Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Failure of Pallidal Deep Brain Stimulation in a Case of Rapid-Onset Dystonia Parkinsonism (DYT12)

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Rapid-onset dystonia parkinsonism (RDP) is a rare disorder characterized by a sudden onset of dystonic and parkinsonian symptoms. It is caused by a loss-of-function mutation in the a3-isoform gene, ATP1A3, which encodes the Na^+/K^+-ATPase α3-subunit (DYT12, OMIM 128235).[1] The pathophysiological mechanism leading to abrupt onset of the extrapyramidal syndrome is unknown, and no treatment is available thus far. In a recent postmortem study, brains of DYT12 patients showed marked neuronal loss and gliosis throughout multiple nuclei of the basal ganglia, brainstem, and cerebellum, compared to non-affected siblings.[2] Here, we report on the results of bilateral pallidal DBS in a young man with sporadic RDP.

A 22-year-old young male of European descent of nonconsanguineous parents with genetically proven heterozygote mutation of the ATP1A3 gene was admitted for further treatment options. He presented with generalized bradykinesia, more pronounced on the upper limbs, dystonic posturing of both hands, severe dysarthrophonia, and sardonic smiling (see Video 1) that had developed over 4 weeks at the age of 17. After the initial period of deterioration that had been preceded by a slight dystonic impairment of the fine motor skills of the right hand for 2 to 3 months, the clinical symptoms have remained stable over a 6-year follow-up period. An alcoholic binge might have been a triggering event for symptom onset.[3]

Neuropsychological testing and psychiatric evaluation were normal. Cranial MRI, cerebrospinal fluid, copper, slit lamp, EEG, and nerve conduction velocity were unremarkable. There was no family history for movement disorders. The patient was born at term with normal development of motor and cognitive milestones. At the ages of 11 and 13, he experienced a seizure, but no further treatment was started. At that time, he also presented with moderate learning problems at school.

Treatment with levodopa (up to 600 mg/day over 2 months) and anticholinergic medication (30 mg/day of trihexyphenidyl over 3–4 months) did not improve motor symptoms. Because of severe motor impairment and after education of the patient and relatives about the experimental character of the procedure, DBS was offered for further treatment. Bilateral DBS electrodes (3389; Medtronic, Minneapolis, MN) were implanted into the internal part of the globus pallidus (GPi). Postoperative MRI confirmed correct placement of the distal two contacts in GPi. Monopolar pallidal stimulation was used with standard parameters (90 μs, 130 Hz, up to 2.8 V) at distal contacts for at least 3 months without significant effect on motor symptoms (preoperative Burke-Fahn-Marsden Dystonia Rating Scale: 28/120; postoperative best setting at 1-year follow-up: 26/120; UPDRS-III preoperative: 25/108; postoperative best score: 23/108). Minor reduction in dystonic symptoms during DBS had no functional significance. Further testing of different stimulation parameters included modulation of stimulation frequency (30, 60, and 180 Hz) and pulse width (210 and 450 μs) as well as bipolar stimulation and stimulation at two contacts per electrode and interleaving stimulation for at least 24 hours each (up to 4 weeks), which revealed no beneficial effects on motor symptoms. Stimulation at proximal contacts (probably located in the external part of the globus pallidus) increased bradykinesia (UPDRS-III OFF-DBS: 24/108; ON-DBS: 28/108) without improvement of dystonia. At 1- and 2-year follow-up, the patient reported no functional improvement and no change of subjective well-being on the 39-item Parkinson's Disease Questionnaire. Eighteen months after implantation of the DBS system, the patient experienced another seizure and anticonvulsant therapy with lamotrigine was started.

