Case Series of Ethylmalonic Encephalopathy from Southern India

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Abstract

Ethylmalonic encephalopathy is a rare neurometabolic disorder with central nervous system involvement and vasculopathy. It is presented in infancy with developmental delay, acrocyanosis, petechiae, chronic diarrhea, and early death. This was a retrospective study of confirmed cases of ethylmalonic aciduria from a tertiary care hospital over a period of 5 years from January 2015 to December 2020. Case details including analysis of clinical history, investigations, and outcomes are presented. Of six cases, male-to-female ratio was 4:2. Mean age of presentation was 35.5 months (range: 14–83 months). Consanguinity, global developmental delay, failure to thrive, skin rashes, microcephaly, hypotonia, and exaggerated deep tendon reflexes were observed in all cases. Chronic diarrhea was presented in five cases. The serum levels of C4 carnitine and urinary levels of ethylmalonic acid were increased in all cases. Magnetic resonance imaging (MRI) of the brain showed heterogenous bilateral symmetrical changes in the basal ganglia in five cases, and in one case, MRI could not be done. Genetic testing in two cases showed a homozygous variant in *ETHE1* gene. Four children died, while the other two cases showed a decreased in recurrent encephalopathies and diarrhea after starting metronidazole. All children had global developmental delay, failure to thrive, skin rashes, central hypotonia, increased C4 carnitine levels in the serum, and increased ethylmalonic acid in the urine. Chronic diarrhea, acrocyanosis, and basal ganglia change in the MRI of the brain also give important clues for diagnosis. Metronidazole is useful in preventing recurrent episodes of encephalopathy.

Keywords
- ethylmalonic aciduria
- purpura
- chronic diarrhea
- petechiae
- *ETHE1* gene

Introduction

Ethylmalonic encephalopathy (EE) is a rare autosomal recessive metabolic disorder affecting the brain, peripheral blood vessels, and gastrointestinal tract, with devastating outcomes. It presents with neurodevelopmental delay followed by regression, petechiae, orthostatic acrocyanosis, and chronic diarrhea.[1] It was first described in Italy, with

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causative gene being *ETHE1*.[1] Commonly described neurological features of EE also included hypotonia, spasticity, ataxia, dysarthria, chorea, athetosis, dystonia, seizures, myoclonic jerks, and epileptic spasms. There are reports of EE without the presence of classical symptoms, such as acrocyanosis or chronic diarrhea.[2] Variable neurologic phenotypes exist even among siblings.[3] Seizures including status epilepticus and generalized tonic–clonic seizures are observed commonly especially during metabolic decompensation,[2,3] and there are reports of focal seizures and absence seizures, but rarely epileptic spasms, in EE patients.[4,5]

Variable neuroradiologic findings described in EE are T2-hyperintensities in the basal ganglia, dentate nuclei of the cerebellum, periventricular white matter and vasculopathy on brain magnetic resonance imaging (MRI), and cavitation on computed tomography (CT) imaging.[6–8] Acute cerebral events such as metabolic stroke or stroke-like episodes and associated neuroradiological findings of stroke-like lesions are similar to other mitochondrial disorders including mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Kearns–Sayre syndrome, myoclonic epilepsy with ragged red fibers, Polymerase Gamma (POLG)-related disorders, and various other genetic causes such as Leigh's and Leigh-like syndromes.[9–12]

Lim et al[13] reported that two-thirds of the patients lacked classical features of EE such as acrocyanosis, petechiae, or chronic diarrhea, although they presented with abnormal biochemical and neurologic findings. The authors also reported a newer phenotype of acute changes in mental status followed by developmental regression, suggestive of stroke-like episodes with neuroradiologic findings consistent with stroke-like lesions. The reported diffusion restriction pattern of increased signal in diffusion-weighted imaging and decreased apparent diffusion coefficient are consistent with cytotoxic edema, frequently seen in strokes. They postulated that abnormal function in aerobic energy production and mitochondrial damage acutely worsens with increased demand in the setting of metabolic stress, leading to the development of stroke-like episodes in EE.

