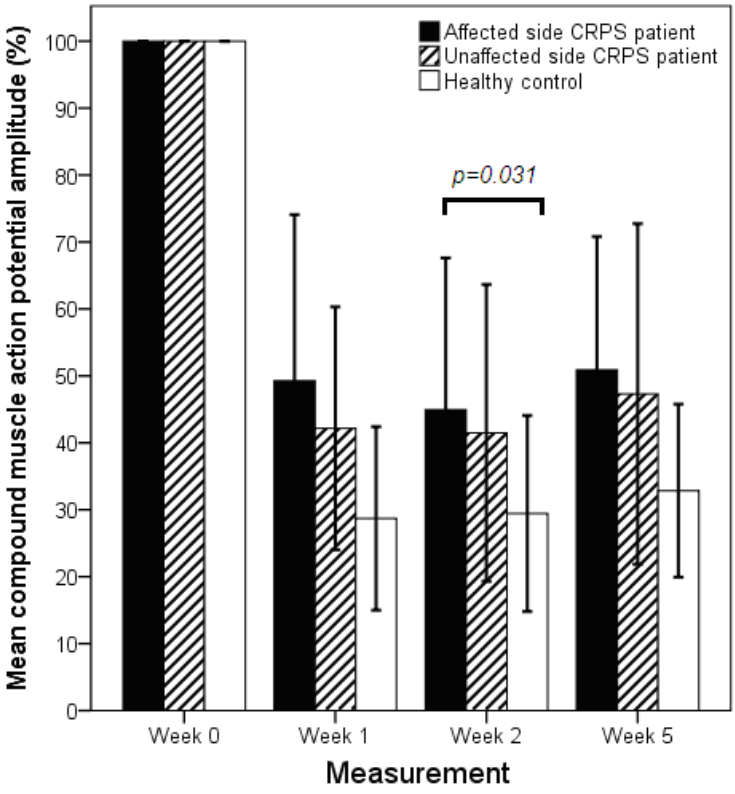
Skin temperature recordings were missing for one patient. Of the remaining 16 patients, mean skin temperature was significantly lower at the affected than at the unaffected side (31.2±2.4 versus 32.1±1.3°C; p=0.045). The mean skin temperature of controls, 32.2±0.6°C, did not differ significantly from that of affected or unaffected sides of patients. Mean skin temperature was not correlated with CMAP amplitude reduction at week 2 (CRPS affected side r=-.05, p=0.85; CRPS unaffected side r=.06, p=*0.85*; control r=.20, p = 0.44).

Table 5.1. Patient clinical characteristics

ID	Gender	Age (years)	Disease duration (years)	NRS pain score	Affected side	Clinical symptoms and signs									
						sensory changes		motor dysfunction		vasomotor dysfunction		sudomotor (edema, hypo/hyperhidrosis)		trophic changes (nail/hair/skin)	
						●	□	●	□	●	□	●	□	●	□
1	F	32.5	7.0	6	L	x	x	x	x	x	x			x	
2	F	46.1	5.3	8	R	x	x	x	x	x		x	x	x	
3	F	52.5	14.0	7	L	x	x	x	x	x	x	x		x	x
4	F	48.5	11.0	6	R	x	x	x	x	x	x	x		x	
5	F	60.7	19.0	6	R	x	x	x	x	x	x	x	x	x	x
6	F	62.1	14.0	4	L*	x	x	x	x	x		x		x	
7	F	21.6	8.0	8	R	x	x	x	x	x	x	x	x	x	x
8	F	47.3	10.3	9	L	x	x	x	x	x		x	x	x	x
9	M	54.2	13.0	6	L	x	x	x	x	x	x	x		x	x
10	F	32.4	10.3	10	R	x	x	x	x	x		x	x	x	
11	F	24.4	2.4	4	R	x	x	x	x	x	x	x	x	x	x
12	F	39.7	10.8	8	L*	x	x	x	x	x		x		x	
13	F	49.8	29.0	9	L*	x	x	x	x	x		x		x	x
14	F	41.9	20.0	8	R	x	x	x	x	x	x	x	x	x	x
15	M	24.8	7.6	6	R	x	x	x	x	x		x			
16	F	31.1	18.0	5	R	x	x	x	x	x	x			x	x
17	F	43.1	0.8	0	L	x	x	x	x	x	x			x	x

F: female, M: male; NRS: numerical rating scale; L: left, R: right, * both legs affected, most affected side; ●: symptom; □: sign

Figure 5.2. Compound muscle action potential amplitudes over time relative to baseline. Mean±standard deviation percentages of amplitudes of compound muscle action potential values of the extensor digitorum brevis muscle at baseline and one (affected: 49.3±24.8; unaffected: 42.2±18.2; controls: 28.7±13.7%), two (affected: 44.0±22.3; unaffected: 40.9±21.3; controls: 29.4±14.6%) and five (affected: 49.1±20.6; unaffected: 46.7±24.5; controls: 32.9±12.9%) weeks after botulinum toxin injection. Error bars indicate standard deviations.