We present a case of pallidal DBS in a patient with genetically proven DYT12. Pallidal DBS is an effective therapy for primary dystonia and idiopathic Parkinson's disease. However, the clinical response is far more limited in patients with symptomatic dystonia (such as cerebral palsy) or hereditary neurodegenerative disease with dystonia.[4,5] In our patient, the GPi target was chosen because of dystonic involvement of the arms and hands and its potential benefit on bradykinesia. Two cases

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Keywords: DYT12, rapid-onset dystonia parkinsonism.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 12 September 2014; revised 28 October 2014; accepted 29 October 2014.
Published online 30 December 2014 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12124

doi:10.1002/mdc3.12124

TABLE 1 DYT12 patients with DBS treatment or pallidotomy reported in the literature

Study	Case No.	Age at Symptom Onset (Years)	Age at Surgery (Years)	BFMDRS Motor Score Before/After Surgery	Clinical Notes
Pittock et al.[8]	1	21	23	Not reported	Unilateral pallidotomy with little effect on dystonia of left arm
Deutschländer et al.[6]	2	21	24	50/120 No change post-DBS	Hypomimia, blepharospasm, torticollis, hypophonia, right hemidystonia, generalized hypokinesia; no effect of bilateral Gpi stimulation; DBS electrodes were removed
Kamm et al.[7]	3	12	24	55.5/120 Post-DBS: 49/120	Severe generalized dystonia of all four limbs, moderate dysarthria and slight hypophonia, tongue bradykinesia, and involuntary facial grimacing; modest improvement was observed mostly in the craniocervical region and trunk
Brücke et al. (this study)	4	17	22	28/120 Post-DBS: 26/120	Generalized bradykinesia, more pronounced on the upper limbs, dystonic posturing of both hands, dysarthrophonia; no effect of bilateral Gpi stimulation

with RDP with pallidal DBS have been reported thus far with poor or no response to DBS (see Table 1).[6,7] Similarly, our patient did not benefit from pallidal DBS during the 2-year follow-up period despite multiple programming sessions to optimize the DBS effect. Pittock et al. reported on 1 patient with inherited RDP, who underwent unilateral pallidotomy for dystonia with sudden onset at age 21 and noticed only very little benefit.[8] These observations suggest that pallidotomy and pallidal DBS have very limited effect on motor symptoms in these patients and should be offered with caution. Alternative DBS targets may be considered in the future (e.g., the nucleus subthalamicus or cerebellar thalamic nuclei). However, there is no evidence thus far for successful treatment of bradykinesia in DYT12 with subthalamic DBS. Moreover, bradykinesia in DYT12 has been reported as not responsive to dopaminergic medication and therefore probably has a different pathyophysiological basis as in PD patients. Recent animal data may support targeting cerebellar thalamic nuclei. In a mouse model of stress-induced dystonia resulting from Na^+/K^+-ATPase inhibitor infusion to both the cerebellum and the basal ganglia, dystonic symptoms are significantly reduced by bilateral lesioning of cerebellar output nuclei or the centrolateral nucleus of the thalamus.[9] In this mouse model, the cerebellar neuronal activity showed an increased abnormal high-frequency burst firing rate.[10] The postmortem finding of cell loss in cerebellar nuclei in DYT12 patients further suggests a cerebellar involment in the pathophysiology of RDP.[2]

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

C.B.: 1A, 1B, 1C, 3A
A.H.: 1C
P.H.: 1C, 3B
A.K.: 1A, 3B
G.-H.S.: 1C, 3B
A.A.K.: 1A, 1B, 1C, 3B

Disclosures

Funding Sources and Conflicts of Interest: The project was supported by a grant from the German Research Council (DFG; KFO 247). The authors report no conflicts of interest.

Financial Disclosures for previous 12 months: P.H. declares that he received grants from the German Research Council (DFG, HU941/2-1) and a grant from the German Israel Foundation (1048/2009). A.K. declares that he received grants from the German Research Council and the German Ministry of Education and Research and honoraria for speaking from Allergan, Boehringer Ingelheim, Ipsen Pharma, Lundbeck, Medtronic, Merck, Merz Pharmaceuticals, Orion, and UCB. A.A.K. declares that she received honoraria from Medtronic, St. Jude Medical, Boston Scientific, and Ipsen Pharma and grants from the German Research Council (KFO 247).

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Supporting Information

A video accompanying this article is available in the supporting information here.

Video 1. The first section (hand movements and walking) of the video shows the patient before DBS followed by the section 1 year after pallidal DBS with monopolar stimulation of the two most distal contacts on both sides, which have been shown to lie within the borders of the internal part of the globus pallidus with 2 V, 130 Hz, and 90 μs. No improvement of dystonic symptoms or bradykinesia occurs during DBS. The last section illustrates the dysarthrophonia.

doi:10.1002/mdc3.12124