The causative gene is located on chromosome 19 and encodes a member of the metallo-β-lactamase family containing iron protein, which carries out mitochondrial sulfur dioxygenase pathway.[1,6] The impaired function of sulfur dioxygenase leads to accumulation of hydrogen sulfide, which affects the normal functioning of mitochondrial respiratory chain. As the source of hydrogen sulfide seems to be the bacterial flora of the intestine, use of metronidazole for eradication of bacteria, glutathione to act as intracellular buffer for hydrogen sulfide, and *N*-acetylcysteine (NAC), which serves to improve the permeability of glutathione, have been tried in EE, with marginal success. The aim of dietary management is to restrict the production of hydrogen sulfide from its amino acid precursors such as methionine and cysteine. Restricting the sources, rather than reducing the toxic effects of accumulated sulfides, has shown clinical and biochemical improvement in the form of regaining developmental milestones and reducing acylcarnitine levels, respectively.[14]

There is a promising treatment for EE with liver transplantation, as transplanted liver restores the sulfur dioxygenase activity and helps in clearing the accumulated metabolites, thereby causing clinical and biochemical improvement. Further, liver-directed gene therapy that corrects the defective protein has shown improvement in clinical and biochemical parameters in EE, same as liver transplantation because the liver serves as a filter for the toxic metabolites produced by the intestinal bacteria.[6] The outcome of liver transplant for EE had shown biochemical and neurologic improvement after liver transplant.[6] Lim et al[13] reported overall psychomotor and metabolic improvement after orthotopic liver transplantation. They proposed that the presence of stroke-like episodes can be used as a measure of severity of the disease and might be consideration in the timing of intervention options such as liver transplantation. However, liver transplantation may not completely protect patients from acute decompensation. Dietary and medical therapy helps buy time for liver transplantation, as suggested by Boyer et al.[14]

The prevalence of EE is unknown. There are very few cases reported from the Indian subcontinent on this condition. This condition also requires early diagnosis to prevent unwarranted therapy for management of chronic diarrhea, such as antibiotics, and to start treatment to prevent further episodes of recurrent encephalopathies. Hence, we describe clinical, biochemical, radiological, and genetic findings of six Indian patients with EE.

Methods

This is a retrospective chart review over a period of 5 years from January 2015 to December 2020. All children who met clinical, biochemical, and radiological criteria were included.[15] The details of clinical, biochemical, neuroimaging, and genetic data were collected. Investigations such as complete hemogram, liver function, renal function, serum ammonia, serum lactate, blood sugars, tandem mass spectrometry (TMS), gas chromatography–mass spectrometry (GC-MS), and arterial blood gas analysis were collected in all cases. Exome sequencing was done in two cases and variants were obtained in *ETHE1* gene in both cases. Statistical analysis was done by using SPSS software version 21. Informed consent was obtained from parents of all participants. Approval from institutional ethics committee was obtained.

Results

Of the six cases, male-to-female ratio was 4:2. All were born of consanguineous marriage. The mean age of presentation was 35.5 months. ►**Table 1** shows a summary of clinical and laboratory findings, treatment, and outcome of cases. ►**Fig. 1a, b** shows ecchymosis and purpuric lesion over the trunk and face. All patients were managed with restriction of methionine and cysteine in the diet to reduce the production of hydrogen sulfide, metronidazole, and NAC.

Case 1

The patient was born after an uneventful pregnancy and normal delivery. She had delayed attainment of milestones and in the last 15 months she had regressed. She presented to

