Clinical Characteristics and Response to Long-Term Botulinum Toxin Type A Therapy in Patients with Cervical Dystonia at a Neurology Clinic

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ABSTRACT

Introduction: To determine the demographic and clinical characteristics and response to botulinum toxin type A (BoNT-A) therapy in patients with cervical dystonia (CD).

Method: A retrospective analysis of the detailed medical records of the patients with CD, followed up at our Botulinum Toxin Outpatient Clinic from 1998 to 2012, was performed. The treatment data were compared between the patients with primary CD and those with secondary CD; between patients receiving BoNT-A treatment for more than 5 years and less than five years, and between first applications and last applications.

Results: Fifty-seven patients (56.15% women) with CD were included in this study. The mean age was 41.01 ± 13.42 years, the mean age at symptom onset was 32.93 ± 15.45 years, and the mean dystonia duration was 8.10 ± 8.5 years. The interval between onset of symptom and first BoNT-A treatment was 5.94 ± 9.06 years, the duration of BoNT-A treatment was 36.13 ± 29.17 months, and the number of applications was 8.48 ± 6.23 in 45 patients with CD who were under treatment with BoNT-A for more than 1 year and had received at least three injections before. There was no difference between the patients with primary and secondary CD in terms of treatment results. The injection interval of the patients receiving BoNT-A treatment for more than 5 years and less than 5 years was 18.37 ± 5.10 and 14.43 ± 2.36 weeks, respectively ($p = .001$). There were no differences in the other treatment values. The mean doses were 559.00 ± 147.60 vs. 681.66 ± 188.09 units ($p = .0001$), the durations of improvement were 11.82 ± 2.71 vs. 13.00 ± 4.00 weeks ($p = .014$), the response scores were 2.71 ± 3 vs. 3.02 ± 5 ($p = .002$), the response ratings were $64.66\% \pm 16.18$ vs. $71.22\% \pm 17.29$ ($p = .001$), and the numbers of muscles applied were 3.15 ± 1.16 vs. 3.51 ± 0.99 ($p = .012$) in the first and last applications, respectively.

Conclusion: There were no differences between the response of the patients with primary and secondary CD. Our results showed a statistically significant increase in the mean dose of BoNT-A, the response rating, the number of muscles applied, the duration of improvement, and the injection interval over time. (Archives of Neuropsychiatry 2014; 51: 383-388)

Key words: Cervical dystonia, clinical characteristics, demographic characteristics, clinical findings, botulinum toxin

Conflict of Interest: The authors reported no conflict of interest related to this article.

Introduction

Cervical dystonia (CD) is a movement disorder, characterized by abnormal head, neck, and shoulder posture due to repetitive clonic and tonic involuntary contractions in muscles of the neck and shoulder region (1,2). It is the most common form of adult-onset focal dystonia. Its pathological mechanism and the exact prevalence are not known (3,4,5,6). Cervical dystonia causes rotation of the head (torticollis), tilting of the head (laterocollis), flexion of the neck (anterocollis), and extension of the neck (retrocollis). Sometimes, it can occur in combination

with all of these clinical forms, and such clinical forms can be combined with elevation or anterior shifting of the shoulders (1,2). Other movement disorders can coexist with this movement disorder (1). Several clinical studies have suggested injections of botulinum toxin as first-line therapy in the treatment of CD (7).

The aims of our study are to determine the demographic and clinical characteristics and to evaluate response to long-term botulinum toxin type A (BoNT-A) therapy and co-existent movement disorders in patients with cervical dystonia (CD) who were followed up at our clinic.

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Methods

A retrospective analysis of the detailed medical records of patients with CD, followed up at our Botulinum Toxin Outpatient Clinic from December 1998 to December 2012, was performed, and their demographic and clinical characteristics were evaluated. The patients who had incomplete medical records were excluded. The treatment data of the patients who were under treatment with BoNT-A for more than 1 year and who received at least three consecutive treatments were investigated. These data were compared between patients with primary CD and secondary CD, patients receiving BoNT-A treatment for more than 5 years and less than 5 years, and first applications and last applications. BoNT-A applications after dose adjustment were accepted as first treatment to increase the reliability of this study.

All patients were diagnosed according to published criteria (8). They were categorized as torticollis, laterocollis, anterocollis, retrocollis, and combined form according to their clinical manifestation. All patients undertook the following: detailed medical history, including past and present medicine, birth trauma, and central or peripheral trauma; complete neurological examination; and magnetic resonance imaging of the brain and cervical portion of the spinal cord for distinguishing known causes of secondary dystonia.

