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REVIEW ARTICLE

Ethylmalonic Encephalopathy: a literature review and two new cases of mild phenotype

Isobel Platt[1] · Atil Bisgin[2] · Sebile Kilavuz[3]

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Abstract

Background Ethylmalonic encephalopathy (EE) is a rare intoxication-type metabolic disorder with multisystem involvement. It is caused by mutations in *ETHE1*, which encodes the ETHE1 enzyme in the mitochondrial matrix that plays a key role in hydrogen sulfide (H_2S) detoxification acting as a sulphur dioxygenase.

Results This review focuses on the clinical, metabolic, genetic and neuroradiological features of 70 reported cases, including two new cases. The common manifestations of EE are psychomotor regression, hypotonia, developmental delay, petechia, pyramidal signs, chronic diarrhoea, orthostatic acrocyanosis and failure to thrive, respectively. A significant difference was found in EMA and C4 levels (p=0.003, p=0.0236) between classical and mild phenotypes. Urinary EMA, C4 and C5 levels were found to exhibit normal values in milder cases during attack-free periods. The most common *ETHE1* gene homozygous state mutations were (p.R163Q) (c.488G>A), exon 4 deletion, (p.R163W)(c.487C>T), (p.Glu44ValfsTer62) (c.131_132delAG) and (p.M1I)(c.3G>T) mutations, respectively. Fifty-two patients underwent cranial MRI. Basal ganglia signal alterations were detected in 42 cases. Of the 70 cases, eight had a mild phenotype and slow neurological progression with low levels of ethylmalonic acid (EMA) and C4 acylcarnitine. The current age of alive patients in the published articles with mild phenotype was significantly higher than the classical phenotype. (p=0.002). Reducing the accumulation and inducing detoxification of sulfide is the main long-term treatment strategy for EE, including metronidazole, N-acetylcysteine (NAC), dietary modification, liver transplantation and continuous renal replacement therapy (CRRT).

Conclusion Measuring EMA and C4 acylcarnitine during metabolic attacks is critical to diagnosing EE, allowing for early treatment initiation to prevent further encephalopathic crises. Experience with liver transplantation, diet and CRRT, is currently limited. An early multidisciplinary approach with combination therapies is vital to prevent irreversible neurological damage.

Keywords Ethylmalonic encephalopathy · *ETHE1* · Mild · Spastic paraparesis · Ethylmalonic acid · H_2S

Introduction

Ethylmalonic encephalopathy (EE) (OMIM: 602473) is an inborn error of metabolism caused by mutations in the *ETHE1* gene located on chromosome 19q13, which encodes a key sulphur dioxygenase enzyme within the hydrogen sulfide (H_2S) detoxification pathway in mitochondria [1]. Less than 100 cases have been reported worldwide since 1991, with the majority of patients being from Mediterranean and Arabic populations [2, 3]. Deficiency in sulphur dioxygenase enzymatic activity results in the toxic accumulation of sulfide in body fluids and tissues, including the colonic mucosa, liver, muscle, and brain. EE is a disorder of mitochondrial energy metabolism that involves inhibition of short acyl-CoA dehydrogenase (SCAD) and cytochrome c oxidase deficiency.

Clinical presentation includes developmental delay, acrocyanosis, petechiae, chronic diarrhoea, and recurrent lactic acidemia associated with the elevation of urinary ethylmalonic acid (EMA) and methyl succinic acid. Increased hydrogen sulfide inhibits cytochrome c oxidase, resulting in high levels of lactic acid in the blood, thiosulphate in

✉ Sebile Kilavuz
dr.skilavuz@gmail.com; sebilekilavuz@marmara.edu.tr

1 Foundation Doctor, Barts Trust, London, UK

2 Department of Medical Genetics, Cukurova University AGENTEM (Adana Genetic Diseases Diagnosis and Treatment Center), Adana, Turkey

3 Division of Pediatric Metabolism and Nutrition, Department of Pediatrics, Marmara University Faculty of Medicine, İstanbul, Turkey

plasma, ethylmalonic acid in urine and butyrylcarnitine (C4) and isovalerylcarnitine (C5) acylcarnitine in the brain, muscle tissue and in the blood [1, 4, 5]. Magnetic Resonance Imaging (MRI) images for this disorder typically reveal T2-hyperintensities in the basal ganglia throughout the periventricular and cerebellar white matter, dentate nuclei, and brain stem. Cases with extensive disease can additionally exhibit cortical atrophy and diffuse leukoencephalopathy [6].

The course of the disease was originally thought to be universally aggressive and prematurely fatal in early life; with onset in the early post-natal period, followed by progressive clinical deterioration. However, there are reports in the literature of milder clinical phenotypes that resemble the new cases we present in this review. Here, we describe two patients with homozygous p.R163Q variants of the *ETHE1* gene and compare them with the clinical phenotypes, biochemical features, and molecular analyses of individuals with EE previously documented, to emphasise the importance of clinical suspicion in patients presenting with milder phenotypes.

