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 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 0000368547) 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

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

[1] ECHS1

[2,3] Since

[4] Since

[5] Since

[6] Since

[7] Since

[8] Since
Letters to the Editor

Annals of Indian Academy of Neurology • Volume 23 • Issue 6 • November-December 2020

Conflicts of interest
There are no conflicts of interest.

Vajramanickam Senthilkumar, Kiruthika Sivaraj*
Consultant Pediatric Neurologist and 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

REFERENCES
1. Bhatia KP. Paroxysmal dyskinesias. Mov Disord 2011;26:1157-65.
2. Friedman J, Feigenbaum A, Chuang N, Silhavy J, Gleeson J. Pyruvate dehydrogenase complex- E2 deficiency causes paroxysmal exercise induced dyskinesia. Neurology 2017;89:2297-8.
3. Erro R, Sheerin UM, Bhatia KP. Paroxysmal exercise induced dystonia within the phenotypic spectrum of ECHS 1 deficiency. Mov Disord 2014;29:1108-16.
4. Olgiati S, Skorvaneck M, Quadri M. Paroxysmal exercise induced dystonia within the phenotypic spectrum of ECHS 1 deficiency. Mov Disord 2016;31:1041-8.
5. Mahajan A. ECHS 1 deficiency – associated paroxysmal exercise induced dyskinesias: Case presentation and initial benefit of intervention. J Neurol 2017;264:185-7.

Nil.