In this study, the patients were evaluated according to the following clinical and demographic parameters: gender, current age, age at CD onset, duration of the disease, clinical form of CD, right or left deviation, onset form of the disease (acute/chronic), medical history, presence of head tremor, pain, sensory trick and other coexistent movement disorders, consanguinity of the parents, the family history of dystonia or other movement disorders, the interval between symptom onset and first BoNT-A treatment (the latency of BoNT-A treatment), and the duration of BoNT-A treatment.

The patients were treated and evaluated by the same experienced neurologist. Two preparations of BoNT-A Dysport®, Ipsen, UK and BOTOX®, Allergan, USA) were used. Electromyographic guidance was used for botulinum toxin injections whenever deemed necessary. At each visit before the BT-A injection, the severity of CD was measured based on the severity of rotation section of the Toronto Western Spasmodic Torticollis Rating Scale (TWSRTS-Severity) (9). Determination of first doses of BoNT-A was made according to the severity of the disorder, and then, the doses of BoNT-A for each subsequent application were tempered to the severity of disorder, the therapeutic response, and adverse effects of the previous injections. Total BoNT-A dose per treatment, number of muscles applied, and BoNT-A dose of per target muscle were recorded for each application. In addition, the efficacy of each application was routinely evaluated 4 weeks after injection, based on a 0-4 scale (0=no effect; 4=marked improvement in severity and function), and the response rate

was assessed using a visual analog scale (VAS) as percentage (0% to 100%) by the patients. A response rate equal to or greater than 50% was accepted as successful treatment. In order to evaluate the duration of the effect, adverse effects, and duration of the adverse effects, all patients were evaluated monthly. The time between the injection of BoNT-A and the first sign of improvement (the latency to response; days); the time between the injection of BoNT-A and the maximal improvement (the peak improvement time; days); the duration of the effect (weeks); and the interval between each injection (the injection interval; weeks) were recorded for each application. The duration of effect was accepted as the time between the peak improvement after injection and the reappearance of symptoms. Re-injections were performed when symptoms of CD became apparent, and the injection intervals were not shorter than 3 months.

This study was approved by the local ethics committee. Statistical analysis was performed using Statistical Package for Social Sciences 15.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean±standard deviation. Paired-samples t-test and independent-samples t-test were used to compare means. $P<0.05$ was considered statistically significant.

Results

Of the 57 patients with CD, 32 (56.15%) were female and 25 (43.85%) were male. The mean age was 41.01 ± 13.42 (range 16 to 69) years, the mean age at symptom onset was 32.93 ± 15.45 (range 1 to 63) years, and the mean dystonia duration was 8.10 ± 8.5 (range .5 to 42) years. Pure torticollis was determined in 34 (59.64%), pure laterocollis was determined in 5 (8.78%), pure anterocollis was determined in 1 (1.75%), and the combined form was determined in 17 (29.83%, of the 17 patients with combined form, 11 had torticollis in addition to retrocollis, 4 had torticollis in addition to anterocollis, and 2 had multiple-sided rotation) of the patients. Of the 56 patients with torticollis and laterocollis, 35 had left-sided CD and 21 had right-sided CD. In addition to CD, 3 (5.27%) of the patients had hand/arm dystonia, 2 (3.5%) had hand/arm and truncal dystonia, 1 (1.75%) had blepharospasm, 19 (33.33%) had head tremor, 2 (3.5%) had postural hand tremor, and 2 (3.5%) had Parkinson disease. Sensory trick was reported by 42 patients (73.68%), and neck pain was reported by 28 (49.12%) of the patients. Of the 57 patients, 44 (77.2%) had primary CD and 13 (22.8%) had secondary CD. Eight (61.5%) patients with secondary CD had a history of long-term neuroleptics use, 2 (15.4%) had a history of Parkinson's disease, 2 (15.4%) had a history of birth trauma, and 1 (7.7%) had a history of head trauma. Seven (15.9%) of the 44 patients were with primary CD, 7 (87.5%) of the eight patients had tardive CD, and 1 (50%) of the 2 patients with Parkinson disease had the combined form. Both of the patients who had multiple-sided rotation had a history of birth trauma. Moreover, 4 (50%) of the 8 patients with tardive CD had additional movement

disorders besides CD (1 had blepharospasm, 2 had hand/arm dystonia, and 1 had hand tremor), and 2 patients with birth trauma had additional hand/arm and truncal dystonia. All patients' onset of symptoms was chronic, except that of a patient whose onset of CD symptoms was acute after head trauma. One of the patients' sons and 2 cousins had a history of focal dystonia, 1 of the patients' parents had consanguinity and his 2 cousins had a history of focal dystonia, and the patient with Parkinson disease had a brother with Parkinson disease.