Patient 1

A 13.5-year-old boy was admitted to the emergency department (ED) with diarrhoea, tachypnea and drowsiness, for which he had been hospitalised in the intensive care unit three times previously. The preceding history included mucoid diarrhoea occurring six times a day. These symptoms worsened during periods of febrile infection. The patient was the second child of unaffected consanguineous parents. His five-year-old sister is unaffected. The patient was born via an uncomplicated vaginal delivery at 38 weeks of gestation, with a birth weight of 2800 grams. At three months of age, he acquired head control; he could sit without support by eight months of age. The patient could say mom and dad at 1.5 years of age and spoke normally by four years of age. He was investigated for developmental delay at 2.5 years of age. His height and weight were as follows: weight 35 kg (4.85p, -1.66 SDS), height 123 cm (<0.02p, -4.43 SDS). He had no dysmorphic facial features. In addition, petechiae and prominent acrocyanosis occurred without any precipitating cause, especially in the pressure areas and lower extremities. His neurological examination exhibited prominently spastic paraparesis and axial hypotonia with decreased muscle power, most prominently in the lower extremities. Hyperreflexia was present in the upper and lower extremities, with bilateral ankle clonus (video 1) and bilateral extensor plantar reflexes. His eye examination was normal, except for right eye amblyopia, and hearing was also intact. Urinary organic acid analysis revealed a high excretion of ethylmalonic acid (130 µmol/mmol creatinine), pyruvic acid, fumaric acid, lactic acid, malic acid, 3-hydroxybutyric acid, 2-hydroxyglutaric acid. An analysis of plasma amino acids and carnitine acylcarnitine profile revealed slightly elevated alanine, C4 carnitine 1.95 µmol/L (0 – 1.2) and C5 Carnitine 0.71 µmol/L (0 – 0.48) respectively. Alanine Transaminase (ALT), Aspartate Transaminase (AST), Lactate Dehydrogenase (LDH), Creatinine Kinase (CK) and coagulation profiles were within normal range. There was persistent metabolic acidosis with the pH ranging between 7.05-7.32, bicarbonate of 4 -12 mEq/L and base excess (BE) of – 12 to -19. Lactate levels ranged from 7.8-9.9 mmol/L (0.5–1.8). Cranial MRI at 2.5 years of age was normal. At 9 years of age, T2 and FLAIR MRI sequences were conducted, with increased signal in bilateral basal ganglia, dentate nuclei and peridental areas, and substantia nigra in the level of cerebral peduncles, in addition to diffusion restrictions. Echocardiography (ECHO) and electroencephalography (EEG) were normal. Based upon the presenting clinical features of diarrhoea, neuromotor retardation, and acrocyanosis (Fig. 3a), together with the laboratory findings of elevation in C4, C5 and lactate, with ethylmalonic acid elevation in urinary organic acid, EE was suspected. *ETHE1* analysis by Sanger sequencing demonstrated a homozygous mutation *ETHE1,* c.488G>A (p.R163Q), confirming EE. The patient was commenced on riboflavine (10 mg/kg), coenzyme Q10 (10 mg/kg), metronidazole (30 mg/kg) and N-acetylcysteine (20 mg/kg). Moreover, N-acetylcysteine 100 mg/kg/day intravenous (IV) infusion was administered during subsequent encephalopathic crises. The patient currently shows a tip-toe walking pattern and can form basic sentences.

Patient 2

A 10-year and 8-month-old girl, the third child of consanguineous parents, presented to the clinic following a history of intellectual disability and spastic paraparesis (Fig. 3b). She was born via caesarian section with a birth weight of 3400g at term. Her other two siblings were healthy. She was able to sit at seven months without any support and could speak at 2 years of age. The patient has never been able to walk. She was followed up for chronic watery, mucoid diarrhoea, with seven episodes daily. Management was for suspected coeliac disease due to malnutrition from 3 years of age, with positive anti-gliadin G antibodies. At 6 months of age, the patient had a febrile seizure. During episodes of infective illness, her neurological symptoms were noted to deteriorate. At 10.5 years of age, her height and weight were as follows; weight: 15.1 kg (< 0.02p, -4.65 SDS), height: 114 cm (< 0.02p, -4.3 SDS). Neurological examination exhibited normal muscle power in the upper extremities and decreased muscle power in the lower extremities. Hyperreflexia was present in the left lower extremity, with left ankle

clonus and an extensor plantar reflex in the left foot. Her eye examination and hearing tests were normal. On this admission and during previous episodes of infective illness, petechiae, purpuric lesions and prominent acrocyanosis were noted. Before this admission, the patient had four encephalopathic crises over the previous year. Urinary organic acids (urinary ethylmalonic acid: 15.37µmol/mmol creatinine, plasma amino acids and carnitine acylcarnitine profile (C4: 0,79 µmol/L C5: 0.29 µmol/L) were within the normal range. Metabolic acidosis was present with pH ranging from 7.05-7.32, Bicarbonate 4-11 mEq/L and BE of -13 to –19. Plasma lactate levels ranged from 4-8 mmol/L (0.5–1.8). Cranial and spinal MRI, EEG and ECHO were unremarkable. Based on the clinical presentation of chronic diarrhoea, developmental delay, positive neurological findings, and orthostatic acrocyanosis, EE was suspected. *ETHE1* sequencing analysis demonstrated a homozygous mutation *ETHE1*: c.488G>A (p.R163Q), confirming EE.

Materials and methods

Literature review

A literature search of PubMed, MEDLINE, and EMBASE databases for articles published between December 1, 1991, and September 10, 2022, was conducted. The following keywords were used in the literature search: "*ETHE1*", "ethylmalonic encephalopathy", ''mild'' and ''atypical''. Clinical, biochemical, molecular, and neuroradiological findings and clinical progress of patients were summarised.

Results

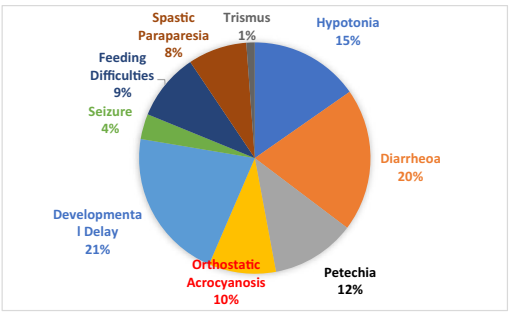
In addition to the two new cases, clinical, laboratory, radiological and molecular data of 68 patients were recorded from forty-three research articles published between 1991 and 2022. The literature search identified research articles, including case reports and case series, of which forty-five patients showed confirmed diagnosis of EE by molecular analyse and twenty-five patients were diagnosed with laboratory and clinical analyses. Data from patients diagnosed without molecular analyses were collected from articles before 2006. Countries according to the published articles were Italy (9), Turkey (7), USA (5), Canada (3), China (3), Spain (3), Kuwait (2), Greece (2), Japan (2), Saudi Arabia (1), Denmark (1), France (1), Israel (1), Australia (1), India (1) and Japan (1). Six out of the 68 patients have been reported as having a mild phenotype in the literature with slow chronicneuromotor deterioration [7–11]. Furthermore, our two presented cases exhibited a mild clinical phenotype.

