Paroxysmal Exercise-Induced Dyskinesia in Siblings due to *ECHS1* Gene Mutation – First Indian Case Report

Sir,

Paroxysmal exercise-induced dyskinesia (PED) is one of the rare forms of paroxysmal disorder when compared to paroxysmal kinesigenic dyskinesia (PKD) and paroxysmal non-kinesigenic dyskinesia (PNKD). It is characterized by recurrent episodes of involuntary movements usually precipitated by sustained walking or running.[1] We hereby describe PED in siblings who had interesting MRI findings, *ECHS1* gene mutation positivity and responded to oral thiamine supplementation. This condition is a newly described entity and worldwide only three cases have been reported since 2016 by Olgiati *et al*. and this is the first Indian case report.

Mast. K, a 7-year-old boy born to non-consanguineous parents by lower segment cesarean section (LSCS) and no significant perinatal events. He had normal developmental milestones. He presented with a history of dystonia induced on exertion from 3 years of age. Initially, it involved the right lower limb and later left lower limb. It was precipitated on playing and running vigorously and lasted for 30 min [Videos 1 and 2]. No history of seizures. On examination, he had normal tone, power, and reflexes.

His younger sibling Mast. T, 5 years of age born of LSCS and normal milestones also had similar dystonia involving both lower limb for the past 1 year. His episodes were short-lasting and recovered in 5 min [Video 3].

On evaluation basic blood investigations like CBC, sugar, urea, creatinine, electrolytes, LFT, thyroid function tests were normal. Serum ceruloplasmin—0.255 g/L (0.2–0.6), Sr. ammonia—50 µmol/L (16–60), and Sr. lactate—34 mg/dL (4.5–19.8). His serum amino acid profile was normal. CSF analysis showed two cells, protein—24.5 mg/dL, glucose—90.6 mg/dL (blood sugar—120 mg/dL). MRI brain showed bilateral globus pallidal hyperintensity [Figure 1a]. His younger sibling had normal serum lactate level—15 mg/dL but the MRI brain showed similar bilateral globus pallidal hyperintensity. [Figure 1b]

This 7-year-old boy and his younger sibling presented with classical PED involving both lower limbs without any associated neurologic symptoms and normal milestones. They were initially tried with levodopa with escalating doses without any benefit. His CSF sugars were within normal limits when compared to blood sugar levels reasonably ruling out GLUT-1 deficiency, though we did not analyze CSF neurotransmitter levels or genetic testing for the same. MRI brain of both the children showed bilateral pallidal

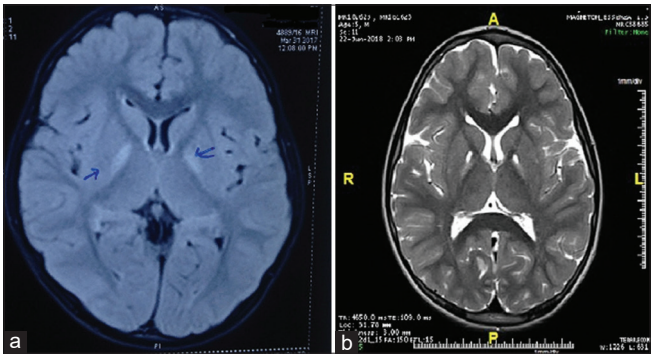

Figure 1: MRI brain showing bilateral pallidal hyperintensity in (a) elder sib—FLAIR. (b) younger sib—T2 sequence

hyperintensity. The clinical picture and imaging findings were strongly suggestive of possible PDH deficiency as the causative factor and hence Tab. thiamine was tried. To our surprise, there was a marked reduction in frequency after starting of thiamine in both the children. PDH deficiency as a cause of PED is a recently described entity.[2,3] Since the patients had bilateral pallidal changes and clinically responding to thiamine PDH deficiency was strongly suspected and samples were sent for genetic testing—whole-exome sequencing.

To our surprise, the results came as *ECHS1* gene mutation for both the sibs—ECHS 1 (ENST 00000368547) two variants were observed Exon 5 c. 518C > T (p.Ala173Val) and exon 1 c. 1A > G (p.Met1?) [Figure 2]. On genetic analysis of parents, the first variant was observed in mother and the second variant was observed in father and both of them were unaffected [Figure 3].

ECHS1 encodes a mitochondrial enzyme involved in the degradation of essential amino acids and fatty acids. Recently, ECHS1 mutations were shown to cause a new severe metabolic disorder presenting as Leigh or Leigh-like syndrome. Simone olgiati[4] described ECHS1 mutation in a sibling where one sib presented with Leigh-like syndrome and other had PED suggesting that this gene mutation can have milder phenotypes also. Later, Mahajan *et al*.[5] have described PED in an 8-year-old boy with *ECHS1* gene mutation and they also showed clinical improvement with mitochondrial cocktail and clonazepam.

The etiologic spectrum of PED is widening. Whenever it has an onset in childhood and not responding to levodopa and GLUT-1 has been ruled out, we have to think of mitochondrial disorder especially with globus pallidal changes. Apart from PDH deficiency, ECHS 1 gene mutations should also be

RESULTS

LIKELY PATHOGENIC VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED

Gene (Transcript) ǂ	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***ECHS1* (-) (ENST00000368547)**	Exon 5	c.518C>T **(p.Ala173Val)**	Heterozygous	Mitochondrial short-chain enoyl-CoA hydratase-1 deficiency	Autosomal recessive	Likely Pathogenic
	Exon 1	c.1A>G **(p.Met1?)**				

Figure 2: Genetic report of elder sib

SEGREGATION OF THE VARIANT(S) IN THE FAMILY MEMBERS

Variations observed in the Index Patient **(K ; Sample Id: 179343)**:

Variant 1: chr10:135180494G>A; (Heterozygous); c.518C>T; p.Ala173Val; (ENST00000368547)
Variant 2: chr10:135186837T>C; (Heterozygous); c.1A>G; p.Met1?; (ENST00000368547)

S. No	Sample ID	Names	Relationship to Index Patient	Variants identified	Mutation status in family member	Read Depth	Clinical condition of family member
1.	179339	K	Mother	Variant 1	Heterozygous (G>A)	50x	Unaffected
				Variant 2	Not present (TT)	61x	
2.	179344	T	Brother	Variant 1	Heterozygous (G>A)	85x	Affected
				Variant 2	Heterozygous (T>C)	85x	
3.	179345	G	Father	Variant 1	Not present (GG)	50x	Unaffected
				Variant 2	Heterozygous (T>C)	55x	

Figure 3: Genetic report of younger sib and parents

considered as they are potentially responsive to thiamine and mitochondrial cocktail.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient father has given his consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Vajramanickam Senthilkumar, Kiruthika Sivaraj[1]

Consultant Pediatric Neurologist and [1]Pediatric Geneticist, Senthil Child Neuro Clinic, Salem, Tamil Nadu, India

Address for correspondence: Dr. Vajramanickam Senthilkumar, 27, Fathima Nagar, Alagapuram pudhur, Salem - 636 016, Tamil Nadu, India.
E-mail: vskneuro1972@gmail.com

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