Variable Phenotypes in Alternating Hemiplegia of Childhood: A Genetically Proven Case Series

Sir

Mutations in the ATP1A2 and 1A3 (Na^+/K^+-ATPase alpha 2/3) genes can present with variable clinical manifestations like movement disorders, seizures, and cognitive deficits. The overall prevalence of this disorder is 1/1,000,000 (1). A thorough understanding of the syndrome is important to avoid fruitless therapeutic interventions.

We describe our experience in the management of 2 boys with epilepsy and paroxysmal dyskinesias.

Patient 1: A 28-year-old boy born to nonconsanguineous parents presented with neonatal onset seizures in the form of a brief period of unresponsiveness for 2–3 min with a frequency of 2–3/month. A change in the seizure semiology was observed from 18 months of age in the form of facial deviation, squinting of eyes with tonic posturing of all four limbs for 2–3 min and post episode dystonia and confusion for 24–48 h with a frequency of 1/month. He was treated with sodium valproate and phenobarbitone. From the age of 5 years, there was also, in addition, an associated hemiparesis that kept alternating with every episode and recovered within 24–48 h. The precipitating factors were anxiety and cold weather. He is developmentally delayed with a current mental age of 10 years. On examination, he was aphasic and wheelchair bound with an ongoing paroxysmal event [Video 1]. He has spastic quadriparesis. With a background history of neonatal onset seizures, developmental delay and alternating hemiparesis with dystonia, alternating hemiplegia of childhood, moyamoya disease, and familial/sporadic hemiplegic migraine were considered. On evaluation, his magnetic resonance imaging (MRI) Brain was normal while electroencephalography (EEG) showed diffuse slowing without epileptiform abnormalities. A 2D Echocardiography showed left ventricular systolic dysfunction with moderate mitral regurgitation. Clinical exome revealed a heterozygous class II variation (c.2440G > A/p. Asp814Asn) in exon 7 of *ATP1A3* gene and both parents tested negative for the same [Figure 1].

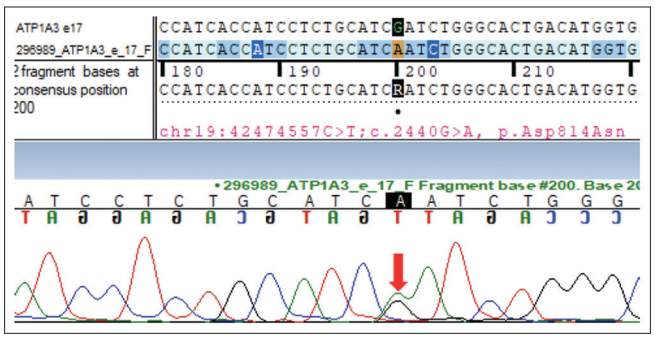

Figure 1: Clinical exome revealed a heterozygous class II variation (c. 2440G > A/p. Asp814Asn) in exon 7 of ATP1A3 gene

He was treated with a combination of flunarizine and topiramate and the current episode frequency is 1/3 months.

Patient 2: An 11-year-old boy born to nonconsanguineous parents had hypoxic ischemic encephalopathy stage 1 at birth. At 9 months of age, he had seizures characterized by cyanosis and myoclonic jerks of the upper limbs and unresponsiveness for 2 min with a frequency of 1–2/month and partially controlled with sodium valproate and clobazam. From 8 years of age, he started to have paroxysmal episodes lasting for 3 days. On the first day of the episode, there are myoclonic jerks followed by clonic movements that would occur every 5–10 min. On the second day, there are frequent episodes of up gaze and unresponsiveness and on the third day, he is encephalopathic and recovers spontaneously in 24 h. He attained walking by 5 years but since past 1.5 years he has recurrent falls and he is currently wheelchair bound. He is cognitively impaired with the developmental quotient of 10%. On examination, he has spastic quadriparesis with dystonia and sluggish deep tendon reflexes. Though the initial history was convincing for epilepsy, the latter episodes were not specific for any seizure variants, leading to suspicion of a channelopathy. On evaluation, his MRI Brain was normal while EEG showed bilateral frontotemporal epileptiform discharges with the paucity of sleep markers [Figure 2]. A Focused exome (a test that combines next-generation sequencing and copy number analysis) revealed a heterozygous missense variation (c.2743T > G/p. Cys915Gly) in exon 20 of *ATP1A2* gene. Insilco analysis by PolyPhen-2 and Mutation Taster implied a potentially deleterious effect for the variant. On treatment with flunarizine, topiramate, and brivaracetam, he has myoclonic jerks and tonic posturing of 4–5 min with a frequency of 1/2 months.