BoNT-A could not be injected in 3 patients, because BoNT-A could not be provided. BoNT-A treatment data of 9 patients who had irregular follow-up or who did not receive at least 3 consecutive treatments were excluded. Most of the patients (N=44) had Dysport injected. BoNT-A treatment data of 45 patients whose treatment results were evaluated are summarized in Table 1.

We did not find a statistically significant difference in the mean dose of BoNT-A, the mean latency to response, the mean peak improvement time, the mean duration of effect, the mean injection interval, or the mean response rate of the first and last injection between patients with primary and secondary CD. The mean BoNT-A injection interval was significantly higher in the patients receiving BoNT-A treatment for more than 5 years compared with less than 5 years (18.37 ± 5.10 and 14.43 ± 2.36 weeks, $p=.001$, respectively). In keeping with this finding, the mean duration of effect was longer in the patients receiving BoNT-A treatment for more than 5 years compared with less than 5 years (13.85 ± 5.23 and 11.36 ± 2.41 weeks, $p=.194$, respectively), but this difference was not statistically significant. There were no differences between both groups in terms of other data on treatment (the results are outlined in Tables 2 and 3).

There were statistically significant differences in the mean dose of BoNT-A, the mean duration of effect, the mean response score, the mean response rate, and the mean number of muscle applied, but there was no difference in the mean injection interval and the mean severity of CD when comparing the data on the first and last treatments (the detailed data are shown in Table 4).

Discussion

It has been reported that women are affected by CD 1.5-1.9 times more often than men. The age of onset of CD is generally observed between the fourth to seventh decades, and the peak incidence is in the fifth decade (2). The age of onset of disorder was lower among females, and the number of females was slightly higher than the number of males, but the rate of females to males (F/M=1.28) was less than previously reported in our patients. It has been reported in several studies that there was no statistically significant preponderance of right or left deviation in CD, and there were different results (2,10). In our series, left-sided CD 1.67 times more frequent than right-sided CD.

We found that the most frequent type of dystonia was pure torticollis (59.64%) in our study. Similarly, other studies have re-

Table 1. The data of BoNT-A treatment in patients with CD

N	45
The latency of BoNT-A treatment (years)	5.94 ± 9.06 (.1-40)
The duration of BoNT-A treatment (months)	36.13 ± 29.17 (12-120)
The number of BoNT-A treatments	8.48 ± 6.23 (3-23)
The dose of BoNT-A (U)	643.23 ± 154.01 (400-1150)
The latency to response (days)	6.11 ± 4.78 (1-30)
The peak improvement time (days)	13.24 ± 6.30 (5-42)
The duration of effect (weeks)	13.02 ± 4.61 (4-36)
The injection interval (weeks)	17.06 ± 4.73 (12-29)
Data were presented as mean $\pm$ standard deviation (range). BoNT-A: Botulinum toxin type A, CD: Cervical dystonia, U: Unit.	

Table 2. The comparison of BoNT-A treatment data of the patients with primary CD and secondary CD

	Primary CD (N=34)	Secondary CD (N=11)	P value
The dose of BoNT-A (U)	640.86 ± 160.73	650.59 ± 137.93	.717
The latency to response (days)	6.73 ± 5.21	4.18 ± 2.40	.200
The peak improvement time (days)	14.11 ± 6.81	10.54 ± 3.35	.187
The duration of effect (weeks)	13.57 ± 4.89	11.31 ± 3.25	.410
The injection interval (weeks)	17.37 ± 4.82	16.09 ± 4.52	.481
The response rate of first application (%)	63.82 ± 16.00	67.27 ± 17.22	.467
The response rate of last application (%)	71.61 ± 17.56	70.00 ± 17.17	.918
Data were presented as mean $\pm$ standard deviation. BoNT-A: Botulinum toxin type A, CD: Cervical dystonia, U: Unit.			

ported that the most frequent type of dystonia was pure torticollis (1,11,12). Jankovic et al. (1) reported in their study that 66% of the patients had the combined form. The percentage of this form was 29.83%, and it was the second most frequent type of dystonia in our study. The reported percentages of anterocollis and retrocollis by these authors were higher than ours, too. It has been reported that the clinical form of CD may change to another form of CD over the years (11,12). Right-sided torticollis changed to right-sided torticollis, in addition to retrocollis, 13 and 15 months after the beginning of the symptoms in our 2 patients, and left-sided torticollis changed to right-sided torticollis, in addition to retrocollis, 12 months after the beginning of the symptoms in another patient.