Clinical features

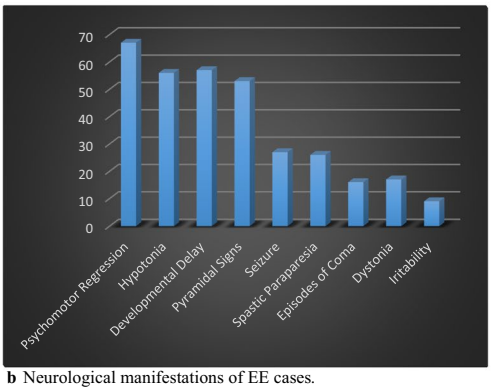
The recognised symptom onset age of 70 cases was mean ± SDS: 11.5 ± 27.8 months (1 day-192 months). The gender distribution was 34 Females (48.5%), and 36 Males (51.5%). Parental consanguinity was detected in 23 (41.3%) out of 55 patients. Recognised first symptoms were diarrhoea (17 patients), developmental delay (18 patients), hypotonia (13 patients), petechia (10), orthostatic acrocyanosis (8 patients), poor feeding (8), spastic paraparesis (7), seizure (3) and trismus (1), respectively (Fig. 1a). While fifteen (21.4%) out of 70 patients had microcephaly, two had macrocephaly. Facial dysmorphia was detected in 9 patients. Neurological manifestations of 70 patients were found as follows; 67 patients had psychomotor retardation, 57 had hypotonia, 57 had developmental delay, 53 had pyramidal signs, 28 had seizures, 27 had spastic paraparesis, 16 had episodes of coma, 17 had dystonia, 9 had irritability and 1 had trismus (Fig. 1b). Gastrointestinal findings included failure to thrive in 42 patients, chronic diarrhoea in 49 patients, feeding difficulties in 34 patients and hepatomegaly in 6 patients (Fig. 1c). Vascular manifestations were as follows; 55 individuals had petechiae and 47 had orthostatic acrocyanosis (Fig. 1d). Four patients exhibited renal involvement, including grade 2 hydronephrosis, diffuse mesangial sclerosis, crescentic glomerulonephritis and renal failure [12–14]. Five infants demonstrated mild to moderate hematuria [15]. One patient had Arnold Chiari malformation type 1 [10], and two had tethered cords and cerebellar tonsillar ectopia [16, 17]. Nine patients had retinal vein tortuosity in the eye examination [7, 15, 18–20]. One set of twins had scoliosis and hip dislocation (Fig. 1e) [11]. Initially, cow's milk protein intolerance, meningococcemia, septic shock, autoimmune disorders, celiac disease, coagulation defects, and mitochondrial disorders (Leigh Syndrome, MELAS) were suspected. Feeding difficulties, malnutrition and diarrhoea brought about suspicion of cow's milk protein intolerance, food allergies, malabsorption syndromes (coeliac disease), bacterial or parasitic infections and inflammatory bowel disease. Although most patients were initially put on a diet due to the misdiagnosis of malabsorption syndromes and milk protein intolerance, diarrhoea and gastrointestinal problems persisted. [3, 5, 9, 21–25] (Table 1).

Laboratory results

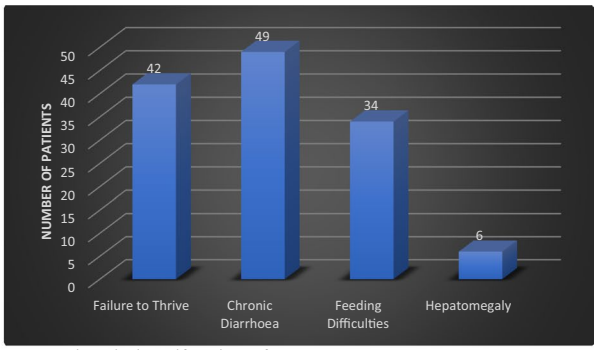
The lactate level of patients was mean ± SDS (min-max): 5.2 ± 3.06 (1-16.7) mmol/L. The ethylmalonic acid level of patients was mean ± SDS (min-max): 253.78 ± 347.1 (28.86-2270)



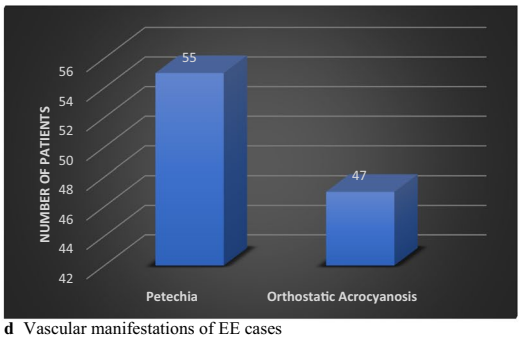
a First clinical manifestations of patients



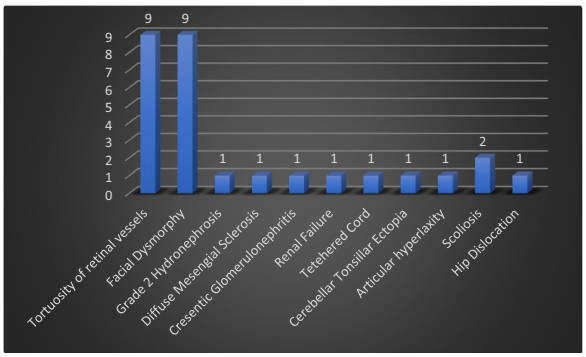
b Neurological manifestations of EE cases.



c Gastrointestinal manifestations of EE cases



d Vascular manifestations of EE cases



e Other manifestations of EE cases

Fig. 1 **a** First clinical manifestations of patients. **b** Neurological manifestations of EE cases. **c** Gastrointestinal manifestations of EE cases. **d** Vascular manifestations of EE cases **e** Other manifestations of EE cases

µmol/mmol creatinine. Plasma C4 and C5 levels of patients were mean ± SDS (min-max): 3.12 ± 3 (0.71-15.4) µmol/L and 1.16 ±1.55 (0.17-8) µmol/L, respectively. When ethylmalonic acid, C4 and C5 levels of patients with classical phenotype were compared to mild phenotype of patients, there was not any significant difference in C5 (Fig. 2c) (p=0,15) and lactate (p=0.92) levels, but a significant difference was found in ethylmalonic acid levels (Fig. 3a) (p=0,003) between classical mean ± SDS (min-max): 294 ± 372.2 (28.86-2270) µmol/mmol creatinine and mild phenotype mean ± SDS (min-max): 58.37± 33.49 (15.37-120.9) µmol/mmol creatinine and in C4 levels (Fig. 3b) (p=0,0236) between classical mean ± SDS (min-max): 3.2 ± 3 (0.91-15.4) µmol/L and mild phenotype mean ± SDS (min-max): 1.39 ± 0.65 (0.79-2.48) µmol/L (Table 1).