Table 1 Clinical and laboratory profiles of study populations

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at first visit (mo)	83	16	14	26	16	58
Sex	F	F	M	M	M	M
GDD/regression	+	+	+	+	+	+
Family history	+	+	+	+	−	−
Consanguinity	+	+	+	+	+	+
Petechiae/purpura	+	+	+	+	+	+
Chronic diarrhea	+	+	+	+	+	−
Recurrent encephalopathy	+	−	+	−	+	+
Acrocyanosis	−	−	−	−	+	+
Weight (kg)	18	8	6.5	8	7	12
WHO z-score for weight	25–50th P[a]	0 to −2 z	< −3 z	< −3 z	< −3 z	−3 z
Length (cm)	112	68	67	73	68	101
WHO z-score for length	10–25th P[a]	< −3 z	< −3 z	< −3 z	< −3	0 to −2 z
Head circumference (cm)	46	42	42	43	42	43
WHO z-score for head	< −3 z	< −3 z	< −3 z	< −3 z	< −3 z	< −3 z
Hypotonia	+	+	−	+	+	+
Hypertonia	−	−	+	−	−	−
Exaggerated DTR	+	+	+	+	+	+
Dystonia	+	−	+	−	+	−
Seizures	−	+	−	−	+	+
Feeding difficulty	+	−	+	+	+	+
ABG anion gap acidosis (normal: 8–16 mEq/L)	22	15	13	23	13	12
Arterial lactate (normal: 10–20 mg/dL)	45	50	16	46	53	17
Serum butyrylcarnitine C4 (normal: 0–1.30 μmol/L)	1.4	1.5	1.35	1.6	1.35	1.6
Urinary EMA (normal: <8.5 mmol/mol creatinine)	45	35	45	ND	23	44
MRI brain: patchy T2 hyperintensities						
Caudate and putamen	+	+	+	+	+	+
Thalamus	+	+	+	+	+	+
Dorsal pons and dental nuclei	−	−	−	−	−	+
Pathogenic variant in *ETHE1* gene	ND	ND	ND	ND	Exon-5 c.548T > C p. Phe183Ser	Exon 4. c.487C > G P. Arg163Gly
Metronidazole 20 mg/kg/day twice daily on alternate week	−	+	−	+	+	+
Diet: low methionine and cysteine	+	+	+	+	+	+
NAC 100 mg/kg/day twice daily	−	+	−	+	+	+
Outcome	Died	Died	Died	Died	GDD/FTT	GDD/FTT

Abbreviations: ABG, arterial blood gas; DTR, deep tendon reflexes; EMA, ethylmalonic acid; F, female; FTT, failure to thrive; GDD, global developmental delay; M, male; MRI, magnetic resonance imaging; NAC, *N*-acetylcysteine; ND, not done; P, percentile; +, yes; −, no.
[a]For case 1, weight and length are in percentile as per the Indian Academy of Pediatrics standards and for the others cases they are in WHO z-score.

us at the age of 7 years with fever for 1 week, mucoid diarrhea, purpuric rashes over body, and encephalopathy. She was mechanically ventilated, but she succumbed on day 7 of her illness. On examination, she had microcephaly, failure to thrive, generalized petechiae and purpuric rashes mainly over the trunk, and hypotonia with exaggerated reflexes. Investigations revealed elevated lactate with normal ammonia. Neuroimaging was not done because of poor

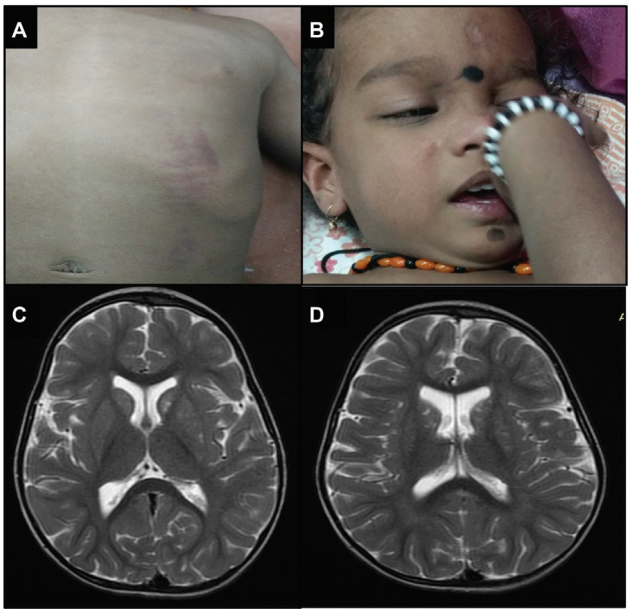

Fig. 1 (**A**,**B**) Clinical photograph showing ecchymosis and purpuric lesion over the trunk and faces. (**C**,**D**) MRI of the brain showing symmetrical heterogenous hyperintensities in the caudate and putamen.

general condition. Urinary amino acid screen showed elevation of ethyl malonate. Given the clinical picture and investigations, a diagnosis of EE was made. Genetics was not performed due to financial constraints.

