



Correspondence

Failure of pallidal deep brain stimulation in DYT12-ATP1A3 dystonia

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Dystonia
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We read with interest the paper by Pauls et al. who reported causes of failure for globus pallidus internus (GPi) deep brain stimulation (DBS) in patients with isolated dystonia [1]. Whether patient selection for GPi DBS should be based on dystonia phenomenology or etiology is currently debated. There is evidence that isolated dystonia syndromes respond to DBS and also that mutations in some genes, such as DYT1, are associated with positive outcome. Pauls et al. reviewed patients with a diagnosis of isolated dystonia at time of implant and reported that, in 11 of them (about 50%), the cause of failure was the observation of a phenomenology exceeding isolated dystonia (on average 24 months after implant). In some of these patients an acquired or inherited etiology was established at follow-up. No correlation between genetic etiology and outcome to DBS was proposed.

We recently observed a case that fits with the methodology for patient selection reported by Pauls et al. [1]. This Caucasian man was born full-term and had normal psychomotor development; personal and family histories were unremarkable. His first neurological manifestation was posturing of the right arm at age 12, with later spread of dystonia to the ipsilateral leg and then to the left arm. By age 14, dystonia was generalized, with mild trunk involvement and a severe oromandibular features, slurred speech and swallowing difficulties. He received medical treatment with trihexyphenidyl and benzodiazepines, with limited benefit. Genetic testing did not show mutations in the TOR1A or THAP1 genes; he was hence classified as having isolated generalized dystonia and received a GPi DBS implant at age 28.

We observed him at age 38, 10 years after implant, because of reported inefficacy of DBS. Lead location, stimulation system integrity and brain MRI assessment were unremarkable. We reviewed each DBS contact and tested different combinations of stimulation settings, including monopolar, bipolar and interleaving. Voltage, frequency and pulse width were changed as needed, while the motor and non-motor effects were evaluated. Clinical phenotyping reviewed a generalized isolated dystonia with mild limb

bradykinesia and remarkable asymmetry (video supplement). A genetic study revealed a novel heterozygous L417P mutation in the ATP1A3 gene.

Supplementary video related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2017.09.008>.

The video shows the clinical features of this patient with an ATP1A3 isolated dystonia. A rostrocaudal gradient of dystonia is evident. It is also of note: increased eye blinking, tonic contractions of oro-mandibular muscles and rotation of the head to the right side with ipsilateral shoulder elevation. Dystonia is asymmetric, affecting mainly the right body side, with elbow flexion, wrist extension, a clenched fist, and plantar and lateral flexion of the foot. There are dystonic movements of the left hand. Eye movements are normal and there is no akinesia. Informed consent was obtained before taking this video.

The classical phenotype associated with ATP1A3 mutations is rapid-onset dystonia-parkinsonism, consisting of asymmetric generalized dystonia combined with a non-tremulous parkinsonian syndrome; dystonia usually has a rostrocaudal gradient of severity with prominent bulbar involvement. In this patient, there were a noticeable bulbar involvement and a remarkable asymmetry of dystonia, but no other clinical clues reminiscent of the classical ATP1A3 phenotype. Parkinsonian signs were absent and the patient remained classified as having idiopathic isolated dystonia until recently. A review of all published cases of ATP1A3 reported seven with isolated dystonia, indicating that this is not an uncommon occurrence. Three cases with isolated dystonia had the rather common T613M mutation and four had the much rarer S148del mutation.

There are four published reports of ATP1A3-mutated patients who received pallidal surgery: one had unilateral pallidotomy and three had GPi DBS [2–5]. All failed to improve (Table 1). Also in this patient GPi DBS implant was unsuccessful, raising the question whether ATP1A3 etiology, rather than phenomenology, is the key predictor of response to neurostimulation in these cases.

Phenotype-genotype correlations may not be sufficient for guiding surgical indications, and we therefore suggest that carrying mutations in the ATP1A3 gene may be a negative predictor for GPi DBS, also in cases with isolated dystonia. By contrast, mutations in the DYT1 gene may be positive predictors of outcome, as also mentioned by Pauls et al. [1], who reimplanted a DYT1 patient who had misplaced electrodes and observed significant improvement after repositioning. We are probably facing the new era of “surgicogenomics”, meaning that the genetic status may predict success or failure to stereotactic surgery. Further observations are needed to assess the sensitivity and specificity of genetic mutations

Abbreviations: DBS, deep brain stimulation; GPi, globus pallidus internus.

Table 1

Published cases of unsuccessful pallidal surgery in patients with mutations in the ATP1A3 gene.

Procedure	Age at disease onset	Age at surgery	Phenomenology	Reference
Unilateral pallidotomy	21	23	Multifocal dystonia (no mention of parkinsonism)	[2]
Gpi DBS	21	24	Generalized dystonia and parkinsonism	[3]
Gpi DBS	12	24	Generalized dystonia and parkinsonism	[4]
Gpi DBS	17	22	Multifocal dystonia and parkinsonism	[5]
Gpi DBS	12	29	Isolated generalized dystonia	Present case

in predicting outcome to stereotactic surgery.

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