Mutations

A total of thirty different *ETHE1* gene variants were identified. Thirty-two homozygous and 13 compound heterozygous mutations were detected in 45 patients. The most common mutations in the *ETHE1* gene were (p.R163Q) (c.488G>A) (14), exon 4 homozygous deletion (12), (p.R163W)(c.487C>T) (9), (p.Glu44ValfsTer62) (c.131_132delAG) (7) and (p.M1I)(c.3G>T) (6) mutations, respectively (Table 1 and Table 2). Mutations of mild phenotypes were (p.R163Q) (c.488G>A) (2), (p.R163W) (c.487C>T) (1), (p.M1I)(c.3G>T) (3), p.Q27K) (c.79C>A) (1) and a compound heterozygous (p.Q27K) (c.79C>A), (p.L185R) (c.554T>G) mutation (1) [7, 9–11, 29].

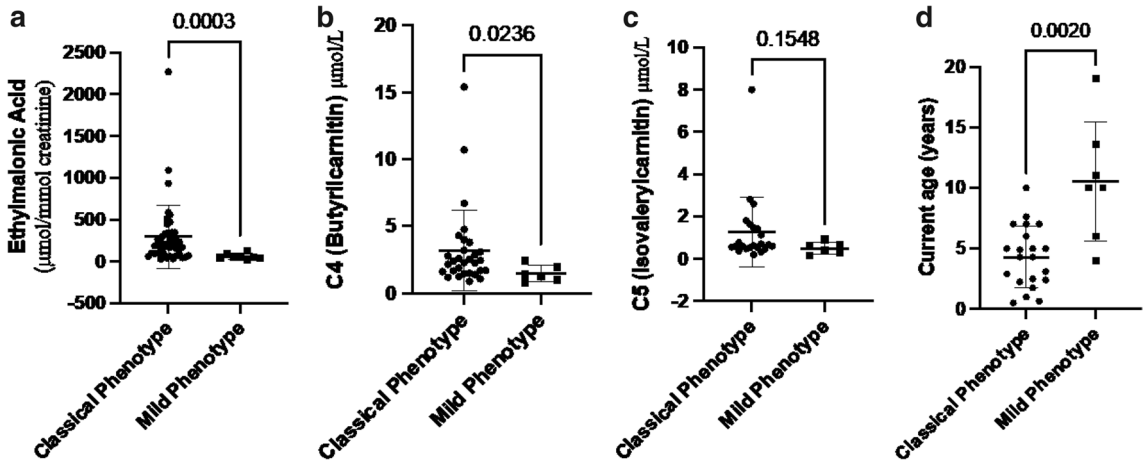


Fig.2 Biochemical parameters of patients with EE and mentioned current age in published articles. **a** Comparison of Ethylmalonic acid between classical phenotype and mild phenotype. **b** Comparison of C4 (Butyrlcarnitin) between classical phenotype and mild phenotype **c** Comparison of C5 (Isovalerylcarnitin) between classical phenotype and mild phenotype. **d** Comparison of current age between classical phenotype and mild phenotype. Statistically significant at $p < 0.05$

Treatment

The majority of patients were treated with oral N-acetylcysteine, intravenous N-acetylcysteine (during attacks), metronidazole, L-carnitine, coenzyme Q10 and other vitamins. Additionally, five patients were treated with liver transplantation, and five patients were on a diet with restriction of protein, sulfur-containing amino acids or methionine. Half of the patients with liver transplantation were reported to remain stable (Table 1). Furthermore, one patient was treated with continuous renal replacement therapy (CRRT) [10].

Radiology

Cranial MRI was performed on fifty-two patients. Signal alterations in basal ganglia were detected in 42 (80.7%) out of 52 patients. Six patients exhibited enlargement of subarachnoid spaces and seven patients with frontotemporal atrophy. Cranial MRI of 2 patients with mild clinical phenotype, 1 of which was a new case we have presented, was normal (Table 3) [18].

Outcome

At the time each article was reported, the mean age of alive patients was 5.77 ± 4.07 (0.5-19) years. The mean age of death was 2 ± 1.99 years (6 months-10 years). Sixteen patients died during an infectious period. The reported causes of death were respiratory tract infection, diarrhoea and septicemia, respectively. Seven out of 8 patients of the mild phenotype were alive. When the current age of patients with mild phenotype 10.5 ± 4.9 years (4-19) was compared to the classical phenotype 4.29 ± 2.54 years (0.5-10), the current age was significantly higher in the mild phenotype (Fig. 2d) (p=0.002). The age of symptom onset was not significantly different between classical and mild phenotypes ($p > 0.05$).

Discussion

Ethylmalonic encephalopathy is a devastating, invariably fatal, multisystem infantile disorder. Symptoms typically start in the infantile period, with progressive clinical deterioration and death within the first few years of life. Although most patients exhibit a severe phenotype with infantile-onset, a minority have been reported with clinically milder phenotypes. Only 6 cases have been reported to date with slow neuromotor deterioration and a slight increase in the metabolic profile, which is classified as a mild or atypical clinical phenotype. However, due to the rare mild cases and missing information in published articles, it was difficult to compare some laboratory values and clinical findings between classical and mild phenotypes [7–11, 29] (Table 1).

Here we share our experience of two patients suffering from mild EE who presented with spastic paraparesis and acrocyanosis. Their clinical progression was slow, and they were also admitted to the emergencwy department with neurological deterioration during episodes of infectious illnesses. Infection is a known precipitant factor for metabolic decompensation with vascular brain changes, resulting in neurological deterioration [22]. The current age of patients with a mild clinical phenotype was significantly higher

Table 1 Clinical, molecular and biochemical data from previously reported patients with EE

