Meta Gene 13 (2017) 115–118

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Ethylmalonic encephalopathy masquerading as malabsorption syndrome - A case report

Amit Kumar Satapathy[a], Alec Correa[a], Madhulika Kabra[a], Sabrina Eichler[c], Arndt Rolfs[d], Manisha Jana[b], Neerja Gupta[a,*]

[a] Division of Genetics, Department of Pediatrics, All India Institute of Medical Science, New Delhi, India
[b] Department of Radiology, All India Institute of Medical Science, New Delhi, India
[c] Centogene AG, The rare disease Company, Rostock, Germany
[d] Albrecht Kossel Institute for Neuroregeneration, University of Rostock, Rostock, Germany

ARTICLE INFO

Keywords:
EME
ETHE1
Ethylmalonic aciduria
Mitochondrial disorder

ABSTRACT

Ethylmalonic encephalopathy (EME) is a rare autosomal recessive inherited metabolic disease characterized by developmental delay, ecchymotic patches, and acrocyanosis with chronic diarrhea. We report a first case of EME from India who primarily presented with chronic diarrhea since early infancy and developmental delay. Mutation analysis of *ETHE1* showed presence of a previously reported homozygous mutation in exon 4 confirming the diagnosis. She was started on riboflavin, CoQ, carnitine, metronidazole and *N*-acetyl cysteine with improvement in diarrhea but neurological features continue to progress. Prenatal diagnosis was performed in the next pregnancy. Though, EME is a devastating inherited metabolic disorder with mortality usually in early infancy, here we have reported a case presented as late as at 4 years. A high index of suspicion followed by specific molecular diagnosis not only ends the diagnostic odyssey but also ensures prenatal diagnosis in the future pregnancies.

1. Introduction

Ethylmalonic encephalopathy (EME) (MIM 602473) is a rare inherited metabolic disease due to the defects in *ETHE1*, the gene encoding mitochondrial matrix protein leading to accumulation of toxic metabolites resulting in clinical symptoms. It is characterized by developmental delay and regression, chronic diarrhea, ecchymotic patches and orthostatic acrocyanosis due to involvement of brain, peripheral vessels and gastrointestinal tract. It has typical biochemical findings of urinary ethylmalonic aciduria (EMA) with elevated plasma lactate levels (Burlina et al., 1991). Ethylmalonic acidurias can also be seen either in multiple acyl CoA dehydrogenase deficiency or in short chain acyl CoA dehydrogenase deficiency. Majority of the patients present in first year of life with relentless downhill course and die during infancy or early childhood. Worldwide, less than 100 cases with 35 different mutations in ETHE1 gene have been reported (Kılıç et al., 2017). We report molecularly proven Indian patient with EME where diagnosis was delayed till the age of four years due to predominant symptom of chronic diarrhea.

2. Case presentation

Four years old girl born to third degree consanguineous marriage without any adverse perinatal events, presented with recurrent episodes of loose stool since 6 months of age with developmental delay. There was history of petechial rashes over extremities which appeared on mild pressure. There were no other bleeding manifestations. Developmental age corresponded to 1 year at presentation. Child had significant history of three episodes of pneumonia in first year of life for which she received oral antibiotics. There was no history of lethargy, seizures, or sibling death. On examination child was severely malnourished with weight of 7.5 kg (< − 3SD), height of 81 cm (< − 3SD) and head circumference 42.5 cm (< − 3SD). Child had subtle dysmorphism with broad nasal bridge and epicanthic folds. Neurological examination revealed increased tone in both upper and lower limbs with exaggerated reflexes, positive Babinski sign, without any cranial nerve and meningeal involvement. Child had petechial lesions over the upper limb which appears on gentle pressure by inflated blood pressure cuff (Fig. 1). Orthostatic acrocyanosis was not observed.