In a recently performed study, the authors compared characteristics of the patients with primary CD to patients with tardive CD and reported that they did not observe any difference in terms of clinical manifestation between the groups (13). We determined that the majority of tardive CD patients (87.5%) were combined form in our series; however, only 15.9% of the primary CD patients were combined form. Moreover, 4 (50%) of the 8 patients with tardive CD had additional movement disorders be-

Table 3. The comparison of BoNT-A treatment data of the patients with CD receiving BoNT-A treatment for more than 5 years and less than 4 years

	The treatment duration <5 years (N=15)	The treatment duration ≥5 years (N=30)	P value
The dose of BoNT-A (U)	623.95±144.08	652.88±160.24	.350
The latency to response (days)	5.20±3.21	6.56±5.39	.310
The peak improvement time (days)	11.46±4.83	14.13±6.82	.717
The duration of effect (weeks)	11.36±2.41	13.85±5.23	.194
The injection interval (weeks)	14.43±2.36	18.37±5.10	.001*
The response rate of first application (%)	62.33±17.09	65.83±15.87	.792
The response rate of last application (%)	68.66±16.74	72.50±17.70	.975

Data were presented as mean ± standard deviation, *: statistically significant.
BoNT-A: Botulinum toxin type A, CD: Cervical dystonia, U: Unit.

Table 4. The comparison of BoNT-A treatment data of the first applications and last applications in patients with CD

N=45	First application	Last application	P value
The dose of BoNT-A (U)	559.00±147.60 (400-1000)	681.66±188.09 (400-1150)	.0001*
The duration of effect (weeks)	11.82±2.71 (4-20)	13.00±4.00 (4-26)	.014*
The injection interval (weeks)	16.82±4.22 (12-24)	16.86±5.30 (12-32)	.947
The response score	2.71±.3 (1-4)	3.02±.5 (0-4)	.002*
The response rate (%)	64.66±16.18 (40-95)	71.22±17.29 (30-100)	.001*
The severity of CD	3.44±.58 (2-4)	3.12±.61 (2-4)	.768
The number of muscles applied	3.15±1.16 (2-6)	3.51±.99 (2-5)	.012*

Data were presented as mean±standard deviation (range), *: statistically significant.
BoNT

sides CD (1 had blepharospasm, 2 had hand/arm dystonia, and 1 had hand tremor), and 2 patients with birth trauma had additional hand/arm and truncal dystonia.

All patients reported that the onset of their symptoms was chronic, except 1, whose onset of CD symptoms was acute after a head trauma. It has been reported in previously reported studies that the symptoms of CD generally increase gradually, but there may be acute onset of symptoms after head, neck, and shoulder region trauma in 5%-21% of CD cases (10,14,15).

Head and hand tremor may be observed in patients with CD, and CD coexists with other focal dystonias, such as blepharospasm, and writer's cramp (1). The mechanism of head tremor in CD is not exactly known (16), and it has been reported by several authors that head tremor was observed in 35%-80% of the patients with CD (1,16,17,18). Also, 33.33% of our patient group had a head tremor, and 3.5% of them a postural hand tremor. We observed blepharospasm in a (1.75%) patient, hand/arm dystonia in 3 (5.27%) patients, and hand/arm and truncal dystonia in 2 (3.5%) patients. The percentage of both types of focal dystonia (blepharospasm and hand/arm dystonia) was 10% in the Jankovic et al. study (1). It was also reported that anterocollis was observed in patients with Parkinson disease (19). We observed pure anterocollis in 1 of our patients with Parkinson disease and torticollis, in addition to anterocollis, in the other.

Patients with focal dystonia can reduce the severity of dystonic spasms usually by touching the affected body part; it is called "sensory trick." In a recently performed study, it has been reported that sensory tricks were observed in all types of focal dystonia; however, they were most commonly observed in CD. The authors have reported that they observed sensory tricks in 81% of their patients with CD in this study (20). Sensory tricks were reported by 73.68% of our patient group. It has been reported that pain was more frequent in patients with CD when compared patients with other dystonia types, and 58.8%-80% of patients with CD had intermittent or continuous neck pain (1,17,21). Pain can significantly affect the quality of life of patients with CD (21). However, the percentage of pain was lower in our series; 49.12% of our patients had pain in the cervical region.

Cervical dystonia is called primary CD if there is no identifiable underlying cause, such as a structural anomaly in the central nervous system, or secondary CD if it occurs as a consequence of a structural anomaly or metabolic reasons (2,3). Most of the patients with CD are primary CD, as ours were. The most frequent reasons of secondary CD are trauma and previous exposure to neuroleptics (22); 61.5% of the patients with secondary CD had a history of long-term use of neuroleptics, but the percentage of post-traumatic CD was low (15.4% birth trauma and 7.7% head trauma) in our study. In our 2 (15.4%) patients, CD developed over the course of Parkinson disease.