Authors	[21]	[26]	[3]	[22]	[15]	[27]
Country	Italy	Denmark	Italy	Italy	Saudi Arabia	Spain
Year of publication	1991	1993	1994	1994	1994	1997
Number of Cases	3 (NA)	1(M)	4(M)	2 (M)	5 (2M,3F)	2 (1M,1F)(siblings)
Parental consanguinity	NA	-	-/-/-/-	-/+	+/+/+/+/+	-/-
First symptom	Hypotonia Hypotonia Hypotonia	Hypotonia	Hypotonia,diarrhea, petechia	1. Diarrhea, distal limb acrocyanosis and diffuse petechiae. 2.Diarrhea, petechia, failure to thrive, developmenta delay, severe hypotonia	1.Vomiting and diarrhea 2.Hypotonia,seizure 3.Developmental delay 4.Developmental delay 5.Developmental delay	1.Irritability, feeding difficulties 2. Irritability, feeding difficulties
Age at Symptom onset	NA	4 m	1.3 months 2.1 months 3.45 days 4.<6months	1.45 days 2.1st day	1.2months 2.Birth 3.7-8months 4. <1 y 5. 22months	1.45 days 2. NA
Psychomotor Retardation	+/+/+	+	+/+/+/+	+/+	+/+/+/+/+	+/+
Hypotonia	+/+/+	+	+/+/+/+	+/+	+/+/+/+/+	+/+
Spastic paraparesia	+/+/+	NA	+/+/+/+	+/-	-/+/NA/NA/NA	+/+
Seizure	-	+	-/-/-/-	-	+/+/+/-/-	-
Seizure Type	-	NA	-	NA	1.GTCS 2.Tonic 3.GTCS 4.Tonic 5.Gelastic seizure	-
EEG	-	Abnormal	-	-	1.Multifocal discharges 2.Bilateral independent spikes	NA
Dystonia	-	-	-	+	-	+/+
Pyramidal signs	+/+/+	+	+/+/+/+	+ /+	+/+/+/+/+	+/+
Muscle wastng	NA	NA	NA	+/-	NA	NA
Eisodes of coma				NA	+/+	+/+
Microcephaly	-	-	-/-/-/+	NA	+/-/-/+/-	+/+
Skin (Petechiae)	+/+/+	+	+/+/+/+	+/+	+/+/+/+/+	+/+
Orthostatic acrocyanosis	+/+/+	NA	+/+/+/+	+/+	+/+/+/-/-	-/-
Chronic Diarrheoa	+/+/+	NA	+/+/+/+	+/+	+/+/-/-/-	+/+
Failure to Thrive	NA	+	+-/-/+	+/+	-/+/-/-/-	+/+
Feeding difficulties	NA	NA	Tube feeding/+/+/+	+/+	NA	+/+
Irritabılity	NA	NA	NA	NA	+	+/+
Developmental Delay		+	+/+/+/+	+/+	+/+/+/+/+	+/+
Other Malformations	NA	NA	-	NA	-	-

Table 1 (continued)

Eye	NA	NA	NA	NA	1. Retinal vessel tortuousity,left pale optic disc 2. Retinal vessel tortuousity 3. Retinal vessel tortuosity 4. Retinal vessel tortuosity 5. Retinal vessel tortuosity	-
Liver involvement	NA	NA	NA	NA	MildHMG+SMG/HMG/-/-	HMG/ HMG
Facial dysmorphy	-	NA	-	-	+/+/+/+/+	+/-
Misdiagnosis	Food intolerance (gluten, cow's milk proteins, lactose), bacterial or parasitic infections, or inflammatory bowel disease.	MADD	Cow milk protein intolerance	Haemorrhagic disorders, malabsorption,autoimmune disorders, and chromosome Abnormalities,coagulation factor deficiency	-	1.Peripheral dysautonomia, autoimmune disorder 2.Coagulopathy or platelet dysfunction
Lactat mmol/L	1. 3.3 2. 6 3. NA	NA	1. 3.4 2. 3,6 3. 4.2 4. 3.5	1. 4.5 2 .2.9	1. 4.4 NA	1.4.7 2. 9.5
Ethylmalonic Acid µmol/mmol creatinine	62-933	⇑⇑	1. 1.446-1090 2. 2.180-264 3. 3.272 4. 4. 96-209	⇑⇑⇑	54-2270	1. 1.196 2. 2.343
C4 µmol/L	NA	NA	NA	NA	NA	NA
C5 µmol/L	NA	NA	1.0.2 2. 8	NA	NA	NA
Carnitine µmol/L	NA	NA	NA	Normal	NA	NA
ETHE1 gene mutation	NA	NA	NA	NA	NA	NA
Others	-	NA	-	-	Mild-to-moderate hematuria (5 patients)	-
Treatment	Riboflavine carnitine	NA	1.Metronidasole, L-carnitine riboflavin 2.Lcarnitine,riboflavino 3.Lcarnitine,riboflavino	NA	1.L-carnitine, riboflavin, Phenobarbital, Tegretol, pregestemil 2.Riboflavin, ascorbic acid, vitamin E, glycine, L-carnitine. 3.Prolonged large doses of methylprednisolone	1.L-carnitine, riboflavin, thiamine, vitamin C, coenzyme Q10 mg/d 2.L-carnitine, riboflavin, thiamine vitamin C coenzyme Q10 mg ay
Outcome Alive	1 patient is alive (6 years of age)		6 years of age	7 years of age alive	-	

Table 1 (continued)

Age of Death	1.24 months 2.23 months	1.13 months	1.2 years 2.23 months 3.- 4.20 months	1.1.5 years	1.16 months 2.7 months 3.2 years 4.4 years	1.20 months 2.7,5 months
Death Reason	NA	Bronchopneumoniae	Respiratory tract infection (3 patients)	Acute respiratory failure	Septicemia	1.Bronchopneumoniae 2.Bronchopneumoniae
Authors	[28]	[29] Mild	[30]	[31]	[32]	[20]
Country	Italy	Turkey	Japan	Italy	Turkey	USA
Year of the Article	2015	2015	2016	2016	2017	2017
Number of Cases	1 (F)	1 (F)	1 (M)	1 (F)	1 (F)	1 (F)
Parental consanguinity	-	+	-	-	+	NA
First symptom	1.Sudden bilateral and symmetrical spasms of the neck, trunk and extremities	1.Tip toe walking	1.Developmental delay, hypotonia	1.Psychomotor delay, mild drowsiness and axial hypotonia with spasticity of lower limbs	1.Fever, rash, poor feeding, respiratory difficulty, shock, encephalopathy	1.Developmental delay, hypotonia, infantile spasms
Symptom onset age	3 months	2 years	Infancy	7 months	NA	10 months
Psychomotor Regression	+	NA	+	+	+	+
Hypotonia	+	-	+	+	+	+
Spastic paraparesia	NA	+	NA	+	NA	NA
Seizure	+	-	+	-	-	+
Seizure Type	Infantile spasms		NA			Infantile spasms
Ataxia	NA	NA	NA	NA	NA	NA
EEG	High voltage slow waves and spikes, hypsarrhythmia		NA			Hypsarrhythmia
Dystonia	+	NA	NA	NA	NA	NA
Pyramidal signs	NA	+	+	+	+	+
Eisodes of coma	NA	NA	NA	NA	+	NA
Microcephaly	-	-	+	-	-	-
Skin (Petechiae)	+	-	+	+	+	+
Orthostatic acrocyanosis	+	+	+	+	+	+
Chronic Diarrheoa	+	-	+	NA	-	+
Failure to Thrive	NA	NA	NA	NA	NA	NA
Feeding difficulties	NA	NA	NA	NA	+	NA
Irritability	NA	NA	NA	NA	NA	NA
Developmental Delay	+	NA	+	NA	+	+
Other Malformations	-	-	-	-	-	-

