Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Brittle Biballism-Dystonia in a Pediatric Patient with GNAO1 Mutation Managed Using Pallidal Deep Brain Stimulation

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Early onset movement disorders are a clinically and genetically heterogenous group of disorders. Mutations in GNAO1 were first reported in patients with Ohtahara syndrome and early infantile epileptic encephalopathy 17 (EIEE17).[1,2] GNAO1 (guanine nucleotide-binding protein 1) encodes the α-subunit of a heterotrimeric guanine nucleotide-binding protein (Gαo) which is the most abundant membrane protein in the mammalian central nervous system.[3] The early recognition of worsening extrapyramidal symptoms may facilitate intervention or prevent progression to status dystonicus.[4] A dystonia severity and action plan (DSAP, grades 1–5) can be very useful in assessing the threat of status dystonicus.[4]

We report a case of a 12-year-old boy with GNAO1 mutation who presented with severe biballistic symptomatology with dystonic features (DSAP 3) and required emergency deep brain stimulation (DBS) to avoid life-threatening symptoms. The boy was first examined at the Department of Pediatric Neurology at the age of 2 years. The clinical course is summarized in Table 1. At the age of 12 years, the patient deteriorated after respiratory infection and worsening of extrapyramidal symptomatology with dominating biballism and dystonic features developed with the threat of status dystonicus (Video S1). He experienced almost continuous generalized ballistic movements combined with dystonic postures, which were very painful and limited his normal activity, feeding, or sleep (DSAP 3). The patient was hospitalized in the ICU with the necessity of muscle relaxation. The course of treatment is summarized in Table 1. Taking into consideration the seriousness of this condition, DBS of bilateral globus pallidus internus (DBS-GPi) was performed. The sedative medication was gradually tapered off over the next 14 days and his condition rapidly improved to DSAP 1 (Video S2). Half a year after DBS, motor functions returned to the condition before the brittle biballism-dystonia developed. Whole exome sequencing (WES) identified a heterozygous missense variant in GNAO1 gene *c.625 C > T; p. (Arg209Cys)* previously described in the study by Koy et al. (2018)[5] and considered as pathogenic. The mutation was absent in the patient's parents and considered as de novo.

When pre-status dystonicus persists despite orally active antidystonia drugs and unsuccessful weaning from sedative or anesthetic agents, intrathecal baclofen or deep brain stimulation should be considered.[4] Several case reports and one small series have been published in which DBS was effective in patients with a GNAO1 mutation.[3,5] DBS may be effective due to its general effects in modulating aberrant synchronization in the basal ganglia-thalamo-cortical loops. The effect of DBS in our patient was very fast, with the improvement to DSAP 1 in 14 days. The patient tolerated the stimulation very well; however, only 3 months after initiation he developed generalized epileptic seizure. It is uncertain whether this occurred as a result of DBS (potentially triggered by tapering off the medication during the switching on and adjusting the DBS parameters) or was merely a coincidence in a patient with a history of epilepsy. In any case, stimulation should be increased cautiously and mildly in patients with epilepsy. After the introduction of levetiracetam, no further seizures occurred.

In patients with GNAO1 mutation and severe dystonia, GPi-DBS could be a treatment option with life-saving potential.

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TABLE 1 *Clinical course and therapy*

Age	Clinical characteristics	Neurological and psychological examination	Therapy	Effect	Note
3 months	episodes of apnoe and cyanosis - gastroesophageal reflux	normal	none	spontaneous remission	
2 years	epilepsy - generalised tonic–clonic seizures (GTCSs)		valproic acid	seizure freedom	discontinuation at the age of 10
		severe central hypotonia, developmental delay, speech delay	physiotherapy, speech therapy		
3 years		generalised spasticity with persistent axial hypotonia, dystonic postures, developmental delay, speech delay	physiotherapy, speech therapy		
5 years	severe dystonic storm after thiethylperazin (DSAP 4)		i.v. continuous clonazepam	partial with sedation	
			i.v. continuous midazolam	partial with sedation	
			baclofen p.o.	good effect	
12 years	brittle biballism-dystonia (DSAP 3) after respiratory infection		i.v. continuous clonazepam	partial with sedation	
			i.v. continuous midazolam	partial with sedation	
			i.v. pulses of phenobarbital	partial with sedation	
			i.v. pulses of propofol	very good effect	used with precaution for the risk of propofol infusion syndrome
			tetrabenazine p.o.	worsened	
			i.v. tiapride	no effect	
			i.v. valproic acid	no effect	
			gabapentin p.o.	no effect	
			GPi-DBS[a]	very good effect	initial stimulation: 0.5 V/130 Hz/90usec actual parametres: 3.2 V/130 Hz/120usec
12 years - 3 months after DBS	GTCS		levetiracetam	seizure freedom	

[a]GPi-DBS electrodes position: contacts 0 and 9, with distal contacts of electrodes on the right side: 1.6 mm anteriorly, 3.1 mm caudally and 18.1 mm laterally from mid-commisural point. On the left side: 2.6 mm anteriorly, 3.7 mm caudally and 19.8 mm laterally from mid-commisural point.

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3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

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ZB: 1A, 2B, 2C, 3B
MB: 1C, 2B, 3B
RJ: 1C, 2C, 3B
HO: 1C, 2C, 3B

Disclosures

Ethical Compliance Statement: The study was approved by the Ethical Committee of the institutions concerned and both parents and the patient agreed with the publication after receiving all information relevant to the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Video 1. Clinical condition before DBS implantation. Deterioration into the picture of brittle biballism-dystonia and impending status dystonicus. Almost continuous biballistic movements with dystonic postures that impede normal movement, they are painful and exhaust the patient.

Video 2. Clinical condition of the patient 2 months after DBS implantation. He is able to climb independently on all fours. Motor skills and coordination of movements are improved.

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