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LETTER TO THE EDITOR

GNAO1 mutation presenting as dyskinetic cerebral palsy

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Introduction

GNAO1 mutations, described in early-onset epileptic encephalopathies, have been recently (since 2013) linked to hyperkinetic movement disorders with developmental delay. The growing number of recognized cases allowed for the identification of a genotype-phenotype correlation with diagnostic and prognostic importance. The resistance of the disease to pharmacological management sets deep brain stimulation as a relevant therapeutic option [1].

Case report

The patient is an 18-year-old girl, who was the only child of a healthy non-consanguineous couple. Her family history included two relatives on the father's side with cognitive delay that were wheelchair-bound and suffered premature death (before the 20s). Following an unremarkable pregnancy, she was born at term, after an induced delivery due to metrorrhagia. Her perinatal period was uneventful.

Axial hypotonia and an abnormal posture of the left hand became evident at age of 6 months. Gradually, the patient developed a hyperkinetic movement disorder (HMD), characterized by chorea and dystonia, with some fluctuations, mainly precipitated by infections. Parents recalled one of these episodes, at age of 17 months, when the child had typhoid fever. A progressive developmental delay became apparent, involving gross and fine motor, language, and social skills. Her first steps occurred at the age of 3 years and independent walking at 7, and she was never able to sit without support or meet the language skills for her age (first words at 4, never being able to complete a full sentence). At the age of 7, she was started on a trial of levodopa, which was later interrupted due to gastric intolerance. The neurological examination at the age of 12 described a girl with a moderate intellectual disability and a hyperkinetic movement disorder with axial hypotonia and gait ataxia. The patient remained stable until the age of 14; at that time, she was able to stand and walk briefly, use the toilet unattended, use a communication board, and participate in school activities (video–segment 1).

The fluctuations of the HMD became more exuberant in the following years, with severe episodes of persistent, rapid, irregular choreodystonic movements. During these episodes, she developed a generalized disabling tremor that prevented autonomous feeding and toileting. Dysautonomic features (palpitations, chest pain), anxiety, and oculogyric crises also occurred. The off periods became more frequent, with tremor even at rest and nocturnal worsened (video–segment 2). Then, levodopa was restarted with a dopaminergic agonist leading to a moderate improvement of the HMD and gait (video–segment 3). A trial of clonazepam and trihexyphenidyl was unsuccessful. The patient is currently under evaluation for deep brain stimulation of the globus pallidus internus (GPi-DBS).

Extensive diagnostic workup was performed over the years without positive findings, namely, metabolic screening in serum, CSF, and urine, karyotype analysis,

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microarray, SCA1 and SCA2, and next-generation sequencing (NGS) targeted genetic testing (ABAT, DDC, GCH1, TAF1, TIMM8A, ACTB, ATP1A3, DRD2, GNAL, PLA2G6, SCP2, SLC6A3, TH, TOR1A, ANO3, DBH, FTL, HPCA, PRKRA, SGCE, SPR, THAP1, and TUBB4A). An EEG at 2 years old showed diffuse slow activity. A brain MRI early in the course of the disease displayed a posterior left periventricular hypersignal (Fig. 1). Metabolic screening at age of 17 months detected a mild orotic aciduria, not confirmed in a second test. Neurotransmitter tests found slightly low LCR biopterin levels (10 mmol/L; normal range 12–36).

At 17 years old, whole exome sequencing (WES) analysis identified a mutation in exon 6 of GNAO1 (c.625C>T, p.Arg209Cys). Demonstration of a de novo mutation was confirmed using Sanger sequencing of the target gene on both parents.

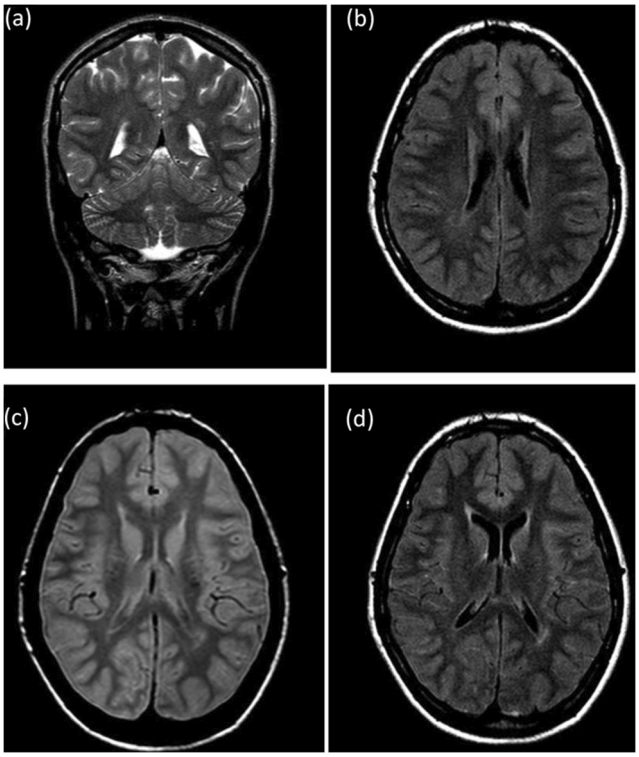

Fig. 1 Brain MRI features. T2-weighted coronal image (**a**). FLAIR-weighted axial image by the level of the corona radiata (**b**). DP-weighted and FLAIR-weighted axial images through the superior plane of the basal ganglia (**c** and **d**). Posterior left periventricular white matter hypersignal can be observed as a non-specific finding (**d**). There is no atrophy of cerebellum or cerebrum (**a**, **b**). Basal ganglia are normal and the ventricles are not enlarged (**a**, **c**)

