CASE REPORT

Ethylmalonic Encephalopathy in an Indian Boy

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Background: Ethylmalonic encephalopathy is a rare inborn error of metabolism characterized by neurodevelopmental delay / regression, recurrent petechiae, orthostatic acrocyanosis, and chronic diarrhea. **Case Characteristics:** 4-year-old boy with developmental regression, chronic diarrhea, petechial spots and acrocyanosis. MRI brain showed T2W/FLAIR hyperintensities in bilateral caudate and putamen. Abnormal acyl-carnitine profile and metabolites on urinary GC-MS analysis suggested the diagnosis. **Intervention:** Sequencing of *ETHE1* gene revealed mutations: c.488G>A and c.375+5G>T (novel). **Message:** EE is clinically-recognizable disorder with typical clinical features.

Keywords: *Inborn error of metabolism, Neuroregression, ETHE1 gene.*

Ethylmalonic encephalopathy (EE) is a rare inborn error of metabolism affecting brain, peripheral blood vessels and gastrointestinal tract, with devastating consequences. Caused by recessive mutations in *ETHE1* gene, it is characterized by neurodevelopmental delay follow by regression, recurrent petechiae, orthostatic acrocyanosis, and chronic diarrhea [1]. Due to similar biochemical finding of ethylmalonic aciduria, the disorder is often misdiagnosed as Short-chain acyl CoA dehydrogenase (SCAD) deficiency, which is a less severe IEM, considered only a benign entity [2]. Thus molecular genetic testing is required for confirmation and providing accurate counseling to family and streamlining the management of these children. We present an Indian child of ethylmalonic encephalopathy with mutation confirmation.

CASE REPORT

A 4-year-old boy was referred to the genetic clinic in view of developmental delay followed by regression after two years of age. The boy was born to non-consanguineous couple who also have another healthy child.

He was born at term with birthweight of 3 kg, by vacuum delivery. He did not cry after birth and had required NICU stay for 3-4 days. He was noted to have developmental delay associated with hypotonia in infancy and could speak only a few monosyllables.

After two years of age, parents noted loss of milestones. He was speaking less than before and stopped sitting without support. The hypotonia in infancy gradually gave way to spasticity after 2 years of age which was progressive in nature. There was history of easy bruisability since infancy, not associated with obvious bleeding or joint swelling or bigger blue patches over the skin. There was also a history of chronic diarrhea since infancy – increased frequency of stools as well as loose in consistency, with mucous. There was no history of seizures or of any episode of acute decompensation with lethargy or dehydration requiring hospitalization.

On examination at 4 years of age, the boy was alert. but showed no verbal interaction. Ecchymosis and petechial spots were noted over lower limbs, especially legs. Peripheries seemed cooler than rest of the body. Head circumference- 45 cms (<3rd centile), weight was 15.2 kg (25^{th} centile) and height was 100.4 cm (25^{th} centile for age). Motor nervous system examination revealed peripheral hypertonia with exaggerated deep tendon reflexes including a bilateral ankle clonus. No organomegaly was observed. The fundus examination was normal.

Complete blood counts, coagulation profile, venous plasma lactate and 2D echocardiography were normal. MRI brain showed abnormal hyperintense signals in T2W/FLAIR in bilateral putamen and caudate nuclei.

Subtle hyperintensities were also noted in bilateral peritrigonal regions. Urine organic acids by GCMS (semi-quantitatve method) showed increased level of ethlymalonate, 2-methlysuccinate with slight increase of iso-butyryl glycine and isovalerylglycine, with mild increase in lactate. Glutarate and 3-hydroxy glutarate were not present in the urine sample. A final impression was that of a possibility of ethlymalonic encephalopathy or SCAD deficiency. MS/MS showed increased C4 (3.22nmol/mL; normal <1.0), C5 (1.12 nmol/mL; normal <0.5) and C5DC (0.29 nmol/ml; normal <0.25) – suggesting another differential diagnosis of Multiple Acyl CoA dehydrogenase deficiency (MADD) also known as Glutaric Aciduria type II. Child received a clinical trial of riboflavin (50 mg per day for 2 months) but with no clinical improvement.

Molecular analysis was undertaken to confirm the diagnosis of ethylmalonic encephalopathy. Sequencing of *ETHE1* gene revealed compound heterozygous mutations, c.488G>A (p.Arg163Gln) in exon 4, and c.375+5G>T in intron 3 thus confirming the diagnosis of EE. The parents were studied and noted to harbor one mutation each, thus confirming their carrier status.

On follow up, the child developed an acute decompensation following an episode of fever, deteriorated rapidly with uncompensated shock and metabolic acidosis and succumbed to illness at 4.5 years of age. The parents were counseled about the genetic condition and informed of possibility of prenatal diagnosis, if another pregnancy is planned.

DISCUSSION

Ethylmalonic encephalopathy is a rare, devastating IEM affecting the mitochondrial metabolism with relentless progression and eventual death in first decade of life. Our case showed all classical features of EE and was confirmed by mutation analysis in *ETHE1* gene. Amongst the two mutations detected, p. Arg163Gln is a well-known mutation identified earlier [2,3], the other mutation c.375+5G>T is a novel splice site mutation, predicted to be pathogenic based on software tools analysis.

ETHE1 is a member of the metallo b-lactamase enzyme super family whose crystal structure has been identified in 2015 [4]. It is a mono-iron-binding mitochondrial matrix protein, a sulfide dioxygenase that is involved in the mitochondrial sulfide catabolic pathway [3]. Loss of function of the protein leads to accumulation of sulfide (H2S) causing multitude of clinical problems secondary to inhibition of various biochemical pathways. The damage to intestinal mucosa and endothelia results in diarrhea, episodic petechial purpura, acrocyanosis as well as progressive neurological failure. The ethylmalonic acid accumulation has been postulated to lead to a competitive inhibition of succinate as well as malate transport across mitochondrial membrane, thus disrupting the energy production pathway [5]. Elevation of lactate is noted in many patients, suggesting the disruption of the oxidative phosphory-lation mechanism [5].

Clinically, the disorder may not be difficult to recognize, given the peculiar constellation of symptoms, even though all symptoms may not be present in each patient. Two close differential diagnosis of SCAD deficiency and Multiple Acyl CoA dehydrogenase deficiency exist where ethylmalonate is significantly elevated. Both these disorders are quite distinct in the absence of non-neurological features such as petechiae/ easy bruisability showing vascular involvement and chronic diarrhea [1]. Another disorder, glutaric aciduria type 1 may also present with neuroregression, but our case lacked the typical history (trigger induced regression), clinical features (dystonia/movement disorder) and brain MRI 'batwing' appearance. The disorder does not have any established treatment. Dietary restriction of protein (especially isoleucine) has not proven beneficial [6]. A combination of metronidazole and N-acetylcyteine has been used in patients. The drugs help in reducing sulphide load in intestines secondary to bacterial inhibition (Metronidazole) and activation of sulfide-buffering through Glutathione (N-acetylcysteine) [7]. Experiments in mouse models of EE with AAV-associated gene therapy have provided a proof of concept of efficacy of gene therapy giving a hope for the future [8].

The disorder is autosomal recessive and carries a 25% risk of recurrence in future siblings in a family. The diagnostic confirmation by genetic molecular studies has clear benefit, at least for the family where rational counseling can be provided leading to prevention of recurrence in family through timely prenatal diagnosis.

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