Table 1 (continued)

Eye	-	Esotropia	-	NA	NA	Retinal vessel tortuosity
Liver involvement	NA	NA	-	NA	NA	NA
Facial dysmorphy	-	-	NA	-	-	-
Misdiagnosis	NA	NA	NA	NA	Meningococcemia and septic shock	Mitochondrial disorder
Lactat mmol/L	NA	2.92	NA	8.1	NA	3.1
Ethylmalonic Acid µmol/mmol creatinine	NA	41	⇑⇑	169-210		299
C4 µmol/L	1.72	NA	3.22	1.47-1.53	NA	1,69
C5 µmol/L	0,71-1.62	NA	1.12	0.45-0.6	NA	NA
Carnitine µmol/L	247.4	NA	NA	NA	NA	NA
ETHE1 gene mutation	1. (p.E208del) (c.622_624delGAG) (p.I114F) (c.340A>T) (p.R163Q) (c.488G>A) CH	1.(p.Met1Ile)(c.3G>T) Hom	1. (p.R163Q) (c.488G>A) (c.375+5G>T) CH	1. (p.Glu44-ValfsTer62) (c.131-132delAG)	1.(p.L185R)(c.554T>G) Hom	1. (p.R163Q) (c.488G>A) Hom
Treatment	Metronidazol, NAC	Riboflavine, Coenzyme Q10	Riboflavin	Metronidazole, NAC Liver transplantation	Riboflavine, Coenzyme Q10, Metronidazole NAC	Metronidazole, NAC, Vigabatrin
Outcome Alive		4 Years		1 years very much improved	NA	
Age of Death	9 months		4.5 years			
Death Reason	Respiratory infection		Infection			
Authors	[10]* Mild	[33]	[9]* Mild	[23]	[34]	[35]
Country	Canada	USA	Turkey	China	India	China
Year of the Article	2018	2019	2020	2020	2020	2020
Number of Cases	1 (M)	2 (1F, 1 M)	1 (M)	1 (M)	1 (M)	1 (M)
Parental consanguinity	-	+/+	+	-	+	-
First symptom	1.Long-standing spastic paraplegia, dysarthria (Trismus during first hospitalisation)	1.Diarrhea 2.Hypotonia	1.Diarrhoea.	1.Poor feeding, diarrhea,	1.Poor feeding,sepsis	1.Diarrhea, petechia, echymosis
Symptom onset age	16 years	Birth na	6 months 5 years Spastic parapareisa diarrheoa	Birth	Birth	Birth
Psychomotor Regression	-	+/+	+	+	+	+
Hypotonia	-	+	-	+	+	+

Table 1 (continued)

Spastic paraparesia	+	-/+	+	NA	+	+
Seizure	-	-/-	-	+	+	-
Seizure Type				During attack	NA	
Ataxia	+	NA	NA	NA	NA	NA
EEG				Normal		
Dystonia	-	NA	NA	-	+	NA
Pyramidal signs	+	NA	NA	+	+	+
Eisodes of coma	+	+	-	NA	+	NA
Microcephaly	Macrocephaly	-	-	Macrocephaly	+	-
Skin (Petechiae)	-	+/-	-	+	+	+
Orthostatic acrocyanosis	-	+/-	-	+	NA	+
Chronic Diarrheoa	-	+/+	+	+	NA	+
Failure to Thrive	NA	NA	NA	NA	NA	+
Feeding difficulties	NA	+ /+gastrostomy	NA	+	+	NA
Irritabılity	NA	NA	NA	+	NA	NA
Developmental Delay	+	+/+	NA	+	NA	+
Other Malformations	Arnold-Chiari malformation type I	-	-	-	-	-
Eye	-	NA	NA	-	NA	NA
Liver involvement	-	NA	NA	-	NA	NA
Facial dysmorphy	-	-	-	-	-	-
Misdiagnosis	NA	NA	Food allergies or malabsorption syndromes	SCADD or MADD	NA	NA
Lactat mmol/L	1-14.8	1. 4.2 2. NA	1.4	NA	3.8-5.3	NA
Ethylmalonic Acid µmol/mmol creatinine	20-100 (min-max)	1. NA 2. 177	46	34.6	⇑⇑	74.93-142.53
C4 µmol/L	(0.71-6,71)	1. 2,31 2. 2,17	1.26	2.28	⇑⇑	2.4
C5 µmol/L	(0.17-0.92)	1. 0,59 2. 0.77	0.39	1.47	⇑⇑	1.42
Carnitine µmol/L	NA	NA	NA	NA	NA	NA
ETHE1 gene mutation	1. (c.79C>A) (p.Gln27Lys) Hom	1. Hom deletion of exon 4 2. (p.R163W) (c.487C > T) Hom	1. (p.Met1Ile) (c.3G > T) Hom	1. (p.Q99*) (c.295C>T) Hom	1. (p.D165H) (c.493G>C) Hom	1. (c.375+5G>A) a novel mutation (c.462T>A) (p.D154E) CH

Table 1 (continued)