Discussion

We report a new case of a GNAO1 mutation, in an 18-year-old girl with global development delay, hypotonia, and HMD, from an early age with a long period of stabilization, mimicking a full-term dyskinetic cerebral palsy [2].

The phenotypic spectrum associated with mutations in GNAO1 has revealed a genetic overlap between epileptic encephalopathies, developmental delay/intellectual disability, and HMD. A biochemical analysis of 15 different GNAO1 mutant alleles, conducted by Feng et al., established that gain-of-function (GOF) and normal-function (NF) mutations for inhibition of cAMP are associated with the phenotype of movement disorder, while the loss-of-function (LOF) mutations are related to epileptic encephalopathy phenotype [3]. To our knowledge, seven other cases of GNAO1 mutation (c.625C>T) with normal function have been previously reported, all with movement disorder phenotype (Table 1) [4–8].

Patients with GNAO1 mutations can present with a severe, progressive HMD with prolonged life-threatening exacerbations which are refractory to medication. However, our patient presented with a more indolent course, completely free from epileptic seizures, which was reported in very few other cases. Among patients with movement disorder, tetrabenazine appears to be the most effective drug [1, 9] and GPi-DBS, the most effective treatment [6, 10, 11]. Nevertheless, our patient experienced some benefit with dopaminergic therapy (gait, chorea, and tremor). A positive response to dopaminergic drugs was not common in previously published cases. The identification of GNAO1 mutation as the cause made us consider early GPi-DBS as a valid treatment option for this patient.

Our case highlights the genotype-phenotype correlation which is important for early diagnosis, the variable long-term outcome of the disease, and that the dopamine replacement therapy is a valid therapeutic option in advanced stages of this condition, possibly because of a secondary dopaminergic deficiency in the late disease course.

Authors' roles (1) Research project: A. Conception, B. Organization, C. Execution
(2) Manuscript: A. Writing of the first draft, B. Review and Critique
MJM: 1A, 1B, 1C, 2A
IF: 2B
LL: 2B
LC: 1C, 2B
IA: 2B
MM: 1A, 1B, 2B

Table 1 Clinical features of patients with GNAO1 mutation (c.625C>T)

	Present case	Case 2[4]	Case 3[5]	Case 4[5]	Case 5[6]	Case 6[7]	Case 7[7]	Case 8[8]
Gender	F	F	M	M	F	F	M	F
Current age (years)	18	18	10	5	14	25	17	12
Initial symptoms, onset (months)	Central hypotonia, global DD, 6 months	Central hypotonia, global DD, 7 months	Central hypotonia, global DD, birth	Global DD, complex motor stereotypes of hands/arms, 7 months	Central hypotonia, global DD, 6 months	Central hypotonia, global DD, pyramidal tract signs, 9 months	Central hypotonia, global DD, 6 months	Global DD, 6 months
Type of abnormal movements	Chorea, dystonia, tremor	Chorea, dystonia	Dystonia, choreoathetosis, orofacial dyskinesias	Complex motor stereotypes of hands/arms, dyskinetic motor pattern	Dystonia, choreoathetosis, orofacial dyskinesias, parkinsonism	Chorea, dystonia	Dystonia, choreoathetosis	Chorea, dystonia
First crisis of HMD (years)	14 years	5 years	5 years	No	10 years	6 years	13 years	8 years
ICU admission	No	No	No	No	Yes	Yes	Yes	Yes
Epilepsy, onset (years)	No	Focal onset seizures with impaired awareness, 10 years	GTCS, 6 years	Focal seizures, 2 years	GTCS, 10 years	Yes	GTCS, nocturnal frontal seizures, 10 years	No
Interictal EEG	Diffused low activity	Diffused low activity	Diffused low activity	Bilateral centrotemporal spikes	Normal	NA	NA	Normal
MRI brain	Posterior, left periventricular hypersignal	Atrophy of cerebrum, cerebellum, and brain stem, and thin corpus callosum	Ventricular enlargement, thin corpus callosum, mild hypoplasia of caudate nuclei, hypoplasia of inferior vermis	Normal	Normal	Cortical, subcortical atrophy, bilateral hypointense signals of globus pallidus	Cortical, subcortical atrophy, bilateral hypointense signals of globus pallidus	Temporal atrophy, ventricular enlargement, and mild temporal hypomyelinization

DD development delay, *EEG* electroencephalography, *GTCS* generalized tonic-clonic seizures, *HMD* hyperkinetic movement disorder, *ICU* intensive care unit, *MRI* magnetic resonance imaging, *NA* information not available

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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