Routine hemogram showed presence of microcytic hypochromic anaemia with normal platelet count and coagulation profile. Blood gas

* Corresponding author at: Division of Genetics, Department of Pediatrics, AIIMS, New Delhi 110029, India.
E-mail address: neerja17aiims@gmail.com (N. Gupta).

http://dx.doi.org/10.1016/j.mgene.2017.05.008
Received 4 January 2017; Received in revised form 21 May 2017; Accepted 31 May 2017
Available online 01 June 2017

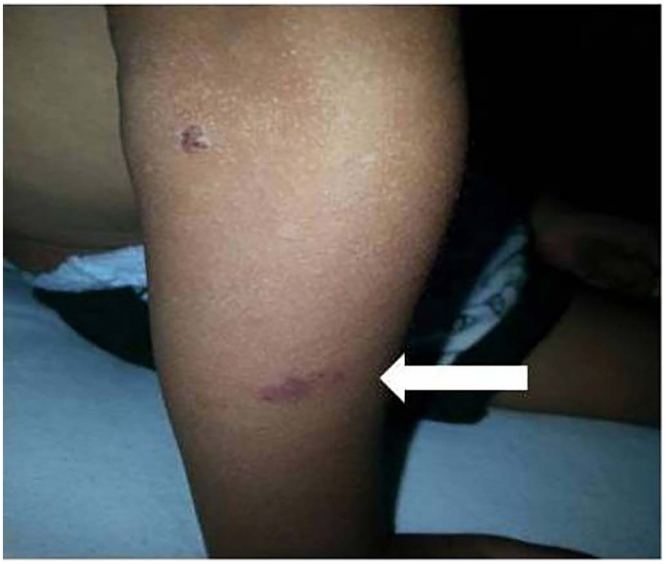

Fig. 1. Ecchymotic spot over the right forearm (white arrow).

showed metabolic acidosis with persistent hyper lactatemia. Evaluation for chronic diarrhea was noncontributory. Celiac serology, retrovirus serology and immunoglobulin profile were normal. Upper GI endoscopy and duodenal biopsy were also normal. Neuroimaging showed bilateral basal ganglia hyperintensity in T2 weighted images along with white matter changes suggestive of mitochondrial disease (Fig. 2a).Tandem mass spectrometry (TMS) did not show any elevated levels of C4–C5 acylcarnitines, Gas chromatography mass spectrometry (GCMS) revealed increased excretion of ethylmalonic acid and neutral amino acids (alanine and glycine) (Fig. 2b).

Presence of chronic diarrhea, characteristic petechial spots appearing on pressure application and characteristic MRI findings a possibility of EME was kept. Mutation analysis of *ETHE1* in child showed a previously reported homozygous pathogenic variant c.488G > A (p.Arg163Gln) (Fig. 3) in exon 4 (Tiranti et al., 2004). Both the parents were heterozygous for the same variation (Fig. 3). This pathogenic variant is reported in the Exome Aggregation Consortium with a frequency of 0.000033, i.e. in 4 among 121,342 alleles. The only case reported previously from India had mutation c.488G > A and c.375 + 5G > T (Bijarnia-Mahay et al., 2016).

Child was started on megavitamin cocktail for mitochondrial disease that included thiamine (100 mg/day), carnitine (100 mg/kg/day), Co Q (10 mg/kg/day), Riboflavin (10 mg/kg/day) and vitamin E (200 IU/day) along with oral metronidazole (30 mg/kg/day) and N acetyl cysteine (20 mg/kg/day) (Kılıç et al., 2017; Yoon et al., 2001; Papetti et al., 2015; Ozand et al., 1994). There was no significant clinical improvement except for decrease in stool frequency. Child died at the age of 6 years due to respiratory failure. We were able to offer prenatal testing in the next pregnancy at 11 weeks and fetus was found to be unaffected.