It is challenging to approach a patient with a dual existence of epilepsy and paroxysmal dyskinesias. The differentiating

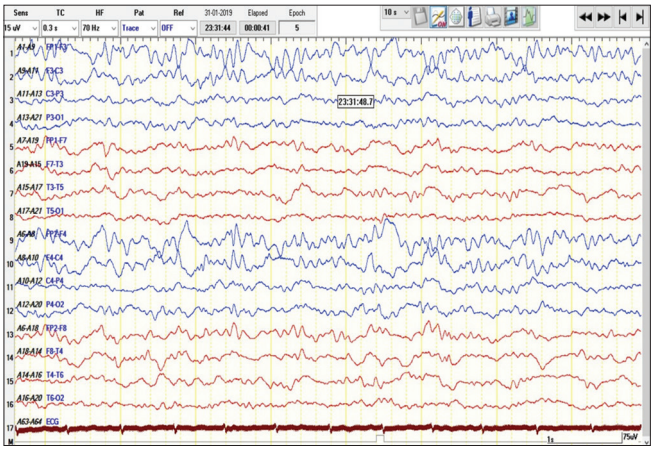

Figure 2: EEG showing bilateral frontal epileptiform abnormalities

Table 1: Distinguishing features between epilepsy and paroxysmal dyskinesia[5]

Features	Epilepsy	Paroxysmal dyskinesia
Duration	Brief duration	Brief, can also be longer lasting for days as seen in AHC.
Awareness	Often with impaired awareness	Usually preserved awareness.
Clinical details	Tonic, clonic, myoclonic, absences, hypomotor events	Abnormal eye movements such as nystagmus/eye deviation ipsilateral to paresis. Dystonia can also be seen (seconds to hours). Myoclonic components are never seen.
Ictal Video EEG	abnormal	Normal.

Table 2: Differential diagnosis for a combined presentation of epilepsy and dyskinesia[5]

Moyamoya disease	Can have alternating hemiplegia and dystonia but abnormal eye movements are not seen during the episode MRI brain. MR angiography will reveal the diagnosis.
Familial Hemiplegic migraine	Occurrence in late childhood, associated with headache, initially thought to have a benign course but overlap with AHC are also seen.
MELAS	Can have paroxysmal hemiplegia, dystonia, epileptic encephalopathy. Lactic acidosis and MRI Brain showing signal abnormalities will help to differentiate.
Channelopathies	Like CACNA1A, SCN8A, etc. can have paroxysmal dyskinesias but not a presentation like AHC. Genetic studies will help in revealing the diagnosis.

features between the two are described in Table 1. A detailed history forms an important basis for evaluation.

ATP1A2/3-related neurological disorders are autosomal dominant caused by heterozygous variations in the genes. Based on the genotypic association, alternating hemiplegia of childhood (AHC) is classified into two variants: AHC type 1 (*ATP1A2)* and AHC Type 2 (*ATP1A3)*. 74% of the cases are related to *ATP1A3*. The clinical spectrum of *ATP1A3* also includes cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) and rapid-onset dystonia-parkinsonism.[1] The prototypic presentation of AHC is not a pure motor weakness but rather a mixture of both pyramidal and extrapyramidal expressions.[2] The differential diagnosis that can be considered in a combined clinical presentation of epilepsy and dyskinesias is described in Table 2.

Timely diagnosis and genetic confirmation can help modifying the clinical course. Drugs like flunarizine and topiramate are found to reduce or even eliminate these paroxysms. Steroids and acetazolamide can also produce improvement.[3] In most situations, this genetic disorder has a poor prognosis with cumulative deficits incapacitating the patient and the paroxysms giving way to a more plateaued or burnt-out disease.[4] Both our patients were diagnosed at an advanced stage of illness but pharmacological interventions and tailoring of antiepileptic drugs did produce substantial improvement. The clinical clues along with an understanding of the genotypic-phenotypic expressions are important in managing this entity.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Algahtani H, Ibrahim B, Shirah B, Aldarmahi A, Abdullah A. More than a decade of misdiagnosis of alternating hemiplegia of childhood with catastrophic outcome. Case Rep Med 2017;2017:5769837.
2. Panagiotakaki E, De Grandis E, Stagnaro M, Heinzen EL, Fons C, Sisodiya S, *et al*. Clinical profile of patients with ATP1A3 mutations in alternating hemiplegia of childhood-a study of 155 patients. Orphanet J Rare Dis 2015;10:123.
3. Stagnaro M, Pisciotta L, Gherzi M, Di Rocco M, Gurrieri F, Parrini E, *et al*. ATP1A3 spectrum disorders: A video-documented history of 7 genetically confirmed early onset cases. Eur J Paediatr Neurol 2018;22:264-71.
4. Wilbur C, Buerki SE, Guella I, Toyota EB, Evans DM, McKenzie MB, *et al*. An infant with epilepsy and recurrent hemiplegia due to compound heterozygous variants in ATP1A2. Pediatr Neurol 2017;75:87-90.
5. Kansagra S, Mikati MA, Vigevano F. Alternating hemiplegia of childhood. Handb Clin Neurol 2013;112:821-6.

Video available on: www.annalsofian.org

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