Arg1441Gly, and Arg1441His in the Roc domain, Tyr1699Cys in the COR domain, Met1869Thr, Ile2012Thr, Gly2019Ser, and Ile2020Thr in the Protein Kinase domain, and Gly2385Arg around the WD40 domain, are associated with the onset of PD, suggesting that malfunction of these domains play an important role in the pathogenesis of PD.19,20

In conclusion, our study indicates that the LRRK2 Gly2385Arg variant is associated with the PD in the Han ethnicity in mainland China. The LRRK2 Gly2385Arg carriers present with classical PD symptoms and share the same founder. It further supports the notion that the LRRK2 Gly2385Arg variant is ethnic-specific in Asian population as a potential risk factor in PD.

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REFERENCES


Molding the Sensory Cortex: Spatial Acuity Improves After Botulinum Toxin Treatment for Cervical Dystonia

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Abstract: Disorganization of sensory cortical somatotopy has been described in adult onset primary torticollis dystonia (AOPTD). Although botulinum toxin type A (BTX-A) acts peripherally, some studies have suggested a central effect. Our primary hypothesis was that sensory cortical reorganization occurs after BTX-A treatment of AOPTD. Twenty patients with cervical dystonia and 18 healthy age-matched control patients had spatial discrimination thresholds (SDTs) measured at baseline and monthly for 3 months. Mean baseline SDT (±SD) was 1.75 ± 0.76 mm in the dystonia group, greater than the control group mean of 1.323 ± 0.45 mm (P = 0.05). Mean control group SDT did not vary significantly over time. A transient improvement of 23% from baseline (P = 0.005) occurred in the dystonia

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group 1 month after injection, which did not positively correlate with changes in physician and patient ratings of torticollis severity. The presumed mechanism of SDT improvement is a modulation of afferent cortical inputs from muscle spindles. © 2007 Movement Disorder Society

Key words: dystonia; botulinum toxin; Johnson–van Boven–Phillips domes; spatial acuity.

Although a disorder of motor control, a number of features suggest that a central sensory processing abnormality exists in adult onset primary torsion dystonia (AOPTD). These include a distortion of sensory cortical somatotopy and impairment of tactile spatial acuity, which appear to be related, as the ability to spatially modulate tactile stimulation of a particular body part is related to the size and organization of its dedicated sensory cortical field. Botulinum toxin type A (BTX-A), an effective therapy for AOPTD, inhibits acetylcholine release from α-motor neurons. However, some features of the clinical response to BTX-A are not fully explained by an exclusive effect at the neuromuscular junction, such as reports of clinical improvement in distant muscles and the phenomenon of clinical response in the absence of noticeable weakness. A CNS response to BTX-A is supported by the transient normalization of the disorganized motor cortical homunculus in patients treated for writer’s cramp and cervical dystonia. The proposed mechanism is an indirect one via muscle spindles and their afferent fibers which, as well as being involved in the spinal stretch reflex, convey proprioceptive information to the sensorimotor cortex. Sensitivity to stretch is mediated by γ-motor efferents which are also susceptible to BTX-A. An effective muscle spindle deaffereentation secondary to chemodenervation of intrafusal fibers may follow BTX-A injection. Cortical remodeling may then occur as a neuroplastic response to afferent manipulation.

Our aim was to look for evidence of a sensory cortical response to BTX-A by assessing spatial acuity at the fingertip following injection for cervical dystonia. The hypothesis was that spatial discrimination threshold (SDT) would transiently improve as a function of sensory cortical remodeling after treatment. We also sought to examine the relationship between changes in spatial acuity and dystonia severity scores.

PATIENTS AND METHODS

Patients

We recruited 20 AOPTD patients (all cervical dystonia) with a mean (± SD) age of 51.1 ± 8.1 years and 18 healthy control patients with a mean age of 46.1 ± 9.8 years; five of the patients were naïve to BTX-A and the remaining 15 had received treatment for at least 1 year. Exclusion criteria for both study groups included evidence of peripheral neuropathy, cognitive impairment, or age greater than 64 years.

Sensory Testing

Assessment of SDTs was performed by the same examiner (RW); an initial baseline examination and then monthly assessments for 3 months. The baseline assessment in the dystonia group was performed just prior to BTX-A injection. SDT was assessed by a grating orientation task using Johnson–van Boven–Phillips domes (Stoelting, Wood Dale, IL), which were applied to the index fingertip bilaterally as previously described. SDT for a given patient was defined as the grating width that would be expected to yield a 75% level of accuracy and was calculated as the average of both hands.

Assessment of Dystonia Severity

In the dystonia group, patients were asked to rate the severity of their dystonia at baseline and each month after BTX-A, using a visual analogue scale (VAS) running from 0 (no symptoms) to 10 (worst symptoms ever experienced). Physician assessment was performed using the motor severity subscale of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), with a minimum score of 0 and a maximum of 35.