Case 2

She is the younger sister of case 1. She had a normal delivery with uneventful perinatal period. She presented at the age of 16 months with developmental delay. There was no history of chronic diarrhea; however, she had intermittent petechiae and purpura, which resolved on their own. On examination, she had microcephaly, failure to thrive, and hypotonia with exaggerated reflexes and extensor plantar response. Investigations showed serum elevated lactate. Neuroimaging revealed patchy T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensity in the caudate and putamen, posterior aspect of midbrain, and cerebellum. Changes in cerebral white matter were also seen bilaterally. Urinary amino acid profile showed elevation of ethyl malonate and plasma acylcarnitine profile showed increased C4 carnitine (4.6; normal $<$ 1 nmol/mL). Based on these features, a diagnosis of EE was made, and treatment of the child was started with metronidazole and NAC, but later the child succumbed to illness at 36 months of age.

Case 3

The patient was born at term after an uneventful pregnancy. He had mild delay in attainment of milestones and developed persistent diarrhea from the fourth month onward. Gradually, global delay and hypotonia became evident. Similar complaints were noted in the patient's elder sister and in a paternal aunt. There was a history of seizures triggered by fever. At 14 months of age, he had microcephaly and failure to thrive. He had good eye contact but no stranger anxiety. There were petechiae over the trunk, hypotonia with mild head lag, brisk reflexes, and extensor plantar response. Serum lactate and ammonia were normal. MRI of the brain revealed T2 and FLAIR hyperintensity in the bilateral caudate, putamen, and thalamus. Plasma acylcarnitine profile showed increased C4 carnitine (4.6; normal $<$ 1 nmol/mL). Urinary amino acid profile showed elevation of ethyl malonate. After 2 months of first visit, the child died after an event of fever, seizures, and encephalopathy.

Case 4

This is a 4-month-old infant with normal birth history who developed persistent diarrhea from the fourth month of age. Gradually, global delay and hypotonia became evident. His elder sister died at 2 years of age with global delay and encephalopathy (not evaluated). On his first visit to our department at 26 months of age, he had microcephaly and failure to thrive. During hospital stay, self-resolving and remitting nature of petechiae over the trunk at different site was noted. The child was hypotonic with brisk reflexes and extensor plantar response. On investigation, serum lactate was elevated. Neuroimaging revealed T2 and FLAIR hyperintensity in the bilateral caudate and putamen. Plasma acylcarnitine and amino acid profile showed elevated C4 and C5 acylcarnitine esters and plasma thiosulfate. Urinary amino acid profile showed elevation of ethyl malonate, 2-methylsuccinate, and isobutyrylglycine. The child was started with metronidazole and NAC. The child succumbed to illness due to encephalopathy at around 40 months of age.

Case 5

This child, born at term with normal birth history, was presented at 15 months of age with diarrhea, which is persisting. Gradually, global delay and hypotonia became evident. On the first visit to our department at 16 months of age, he had microcephaly, failure to thrive, and petechiae over the trunk. The child was hypotonic with brisk reflexes and extensor plantar response. On investigation, serum lactate was elevated. Neuroimaging revealed T2 and FLAIR hyperintensity in the bilateral caudate and putamen (►**Fig. 1C, 1D**). Plasma acylcarnitine and amino acid profile showed elevated C4 and C5 acylcarnitine esters and plasma thiosulfate. Urinary amino acid profile showed elevation of ethyl malonate. Next-generation sequencing revealed a novel homozygous variant p. Phe183Ser in exon 5 of *ETHE1* gene. Mutation was validated by Sanger sequencing and carrier status of parents was positive. The child was started with metronidazole and NAC. The child is currently having a stable disease.

