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SHORT COMMENTARY

ECHS1 deficiency-associated paroxysmal exercise-induced dyskinesias: case presentation and initial benefit of intervention

Abhimanyu Mahajan[1] · Jules Constantinou[1] · Christos Sidiropoulos[1,2]

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Abstract Paroxysmal exercise-induced dyskinesias (PED) are paroxysmal dyskinesias which manifest as dystonic movements brought on by sustained exercise. ECHS1 deficiency-induced EID was recently described by Olgiati et al. Our patient is an 8-year-old boy, who presented with intermittent episodes of stiffness and contractions affecting the legs which were always brought on by vigorous exertion. They began with curling of the toes and flexion, followed by stiffening of gait. These episodes were asymmetric, uncomfortable and often began in the left leg, often spreading to the right leg. They generally lasted for about 30–40 min. The phenomenology was noted to be dystonic affecting mostly the left leg, with equinus at the ankle and hyperextension at the knee. MRI of the brain showed regions of increased T2 and FLAIR signal and of T1 low signal in the globus pallidus bilaterally with mild diffusion restriction. Using Ambry's ExomeNext™, an integrated exome sequencing assay, the patient was found to be heterozygous for alterations in the ECHS1 gene: missense mutations in c.518C>T (p.A173V) and c.817A>G (p.K273E). After 3 months of treatment with a mitochondrial cocktail, the patient reported that his attacks were somewhat less frequent and less severe. We decided to continue the patient on the cocktail and prescribed clonazepam 0.5 mg 1 tab to be given, as needed, for acute dystonic episodes of severe degree. The missense mutation c.817A>G has never been associated with PED before. Further, we present the first case of ECH1-associated PED with initial symptomatic improvement with a mitochondrial cocktail.

Keywords Paroxysmal dystonia · Exercise-induced dystonia · Genetic dystonia · Movement disorders

Introduction

Paroxysmal exercise-induced dyskinesias (PED) are paroxysmal hyperkinesias which manifest as dystonic or choreathetoid movements brought on by sustained exercise [1, 2]. Mutations in the SLC2A-1 gene have been associated with PED whereas mutations in the PRRT-2 and MR-1 genes are associated with kinesigenic and non-kinesigenic dyskinesias, respectively [3].

Mutations in the ECHS1 (enoyl CoA hydratase, encoding for crotonase) gene typically present with lactic acidosis. In 2015, Ferdinandusse et al. reported the clinical and biochemical characteristics of four patients with ECHS1 mutations [4]. ECHS1 mutation resulting in Leigh syndrome has also been described by Tetreault et al. [5].

ECHS1 deficiency-induced PED were recently described by Olgiati et al. [6].

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✉ Abhimanyu Mahajan
amahaja1@hfhs.org

[1] Department of Neurology, Henry Ford Hospital, 2799 W. Grand Boulevard, K-11, Detroit, MI 48202, USA

[2] Department of Neurology and Ophthalmology, Michigan State University, East Lansing, MI, USA

Case presentation

An 8-year-old boy presented to our clinic with intermittent episodes of stiffness and contractions affecting the legs typically brought on by vigorous exertion, such as swimming or playing basketball.

The episodes, by report, began with curling of the toes and flexion. Then, his gait would become stiff. The dystonic symptoms were asymmetric, painful and often starting in the left leg with overflow to the right leg with inversion of the foot and hyperextension at the knee (Supplementary Video 1). They generally lasted for about 30–40 min.

His birth history was unremarkable and his early milestones were appropriate. There seemed to be features of an attention-deficit hyperactivity disorder—predominantly inattentive.

There was no known family history of dystonia. His father had suspect symptoms of an attentional disorder.

Based on his presentation, the initial differential diagnosis included Dopa-responsive dystonia, GLUT-1 deficiency, early Wilson's disease and mitochondrial disorders.

MRI of the brain showed regions of increased T2 and FLAIR signal and of hypointense T1 signal in the globus pallidus bilaterally with mild diffusion restriction. There was no evidence of abnormal enhancement following IV contrast administration (Fig. 1).

Negative workup included the following: urine organic acid, plasma amino acid, LFTs, serum lactate, serum CPK, lysosomal screening, serum copper, ceruloplasmin and other heavy metal screen. Genetic testing for PANK2 and SLC2A1 was unremarkable.

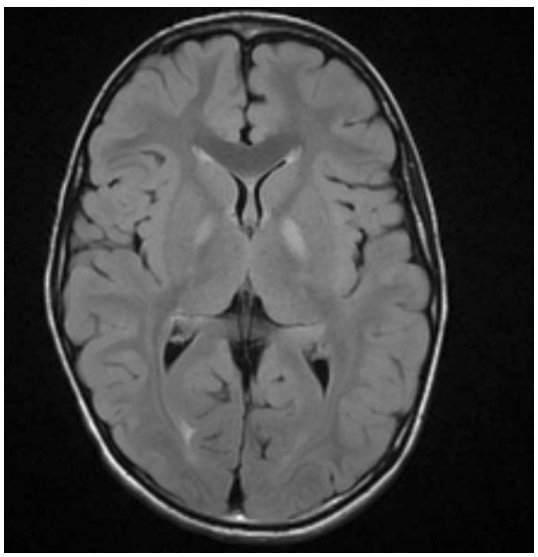

Fig. 1 Axial T2 FLAIR sequence showing hyperintensity in globus pallidus, bilaterally

Using commercially available whole exome sequencing through Ambry Genetics ExomeNext™, an integrated exome sequencing assay, the patient was found to be heterozygous for alterations in the ECHS1 gene: missense mutations in c.518C>T (p.A173V) and c.817A>G (p.K273E).

His mother was found to carry a deleterious mutation of the ECHS1 gene c.817A>G (p.K273E) while his father was carrier for known mutation pathogenic for PED c.518C>T (p.A173V) [4, 6].

Given the diagnosis of ECHS1 mutation-associated PED, we decided to proceed with a mitochondrial cocktail, including thiamine, riboflavin, carnitine, coenzyme Q, vitamin B6 and vitamin C to assess for symptomatic improvement [7].

Three months into treatment, we noted some possible benefits from treatment with the mitochondrial cocktail. The patient reported that his attacks were somewhat less frequent and less severe. We decided to continue the patient on the cocktail and prescribed clonazepam 0.5 mg 1 tab as needed to be given for acute dystonic episodes of severe degree.

Discussion

While the missense mutation in c.518C>T has been described by Olgiati et al., the missense mutation c.817A>G has never been associated with PED before, to the best of our knowledge. Further, we present the first case of ECHS1-associated PED with initial symptomatic improvement with a mitochondrial cocktail, as described above.

Our case provides further corroborative evidence of the benefit of screening for ECHS1 in cases with unexplained PED. Early recognition might lead to early intervention with good initial benefit, as noted in our patient.

Compliance with ethical standards

Conflicts of interest Authors report no conflicts of interest.

Ethical statement This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Funding Authors report no external funding.

Informed consent All persons gave their informed consent prior to their inclusion in the study. Patient provided written consent for the video to be included in the paper. No patient identifiable information was included in the text.

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