Treatment	MNZ, NAC, L-carnitine, Baclofen CRRT CVVVHDF	At 19m and 13 m Liver Transplantation Metronidazole and NAC	NAC, MTZ, coenzyme Q10, riboflavine Achile tendon strengthening	Carnitine, NAC, coenzyme Q10), multivitamins vitamin B12; vitamin B1, vitamin B2, vitamin A, vitamin D	Baclofen , biotin, L-carnitine, coenzyme Q , multivitamins Levatiracetam	Liver transplantation A sulfur-containing amino acids restricted diet and the combined use of Metronidazole and NAC
Outcome Alive	19 years	1. 27 months 2.35 months	11 years Walking without support, IQ normal		52 months	38 months
Age of Death	-					
Death Reason	-					
Authors	[16, 17]	[25]	[5]	[36]	[13]	
Country	Canada	Japan	Italy	USA	Kuwait	
Year of publication	1998	2001	2002	2004	2006	
Number of Cases	2 (1M,1F)	3 (3 F) 2nd patient is sister of first patient	2 (2F)	2 (1F, 1M)	2 (2 M)	
Parental consanguinity	NA	NA, NA, -	+/-	+/+	+/+	
First symptom	NA	1. Developmental delay, spastic quadriplegia and diarrhoea 2.Acrocyanosis, petechiae and spastic quadriplegia 3. Diarrhea	1. Petechiae, diarrhea, Orthostaticacrocyanosis and failure to thrive 2. Feeding difficulties, irritability, abdominal distension and diarrhea	1.Psychomotor delay 2.Irritability	1.Diarrhea 2.Purpuric skin rash	
Age at Symptom onset	1.3months 2.2months	1.NA 2.NA 3.Few days after birth	1.7months 2.1months	NA	1.4 months 2. NA	
Psychomotor Retardation	+/+	+/+/+	+/+	+	+/+	
Hypotonia	+	+	+/+	+/+	+/+	
Spastic paraparesia	NA	+/+	-/+	NA	NA/NA	
Seizure	-	NA	+/+	+/+	-/+	
Seizure Type	-	-	1.Tonic 2.Infantil spasm	1.Infantilespasm, absence seizure 2.Myoclonic seizure	NA	
EEG	-	-	1.Generalized polyspike-waves activity 2.Hypsaritmia	1.Hypsarrythmia 2.NA	NA	
Dystonia	+	-	+/-	NA	-	
Pyramidal signs	NA	+/+/-	+ /+	+/+	+/-	
Muscle wastng	NA	NA	NA	NA	NA	

Table 1 (continued)

Eisodes of coma		+/+/+	NA	+/+	
Microcephaly	-	-	+/-	+/	+
Skin (Petechiae)	+	+/+/+	+/+	+/+	+/+
Orthostatic acrocyanosis	+/+	+/+/+	++	+/	NA
Chronic Diarrheoa	++	+/+/+	++	NA	+/-
Failure to Thrive	NA	NA	+/+	+/-	NA
Feeding difficulties	-	+/+/+	+/+	NA	-
Irritabılity	NA	NA	+/-	NA	NA
Developmental Delay		+/+/+	+/+	+/+	
Other Malformations	1.Tethered cord, 2.Cerebellar tonsillar ectopia (Chiari I malformation)	-	NA		1.Grade 2 hydronephrosis
Eye	NA	NA	NA	NA	Nystagmus
Liver involvement		HMG /-/-	NA	-	1.Increased liver echogenecity 2. HMG
Facial dysmorphy	-	-	NA	+/+	-
Misdiagnosis	-	1.Lactose, cow's milk proteins) 2.Bacterial or parasitic infections 3. Inlammatory bowel disease	1.Celiac disease 2.Cow milk protein intolerance	1.Hematological investigation 2.Leigh disease	-
Lactat mmol/L	1. 4,3- 6,06 2. NA	1.2.1 2. 3,2 3. 8.7	1. 3 2. 4.35	1. 4.1-5.1 2. NA	1. 2,8-7,8 2. 2.1-11.8
Ethylmalonic Acid µmol/mmol creatinine	1. 1.92.5 2. 2.NA	1.93.1 2.158.4 3.234.9	⇑⇑⇑	1. 1.276 2. 2. NA	NA
C4 µmol/L	NA	1. 15.4 2. 10.7 3. 2.6	NA	⇑	NA
C5 µmol/L	NA	1. 2.6 2. 1.8 3. 2.8	NA	⇑	NA
Carnitine µmol/L	NA	51.8	1. 19 (24-76) 2. 11	14	NA
ETHE1 gene mutation	NA	NA	NA	NA	1.(p.N77fsX144) (c.230delAA), Hom 2. NA

Table 1 (continued)

Others	-	-	NA	-	1.Grade II hydronephrosis. mild tricuspid regurgitation and dilatation of the pulmonary artery 2.Undescended testes, small penis,
Treatment	1.L-carnitine riboflavin, coenzyme Q10 2. L-carnitine riboflavin, coenzyme Q10	1.L-Carnitine, riboflavin coenzyme Q10 2.Riboflavin, coenzyme Q10 3.L-Carnitine, riboflavin ,thiamin, pyridoxine, vitamin B12 and a low-protein diet	1.Valproic Acid 2.Vigabatrin, Valproic Acid, Vigabatrin and ACTH	1.Methionine restricted diet 2. Methionine restricted diet	1.Vitamins B1, B2, B6 , C, E, biotin, coenzyme Q10, L-carnitine 2.Vitamin B1, B2, B6, coenzyme Q10, L-carnitine, sodium bicarbonate,phenobarbitale
Outcome Alive	7 years alive 5 years alive	7 years alive	+	8 months alive	
Age of Death	-	1.46 months 2.23 months	1.10 years	1.8 months	1.8 months
Death Reason		1.Apnea, Intractable metabolc asidosis	1.Respiratory tract infection		Leigh disease
Authors	[37]	[38]	[7]* Mild	[18]	[39]
Country	USA	Turkey	Turkey	Turkey	China
Year of the Article	2018	2018	2018	2018	2019
Number of Cases	2 (1 F, 1M)	1 (M)	1 (F)	1 (M)	1 (M)
Parental consanguinity	-/-	+	-	+	-
First symptom	1.Newborn screening 2.Poor feeding, hypoglycemia	1.Acrocyanosis	1.Diarrheoa, severe lactic acidosis, encephalopathy	1.Irritability	1.Diarrhea
Symptom onset age	Newborn	3 years 9months	NA	NA	At birth
Psychomotor Regression	+/+	+	+	+	+
Hypotonia	+/+	+	NA	+	-
Spastic paraparesia	NA	NA	NA	NA	-
Seizure	+/+	NA	NA	+	-
Seizure Type	NA			NA	
Ataxia	NA	NA	NA	NA	NA
EEG	1.Normal 2.Hypsarrhythmia				
Dystonia	NA	NA	NA	NA	-