Case 6

The patient is a 58-month-old boy who was well till 7 months of age when he developed diarrhea, which is persisting. On his first visit, he had microcephaly and failure to thrive. He had global developmental delay. He had self-resolving and remitting nature of petechiae over the trunk at different site. The child was hypotonic with brisk reflexes and extensor plantar response. On investigation, serum lactate was elevated. Neuroimaging revealed T2 and FLAIR hyperintensity in the bilateral caudate, putamen, and dentate nucleus.

Plasma acylcarnitine and amino acid profile showed elevated C4 and C5 acylcarnitine esters and plasma thiosulfate. Urinary amino acid profile showed elevation of ethyl malonate. Next-generation sequencing revealed biallelic pathogenic variants of c.487C > G/p. Arg163Gly in *ETHE1* gene. Mutation was validated by Sanger sequencing and carrier status of parents was positive. The child was started with metronidazole, carnitine, and NAC. The child is currently having a stable disease.

Discussion

EE is a severe neurometabolic disease, characterized by progressive central nervous system (CNS) involvement and generalized microvascular damage and death in the first decade of life.[16] The CNS disease manifests as developmental delay, regression, motor abnormalities mainly hypotonia progressing to hypertonia, and seizures. Vasculopathy manifests as petechiae and/or purpura, orthostatic acrocyanosis, hemorrhagic suffusions of mucosal surface, and chronic hemorrhagic diarrhea. In this Indian series of six cases of ethylmalonic aciduria, all of the children presented with failure to thrive, global developmental delay, purpura, and elevated C4 acylcarnitine in the blood and ethyl malonate in the urine. Similar presentation was reported by Peake and Rodan[17] and Bijarnia-Mahay et al.[18]

EE is caused by mutation in *ETHE1* gene that encodes a mono-iron-binding mitochondrial matrix protein, a sulfide dioxygenase that is involved in the mitochondrial sulfide catabolic pathway.[19] Protein function leads to accumulation of sulfide (H_2S), resulting in multitude of clinical problems due to inhibition of several biochemical pathways such as inhibition of short-chain acyl-CoA dehydrogenase and complex IV in mitochondria. The disruption of intestinal mucosa and endothelia results in diarrhea, episodic petechial purpura, and acrocyanosis retinal tortuosity as well as progressive neurological decline. The EE accumulation has been suggested to cause competitive inhibition of succinate and malate transport across mitochondrial membrane, hence disrupting the energy production.[20]

Ethylmalonic aciduria is diagnosed in clinically suspected cases by biochemical, radiological, and genetic tests. A differential diagnosis of EE includes hematologic disorder with petechiae, purpura and hemorrhagic diarrhea, meningococcemia and sepsis with hemorrhagic lesions, diarrhea, encephalopathy, early death, and connective tissue disorders with skin bleeds and articular laxity.

Blood investigations include elevated serum lactate, increased C4 and C5 acylcarnitine esters, thiosulfate, and increased urine ethylmalonic acid (EMA). The hallmark of EE is the presence of EMA in urine. EE can be diagnosed in newborn screening by estimation of C4 levels in dried blood spot using TMS. If found elevated, this can be further followed by estimation of C4 acylcarnitine in urine and acylglycine in plasma. EE has elevation of both C4 acylcarnitine and acylglycine.[21] Persistent ethylmalonic aciduria is also seen in short-chain acyl-CoA dehydrogenase deficiency, which also has elevation of methyl succinic acid. Glutaric aciduria type 2 has elevation of hydroxylglutaric acids in addition to elevation of EMA and methyl succinic acid. Ethylmalonic aciduria is also observed in respiratory chain disorders, but petechiae, purpura, and acrocyanosis are all specific to EE. None of our cases had newborn screening as it is not universal in India. Newborn screening also has its own pitfalls, as elevation of C4 acylcarnitine is found not only in EE, but also in other aforementioned metabolic conditions, which requires further testing of organic acids and genetic testing for confirmation. All six cases had classical clinical features with increased C4 acylcarnitine levels in blood and increased EMA in urine.