3. Discussion

Ethylmalonic encephalopathy (EME) is a rare metabolic disease inherited in an autosomal recessive manner first described in 1991 (Burlina et al., 1991). The real incidence of this disorder may be underestimated because of close resemblance of clinical and laboratory features to other common disorders. Because of severity of disease at initial presentation at infancy, most of the children die within first year of life. Though there are few cases which survive beyond first year of life described in literature (Nowaczyk et al., 1998). Children usually present with developmental delay, regression, ecchymotic patches, acrocyanosis and chronic diarrhea. Neurological manifestations usually begin in early infancy and usually progressive in nature causing early death though there are exceptions. Children present with intermittent petechiae with ecchymotic patches over extremities secondary to application of pressure which is characteristic. Due to such bleeding manifestation at initial presentation, a bleeding disorder is suspected (Garcia-Silva et al., 1997; Pavlou et al., 2013). There may be associated cardiac involvement.

MRI findings though not specific for EME but most of the time there is increased hyper intensity in T2 weighted image in the basal ganglia, caudate and putamen region suggestive of mitochondrial disease. Some time associated CNS malformations in form of tethered cord and Chiari malformation has been described in literature (Heberle et al., 2006). Our patient also had increased hyperintensities in bilateral basal ganglia in the T2 weighted images suggestive of mitochondrial disease, however not specific.

Plasma lactate levels are persistently elevated in this disorder. Elevated levels of ethylmalonic and methylsuccinic aciduria are usually documented in urinary GCMS. Short-chain acylCoA dehydrogenase deficiency and glutaric acidemia type 2 also have elevated levels of urinary ethylmalonic acid but lack the classical presentations as ethylmalonic encephalopathy (Tiranti et al., 2004).

Mutation in the *ETHE1 gene* located on chromosome 19q13, which encodes mitochondrial thioesterase, has been identified in EME (Tiranti et al., 2004). It has been proposed that the mitochondrial matrix esterase help in detoxification of hydrogen sulfide (H_2S) in tissue, accumulation of which leads to respiratory chain failure. More than 30 different mutations have been identified in *ETHE1*, most of which are either frame shift mutation or splicing defect with few being either deletion or missense mutations. Tiranti et al. (Tiranti et al., 2004) has analyzed 29 patients with typical features of EME characterized by presence of:(a) early onset progressive encephalopathy with symmetrical lesions in the basal ganglia and brainstem; (b) vasculopathic petechiae and orthostatic acrocyanosis; (c) chronic diarrhea; and (d) ethylmalonic aciduria. Missense, splice site and frame shift, mutations of ETHE1 were detected in all the typical EME cases whereas none had been identified in cases with progressive encephalopathy and elevated ethylmalonic aciduria without typical features (Tiranti et al., 2006).

Our patient had all the typical features of EME earlier described in literature including the vascular manifestation. Mutation analysis detected a previously reported homozygous pathogenic variant in the exon 4 and both the parents were carrier (Tiranti et al., 2004).

Patients with EME have been treated with L-carnitine, Q10 and riboflavin as well as other vitamins to improve metabolism though have variable response. As failure of detoxification of hydrogen sulfide is supposed to be the main culprit for symptoms of EME, beneficial role of metronidazole has been established in decreasing production of endogenous H_2S by inhibiting the gut flora (Viscomi et al., 2010). Our patient though symptomatic from early infancy but diagnosed at 4 years of age. She was started on mitochondrial megavitamin cocktail along with metronidazole and *N*-acetyl cysteine but had only minimal improvement on initial follow up. However, she succumbed following respiratory tract infection at the age of 6 years. Identification of her mutation led to the confirmation of diagnosis and enabled successful prenatal diagnosis in the next pregnancy.

4. Conclusion

EME has multisystem involvement with specific key peripheral vascular signs which should be carefully looked for in any child presenting with chronic diarrhea and developmental delay. A specific molecular diagnosis not only ends diagnostic odyssey but also ensures prenatal diagnosis in the future pregnancies.

Funding

This research did not receive any specific grant from funding