Brain Metabolic Changes of Cervical Dystonia with Spinocerebellar Ataxia Type 1 after Botulinum Toxin Therapy

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Abstract

We occasionally observe long-term remission of cervical dystonia after several botulinum toxin treatments. However, botulinum toxin transiently acts on neuromuscular junctions. We herein report that a cervical dystonia patient with spinocerebellar ataxia type 1 could have long-term remission as a result of the depression of hypermetabolism in the bilateral putamen and primary sensorimotor cortex after botulinum toxin therapy. We suggest that botulinum toxin impacts the central nervous system, causing prolonged improvement through the normalization of basal ganglia circuits in addition to its effects at neuromuscular junctions.

Key words: cervical dystonia, spinocerebellar ataxia type 1 (SCA1), botulinum toxin treatment, positron emission tomography (PET), basal ganglia circuits

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Introduction

Cervical dystonia is characterized by abnormal involuntary movements and postures of the head and neck. We occasionally observe long-term remission of cervical dystonia after several botulinum toxin treatments. Although botulinum toxin transiently acts on neuromuscular junctions, it may also cause changes at the central level (1-4). We herein evaluated the changes in brain metabolism in a cervical dystonia patient with spinocerebellar ataxia type 1 (SCA1) before and after botulinum toxin A (BTX-A) therapy using ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET).

Case Report

A 33-year-old man was hospitalized because his head had been pulled completely backwards (Fig. 1A). He felt very mild dysarthria during long conversations at 32 years of age and was staggering mildly when running 2 months before admission. He felt occipital stiffness and his head started to pull backwards 3 weeks before admission. Neurological findings on admission revealed severe fixed retrocollis, very mild slurred speech and ataxic gait, and generalized hyperreflexia and spasticity in four limbs. Retrocollis was improved when a hand was placed behind his head, however, his neck was persistently retroflexed and exacerbated by conversation or walking. Thus, a sensory trick, stereotype, and task specificity were observed among his symptoms. Cervical CT showed no abnormality in the cervical muscles. Brain MRI showed mild atrophy in the cerebellum and pons. A genetic analysis revealed expanded 49 CAG repeats and 2 CAT interruptions in the SCA1 gene (5). Although L-dopa/DCI was not effective for retrocollis, trihexyphenidyl hydrochloride 6 mg/day, diazepam 15 mg/day, tizanidine hydrochloride 3 mg/day, and baclofen 30 mg/day were slightly effective. An initial dose of BTX-A (50 units) was injected into the cervi-
218 MBq FDG, the individuals sat down on a chair under
To minimize the effects of external stimuli during a 40-min
patient, had fasted for at least 4 hours before PET scanning.
and after BTX-A therapy. All subjects, including this pa-
group containing 18 normal subjects and this patient before
PET analysis, and then comparisons were made between the
ness-matched subjects (30.3±7.93 years) were subjected to a
studies (Fig. 2).
and doses of drugs were the same in the two FDG-PET
improvement. Retrocollis remained improved 9 months after
first and second scans was 20 months. We evaluated the
Tsui scores for the first and second PET studies (9 and 1
points, respectively). The patient’s ataxia symptoms were
not altered with the change in dystonia symptoms. The types
and doses of drugs were the same in the two FDG-PET
studies (Fig. 2).
This patient and 18 normal age-, gender-, and handed-
ness-matched subjects (30.3±7.93 years) were subjected to a
PET analysis, and then comparisons were made between the
group containing 18 normal subjects and this patient before
and after BTX-A therapy. All subjects, including this pa-
tient, had fasted for at least 4 hours before PET scanning.
To minimize the effects of external stimuli during a 40-min
FDG uptake period after the intravenous injection of 184-
218 MBq FDG, the individuals sat down on a chair under
resting conditions in a quiet, dimly-lit room with their eyes
closed. PET scans were acquired for 10 minutes under rest-
ing conditions in the supine position. PET scans were taken
in a three-dimensional mode using a PET scanner
(SET2400W, Shimadzu, Kyoto, Japan). Each scan was pre-
processed before the statistical analysis using the SPM5
software program (Wellcome Trust Centre for Neuroimag-
ing, London, UK) running under the MATLAB R2011b
software program (MathWorks, Natick, USA). All PET im-
ages were normalized to the FDG template (modified from a
standard template in SPM2b; http://www.fil.ion.ucl.ac.uk/sp
m/software/spm2b/). A three-dimensional Gaussian filter of
10 mm was used to smooth each image. Global normaliza-
ton was performed using SPM’s “proportional scaling,” and
proportional threshold masking was set at 0.8. Two-sample
t-tests were used for comparisons between the normal con-
trol group and the patient before and after BTX-A therapy.
The resulting set of voxel values for each comparison con-
stituted the statistical parametric map, SPM[t]. The SPM[t]
maps were then transformed to the unit normal distribution,
SPM[z]. For these comparisons, the statistical threshold was
set at family-wise error (FWE) p<0.001. The extent thresh-
old was set to 0 voxels. The study protocol was approved by
the Ethical Committee of Tohoku University Graduate
School of Medicine and a written informed consent was ob-
tained from each subject after a complete description of the