On MRI of the brain, EE is characterized by symmetric patchy on T2-weighted signals in the basal ganglia, periventricular white matter and dentate nuclei, brain stem, and cerebellar white matter. In some instances, cortical atrophy and diffuse leukoencephalopathy are present.[3,6,22] Similar findings with predominant basal ganglia involvement were observed in the five of six cases for which neuroimaging was done.

EE is confirmed in genetic analysis where *ETHE* mutation is identified. Case 5 revealed a homozygous missense substitution (p. Phe183Ser) affecting exon 5 of the *ETHE1* gene, altering a conserved residue in the protein. This novel variant is predicted to be damaging by five programs (SIFT, LRT, Mutation Taster, PolyPhen-2, and Mutation Assessor). The clinical significance of the identified variant is unknown; however, missense variants in the vicinity, such as p. Leu185Arg and p.Asp196Asn, have been reported in patients with EE.[23] The phenotype is specific for the gene. The variant can be classified as likely pathogenic according to American College of Medical Genetics (ACMG) criteria.

The variant detected in case 6, c.487C > G (p. Arg163Gly) in exon 4, was found in homozygous state. This variant is predicted to be damaging by SIFT and FATHMM and to be probably damaging by PolyPhen-2. Affected a mutational hot spot is a well-established functional domain without benign variation. The variant is not reported and has an extremely low frequency in control subjects in 1,000 genome and ExAC databases. The variant is reported as pathogenic in ClinVar and was classified as likely pathogenic per ACMG criteria.

Satapathy et al[24] reported the first case of EE in India, in which the patient mainly presented with chronic diarrhea since early infancy and developmental delay. Mutation analysis of *ETHE1* showed presence of a previously reported homozygous mutation c.488G > A (p. Arg163Gln) in exon 4.[24] Govindaraj et al[25] reported a case of unusual EE with a novel pathogenic variation c.493 G > C (p.D165H) in *ETHE1* with mild and inconsistent elevation of EMA and normal C4/C5 acylcarnitine.[25] Bijarnia-Mahay et al[18] reported a 4-year-old boy with developmental regression, chronic diarrhea, petechial spots, and acrocyanosis. MRI brain showed involvement of the bilateral caudate and putamen. Abnormal acylcarnitine profile and metabolites on urinary GC-MS were present and a compound heterozygous mutation in *ETHE1* gene was seen, which were c.488G > A and c.375 + 5G > T (novel).[18]

Metronidazole, a bactericide, or NAC, a precursor of sulfide-buffering glutathione, has been proven to be efficacious in EE, by reducing the toxicity of accumulated

sulfides.[26] Dietary restriction with methionine has also proven beneficial in reducing EMA excretion.[4]

Patients diagnosed with EE were started on both these drugs in our case series. Following the treatment, the frequency of diarrhea and recurrent encephalopathy episodes were decreased and improvement in development could be noted. Though several Indian cases were reported, this is a series of six laboratory-proven cases of EE. However, genetic analysis could not be done for all due to financial issues. Our case series are helpful for planning implementation of newborn screening in India and preventing morbidity and mortality.

Conclusion

All children in this study had global developmental delay, failure to thrive, petechial lesions, and central hypotonia. Chronic diarrhea, acrocyanosis, and heterogeneous signal changes in the basal ganglia in the MRI of the brain also give important clues for diagnosis. Increased C4 carnitine levels in the serum and increased EMA in the urine are useful to confirm the diagnosis. Detoxifying drugs should be started after diagnosis to improve encephalopathy and development. We also suggest newborn screening for early detection and preventing morbidity and mortality.

Authors' Contributions

V. K. G. supervised, guided, and reviewed the manuscript. V. M. S. and S. K. S were involved in the management of the children and the preparation of manuscript. K. S., K. J., M. B., and R. C. were involved in the diagnosis of the children and the preparation of manuscript.

Conflict of Interest

None declared.

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