Botulinum Toxin Administration

All patients in the dystonia group were treated with botulinum toxin type A (BOTOX, Allergan); mean dose (± SD) was 121 ± 51.3 μu (range, 100–250 μu). All received treatment of one sternocleidomastoid muscle and the contralateral splenius capitis muscle. Some patients also had one or both of levator scapulae and trapezius muscles injected. The Ethics and Medical Research Committee of St. Vincent’s Healthcare Group approved the study protocol.

Statistical Analysis

Two types of analysis were planned a priori: (1) a nonparametric analysis of variance of mean SDTs from baseline within patient and control groups over the four testing sessions and (2) a between groups comparison of change from baseline at each time-point. Within group variance over time was thus analyzed using Friedman tests, with Dunn’s multiple comparisons posttest analysis to be applied if significant overall variance was identified. Between groups comparisons were performed using Mann–Whitney U tests. Significant change from baseline SDT at any given time-point was correlated with change.
in torticollis severity scores, and the Spearman correlation coefficient is quoted in the text.

RESULTS

Sensory Testing

The mean ages of the dystonia group (51 ± 8.1 years) and the control group (46 ± 9.8 years) did not differ significantly. The mean baseline SDT of the 20 patients with cervical dystonia was 1.75 ± 0.76 mm, greater than the control group mean SDT of 1.32 ± 0.45 mm (P = 0.05). For the dystonia group, absolute changes in mean SDT from baseline (% reduction from baseline SDT) after BTX-A were as follows: at 1 month, −0.40 mm (−23.13%); at 2 months, −0.13 mm (−7.42%); and at 3 months, −0.23 mm (−12.12%). The equivalent changes from baseline in the control group were as follows: at 1 month, −0.09 mm (−6.63%); at 2 months, −0.12 mm (−8.89%); and at 3 months, −0.17 mm (−12.68%, see Table 1). There was overall variance of the mean SDT in the dystonia group over the 3-month period (P = 0.005; see Fig. 1). Dunn’s posttest comparison of each monthly change identified the change between the mean preinjection SDT and that performed 1 month later as the only comparison meeting significance. No significant change was identified within the control group SDT values over the study period (P = 0.71). A between group comparison of change from baseline at each testing session found that only the change 1 month after BTX-A differed significantly between the two groups (P = 0.027).

Mean improvement in the SDT 1 month after treatment in the five BTX-A naïve patients was −0.59 mm (−26.42%) and did not differ significantly from the improvement of −0.34 mm (−17.68%) in the 15 patients receiving long-term BTX-A, although the number of treatment naïve patients was probably insufficient to allow a meaningful comparison.

| TABLE 1. Monthly change in spatial discrimination thresholds (SDT). |
| Time from baseline SDT | Mean percentage from baseline SDT (mm) | |
| Treatment Group | Control Group | P value |
| 1 month | −23.13% (−0.40)* | −6.33% (−0.09) | 0.027 |
| 2 months | −7.42% (−0.13) | −8.89% (−0.12) | 0.997 |
| 3 months | −13.12% (−0.23) | −12.68% (−0.17) | 0.405 |
| Friedman test | 0.005 | 0.710 |

* P < 0.05 on Dunn’s Multiple Comparison Test within treatment group (patients with cervical dystonia receiving Botulinum toxin).
Dystonic symptoms can be induced or relieved through afferent manipulation, and thus it is possible that the observed sensory cortical change may be therapeutic. The use of a vibratory stimulus triggered symptoms in patients with writer’s cramp and subsequent lidocaine injection to induce “muscle afferent blockade” reduced dystonic movements temporarily.11 Writer’s cramp improved in patients in whom Braille training was used to induce greater sensory cortical differentiation.12 We were unable to correlate clinical response with SDT change in this study. Chemo-denervation of striatal muscle producing weakness is clearly the primary mechanism of action of BTX-A. However, the primary sensory cortex is only one endpoint for numerous afferent pathways. The putamen, in which somatotopy is also lost in focal dystonia, receives extensive afferent inputs. Thus it is possible that parallel neuroplastic responses take place elsewhere after BTX-A treatment. More sophisticated imaging techniques such as voxel-based morphometry or cerebral activation studies may be required to further investigate the nature and therapeutic significance BTX-A-induced changes in cerebral structure and function.

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**Carotid Intima-Media Thickness in Parkinson’s Disease**

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**Abstract:** There have been a few studies and inconsistent results regarding the coincidence of Parkinson’s disease (PD) and atherosclerotic diseases, such as cerebrovascular disease. Carotid intima-media thickness (IMT) is a known marker for subclinical atherosclerosis. The aim of this study was to investigate the carotid IMT between PD patients and controls. We studied 43 patients with PD and 86 matched controls. The carotid IMT in PD patients was significantly smaller than in controls (0.796 ± 0.179 mm vs. 0.913 ± 0.237 mm, P < 0.05). In multivariate analysis, the carotid IMT was inversely associated with the duration of levodopa medication and the severity of PD. These results suggest that PD patients have a lower risk of atherosclerosis. © 2007 Movement Disorder Society

**Key words:** Parkinson’s disease; intima-media thickness; atherosclerosis

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