Figure 1. Patient photograph and brain maps showing differences between the normal control
group and the cervical dystonia patient with spinocerebellar ataxia type 1 (SCA1). This patient
showed retrocollis before botulinum toxin A (BTX-A) therapy (A). After several BTX-A therapies,
retrocollis disappeared (D). The areas showed differences in the standardized positron emission to-
mography (PET) data between the cervical dystonia patient with SCA1 and the normal control group.
Before BTX-A therapy, this patient showed hypermetabolism in the bilateral putamen, primary sen-
orimotor cortex, and occipital lobe compared to the group of 18 normal subjects (family-wise error
(FWE) p<0.001) (B, C). Nine months after the last BTX-A therapy, hypermetabolism disappeared,
however, hypermetabolism in the bilateral occipital lobe was more highly visible in this patient com-
pared with the group of 18 normal subjects (FWE p<0.001) (E, F).
Prior to BTX-A therapy, this patient showed hypermetabolism in the bilateral putamen, primary sensorimotor cortex, and occipital lobe compared to the 18 normal subjects (FWE p<0.001) (Fig. 1B, C). After BTX-A therapy, most of the hypermetabolism in the bilateral putamen and primary sensorimotor cortex disappeared, however, hypermetabolism in the bilateral occipital lobe was more highly visible in this patient compared to in the group of 18 normal subjects (FWE p<0.001) (Fig. 1E, F).

Discussion

This SCA1 patient also had cervical dystonia. The frequency of dystonia in SCA1 patients is approximately 0-15% (6-8). Wu et al. reported a SCA1 patient who had marked dystonia, such as retrocollis and blepharospasm, before the onset of cerebellar ataxia (9). Cervical dystonia may be a presenting symptom in some patients with SCA1. A microscopic study showed that the putamen as well as the cerebellum is affected in SCA1 patients (10). In some FDG-PET studies, cervical dystonia showed significant hypermetabolism in the lentiform nucleus (11) or the putamen (12) compared with normal controls. Cervical dystonia in this patient could be improved by the depression of hypermetabolism in the bilateral putamen and primary sensorimotor cortex after BTX-A therapy (Fig. 1). Therefore, this result indicates that functional disturbance of the bilateral putamen and primary sensorimotor cortex is one of the most important factors for the pathogenesis of cervical dystonia with SCA1.

Cervical dystonia in this patient was improved in the long-term after several applications of BTX-A therapy. BTX-A blocks acetylcholine exocytosis for 3-6 months until new neuromuscular junctions are formed by nerve sprouting (13). A long-term therapeutic benefit, such as a continuing improvement over 6 months after BTX-A injections, is difficult to explain at the neuromuscular junction level. BTX-A may act through afferent pathways from the injected site to cause physiological changes at the level of the central nervous system (CNS) (1). In fact, BTX-A applied in the periphery could directly affect central neurons via retrograde transport and transcytosis in rat and mouse (14, 15). Kanovsky et al. reported that precentral P22/N30 component amplitudes, which correspond to the function of the supplementary motor area, were significantly lower in patients with cervical dystonia after BTX-A therapy compared with before treatment (2). Writer’s cramp (3) and blepharospasm (4), as well as cervical dystonia, demonstrated central changes after BTX-A using H215O PET and functional MRI. To the best of our knowledge, however, there have been no reports which have evaluated brain metabolism in cervical dystonia before and after BTX-A therapy. This patient is the first report to demonstrate that hypermetabolism in the putamen and primary sensorimotor cortex in cervical dystonia returns to normal after BTX-A therapy (Fig. 1). CNS pathophysiological changes in cervical dystonia patients during the early stages are still unstable and may be normalized by
BTX-A therapy (13). We speculate that BTX-A has some effects on the CNS level to cause normalization in basal ganglia circuits and prolonged improvement in addition to its effect at the neuromuscular junctions. Further studies with a greater accumulation of patients would clarify the CNS change after BTX-A therapy.

The authors state that they have no Conflict of Interest (COI).

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