Jankovic et al. (1,23) have reported that the percentage of patients with a family history of a movement disorder was 44% in their group, but only 3 patients (5.26%) had a family history of a movement disorder in our patient group. A low percentage of patients with a family history of a movement disorder was found in the Yildiz et al. (17) study, which is consistent with our study.

When comparing our study results with other studies, which reported the results of long-term BoNT-A treatment of patients with CD, the mean interval between symptom onset and first BoNT-A injection was significantly longer than that reported by Gill et al. (24) (5.94±9.06 and 2.9 years, respectively). The reasons for delay of BoNT-A therapy may be related to slow increase of symptoms of CD, misdiagnosis, difficulty in reaching centers

for BoNT-A treatment, or difficulty in providing BoNT-A. In our study, the mean dose of BoNT-A was higher than the result of Mohammadi et al. (25) and lower than the result of Haussermann et al. (26) (643.23 ± 154.01 ; 389 ± 144 and 833 ± 339 units [U], respectively). The mean latency to response was 6.11 ± 4.78 days, and the mean peak improvement time was 13.24 ± 6.30 days in our study. Bhaumik et al. (27) have reported that the mean latency to response was 9.7 ± 5.7 days. The mean duration of the effect of BoNT-A treatment was 13.02 ± 4.61 weeks in our patients. In the Mohammadi et al. (25) study, this period was 11 ± 1.6 weeks.

It has been reported that adverse effects occurred in 34%-75% of the patients who were treated with BoNT-A, and the most common adverse effects were dysphagia, weakness in cervical muscles, hypophonia, dry mouth, and atrophy of muscles (26,28). Forty percent of our patients developed dysphagia at any application; 11.11% of the patients had atrophy of some applied muscles, 11.11% of them had weakness in cervical muscles, 2.22% had hypophonia, 2.22% of them had hoarseness, and 4.44% of them developed syncope when they received the injection. The mean duration of dysphagia, which was the most common adverse effect, was 11.18 ± 7.51 (range: 1-30) days, and it was shorter than the Kessler et al. (28) result (average: 3.5 weeks). Severe dysphagia and need for nasogastric tube feeding, as experienced by a patient in Haussermann et al. (26), did not occur in our patients. All adverse effects were mild and reversible. The difference between the mean duration of effect and the rate and severity of adverse effects of the studies may be related to different mean doses of BoNT-A used in each study.

The majority of patients reported being satisfied with their treatment results. Evaluation results of the doctor who evaluated the treatment correlated with the evaluation results of the patients. There was a significant increase in the efficacy of treatment over time in both evaluations. In the study by Skogseid and Kerty (29), whose mean treatment time was 5.5 years, the percentage of patients reported being excellent, good, or moderate efficient (85%) were correlated with evaluation of the treating doctors (92%). Hsiung et al. (30) performed a retrospective evaluation of the patients whose mean treatment time was more than 10 years and reported that their success rate was 68%. Our percentage of patients, considering the results of successful treatment (response rate equal to or greater than 50%) was higher (95.5%) than the results of these authors. The difference between the results may be related to our more satisfied patients having had regular follow-ups, and we excluded patients who had irregular follow-ups.

None of our patients observed spontaneous remission, and none of the patients had primary resistance, but a patient who was treated with BOTOX had secondary resistance. We did not perform a BoNT-A antibody test to a patient who developed secondary resistance, but this patient showed an adequate and efficient response to Dysport administration, with a mean dose ratio of 4 between toxins. It has been reported Dysport is more efficient, and its incidence of adverse effects is higher in

the treatment of CD; there were differences between different serotypes of BoNT or different preparations of one serotype in terms of clinical efficiency, safety, development of antibody, and specificity (31,32). Although the development of neutralizing antibodies was mostly considered the reason of poor or no response to BoNT in past years, recently, it has been indicated that it is more frequently due to factors other than immunogenicity, such as a change in the course of the disease (33,34,35).

In conclusion, based on our findings, the combined form was more common in patients with tardive CD, and multiple-sided CD was more common in patients with birth trauma. Moreover, in addition to CD, dystonia in other body parts was more commonly observed in these patients. However, there were no differences between the response of the patients with primary and secondary CD. Our results showed an increase in the dose of BoNT-A, the response rating, the number of muscles applied, the duration of improvement, and the injection interval-especially after treatment for more than 5 years-over time, and long-term BoNT-A treatment is an efficacious and safe treatment option in CD.

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