Discussion

Based on case reports and reviews on BoNT in CRPS patients with tonic dystonia [6,7,9-11] we anticipated a higher number of nonresponsive EDB muscles in patients than in controls, at least at patients' affected sides. Our results indicate that numbers of nonresponsive muscles were very low in both affected and unaffected legs of CRPS patients, and did not differ between patients and controls. There was a subtle

difference in the decrease in CMAP amplitude two weeks after injection, which was less in CRPS patients' affected sides (56%) than in healthy controls (70%).

The clinical relevance of this difference is probably low. The decreased response to BoNT-A in CRPS patients may in part be explained by a lower degree of physical activity: in spasticity and other forms of dystonia muscle activation post-injection enhanced the effect of BoNT-A [29-31]. This enhanced effect is thought to result from a facilitated penetration of BoNT at the presynaptic level [29-31]. The activity level of CRPS patients in this study was low: six were wheelchair-bound, and another five had severe impairments in standing and walking, so this might have contributed to the smaller response in CRPS patients' affected and unaffected sides than in the normally active controls.

Unavoidable methodological factors may also have contributed to the small differences in responsiveness between patients and controls. Though great care was taken to inject BoNT-A at a standardized anatomically based location, EMG-guided localization of the EDB muscle was still more difficult on the affected side since most patients were unable to voluntarily contract this muscle. This might have resulted in less accurately localized injections, which has been shown to reduce drug efficacy [32,33]. Then again, no differences were found between patients' affected and unaffected sides, so this explanation probably does not account for the difference.

This study also shows that skin temperature, which was significantly lower in CRPS patients' affected legs, was unrelated to the magnitude of CMAP amplitude decrease after BoNT-A injection. Beforehand, it was hypothesized that the low temperatures often found in chronic CRPS could play a role in the expected decreased responsiveness to BoNT-A, as animal studies had shown that some steps in the action of BoNT-A such as neurotoxin binding and internalization, but also the amount of remaining acetylcholine release in by BoNT poisoned neuromuscular junctions, depend on temperature [19-21,34,35]. For methodological reasons the effect of BoNT-A was examined in the EDB muscle, which is known to be a reliable method for testing responsiveness to BoNT [23,24,25,36]. Using the same target muscle in all patients contributes to comparability and reduces variability, but it may be argued that this muscle is not involved in the flexion postures that are so common in these patients. Consequently, we cannot exclude that flexor muscles involved in the abnormal postures of patients CRPS patients might respond differently than the EDB, but this seems very unlikely.

In the light of our findings of a normal nonresponder rate in patients with CRPS and dystonia, the question remains what may have contributed to the reported disappointing experiences of clinicians with BoNT in the management of abnormal

postures in this population. Recent studies have shown that muscular activity is not necessarily increased in muscles involved in the abnormal postures of CRPS patients [37,38]. This indicates that other factors than sustained muscle contractions may also play a role, which complicates the selection of an appropriate treatment modality. When the abnormal postures result from substantial hyperactivity, as can be easily detected with EMG, it is very likely that BoNT may be helpful in relieving symptoms. However, when hyperactivity is absent, for example if abnormal posturing is caused by shortening of muscle fibers or changes in capsules or joints, an effect of BoNT is not to be expected and injection must be omitted. Another factor that might contribute to abnormal posturing, but is not related to muscle hyperactivity per se, is pain [38]. BoNT has been shown effective in relieving pain in different neuropathic pain syndromes, via direct inhibition of the release of local nociceptive neuropeptides such as substance P and bradykinin, resulting in reduced neurogenic inflammation and neuroplastic reorganization (see [39] for review). As pain is inversely related to motor function in CRPS [40], it is conceivable that injection of BoNT contributes to the improvement of abnormal postures via pain relief. In the present study, however, an effect of BoNT injection on pain scores was not investigated. Given, however, that randomized trials on this topic are scarce, these speculations have to be investigated in future studies. Taken the current state of knowledge on this topic into account, it seems rational to restrict the selection for this intervention to CRPS patients with fixed postures who suffer from proven muscular hyperactivity.

In conclusion, this study shows a normal nonresponder rate to BoNT-A in patients with CRPS and tonic dystonia. There is a quantitatively slightly decreased effect; which can probably be countered by using a relatively high dose. In contrast to the concept that BoNT's efficacy in CRPS with fixed postures frequently is disappointing, our results indicate that it may be important to reserve this treatment for patients with demonstrated muscular hyperactivity as the underlying cause for the abnormal postures, while other factors like contractures should be excluded.

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