Table 1 (continued)

Pyramidal signs	+/+	NA	+	NA	-
Eisodes of coma	NA	NA	NA	NA	-
Microcephaly	-/-	NA	NA	+	NA
Skin (Petechiae)	-/-	+	NA	+	+
Orthostatic acrocyanosis	+/+	+	NA	+	-
Chronic Diarrheoa	-/-	+	+	+	+
Failure to Thrive	NA	NA	NA	+	NA
Feeding difficulties	Gastrostomy/ +	NA	NA	NA	NA
Irritabılity	NA	NA	NA	+	NA
Developmental Delay	+/+	+	+	+	+
Other Malformations	-	-	-	NA	
Eye	NA	NA	Retinal vessel tortiosity	Retinal vessel tortiosity	Abnormal VEP Abnormal auditory potencial
Liver involvement	NA	NA	-	NA	NA
Facial dysmorphy	-	-	-	NA	NA
Misdiagnosis	-/ Meningococcemia	Rheumatologic disorder	Leigh syndrome	SCAD deficincy	Superficial gastritis,cholitis
Lactat mmol/L	5.8/	NA	⇑ (mild)	NA	9.05
Ethylmalonic Acid µmol/ mmol creatinine	1. 556 2. 585	93.63	96	⇑⇑	28.86-71.84
C4 µmol/L	1. 1.62-1,73 2. 1.09-2.55	2.89	⇑ (mild)	⇑⇑	0.91
C5 µmol/L	1. 0.56 2. 0.48	NA	⇑ (mild)	⇑⇑	NA
Carnitine µmol/L	N/low	NA	NA	NA	NA
ETHE1 gene mutation	1. (p.Cys189PhefsTer2) (c.505 + 1G > A) Hom 2. Novel (c.566delG) (p.Glu44-ValfsTer62) (c.131_132delAG) CH	1.(p.R163Q) (c.488G>A) Hom	1. (p.Met1Ile) (c.3G>T) Hom	1. (p.R163W) (c.487C > T) Hom	1. (c.595C+ 1G>T) (p.D196H) (c.586G>C) CH

Table 1 (continued)

Treatment	1.NAC,Metronidazole alternating neomycin Ascorbic acid, restricting sulfur containing amino acids at 1 years of age (not compatible) 2.Metronidazole or neomycin and NAC, Ascorbic acid, restricting sulfur containing amino acids Adrenocorticotropic hormone and phenobarbital, felbemate	Metronidazole, NAC, Coenzyme Q10, Riboflavin	NA	L-carnitine, Metronidazole NAC	L-carnitine,vitamin B1 and vitamin B2, NAC, Metronidazole, Clostridium butyricum tablets
Outcome Alive	NA		6 years	21 months	29 months
Age of Death	NA		-	-	
Death Reason	NA	NA	-		
Authors	[40]	[41]	[6]	[42]	Presented Cases* Mild
Country	Spain	Italy	USA	Australia (Afganian patient)	Turkey
Year of the Article	2021	2021	2021	2022	2022
Number of Cases	1 (M)	1 (F)	3 (1 F, 2 M)	1 (F)	2 (1F, 1M)
Parental consanguinity	-	na	-	+	+/+
First symptom	1.Developmental delay, mild language regression with the loss of the 3 words, hypotonia, and failure to thrive		1.Psychomotor delay 2.Psychomotor delay 3.Enteropathy	Acute deterioration, involving depressed conscious state, hypotonia, reduced peripheral perfusion with only central pulses palpable, and a rapidly evolving widespread purpuric rash	1.Encephalopatic crises, diarrhea spastic paraparesia 2. Diarrhea, spastic paraparesia
Symptom onset age	10 months	7 months	1.24 months 2.41 months 3.20 months	1.9 months	1.2,5 years 2.3 years
Psychomotor Regression	+	+	+++	+	+/+
Hypotonia	+	+	-/-/+	+	-/-
Spastic paraparesia	NA	+	+/+/+	NA	+/+
Seizure	-	-	-	-	-/+
Seizure Type					NA

Table 1 (continued)

Ataxia	NA	NA	NA	NA	-/-
EEG					-/NA
Dystonia	NA	NA	NA	NA	+;/+
Pyramidal signs	+	+	-/+	+	+/+
Eisodes of coma	NA	NA	NA	+	+/+
Microcephaly	-	-	-	-	-
Skin (Petechiae)	+	+	-/-		+/+
Orthostatic acrocyanosis	NA	+	-/-/+	+	+/+
Chronic Diarrheoa	+	+	-/-/+	NA	+/+
Failure to Thrive	+		-/-/+	+	+/+
Feeding difficulties	NA	NA	-/-/+	NA	+/+
Irritabılity	NA	NA	NA	NA	NA
Developmental Delay	+	+	+//+//+	+	+/+
Other Malformations	Dolichocephaly, prominent forehead, retrognathia, low-set ears a small mouth with thin lips	-	-	-	-
Eye	NA	NA	NA	NA	NA
Liver involvement	NA	NA	NA	NA	-
Facial dysmorphy	+	-	-	-	-
Misdiagnosis	NA	NA	MELAS	Meningococcemia	-
Lactat mmol/L	NA	6.4 -2.8	1. 6.2 2. 9.3	6.6	8-9.9/4-8
Ethylmalonic Acid µmol/mmol creatinine	NA	205.8-66.2	⇑⇑	⇑⇑	1.130 2.15.37
C4 µmol/L	NA	NA	1.1.53 2. 1.17 3. 2.17	⇑⇑	1. 1.95 2. 0.79
C5 µmol/L	NA	NA	-/-/0.77	⇑⇑	1.0.61 2.0.29
Carnitine µmol/L	NA	NA	NA	NA	NA

Table 1 (continued)

ETHE1 gene mutation	1. (p.R163Q) (c.488G>A)	1. (p.Glu44ValfsTer62) (c.131_132delAG) Hom	1. (p. Ser88Leu). (c.263C>T) (p. Thr136Ile) (c.407C>T) CH 2. (p. Ser88Leu), (c.263C>T) (p. Thr136Ile), (c.407C>T), 3. (p.R163W) (c.487C>T) Hom	1.(p.Glu44ValfsTer62) (c.131_132delAG) Hom	1. (p.R163Q) (c.488G>A) Hom 2. (p.R163Q) (c.488G>A) Hom
Treatment	Biotin, coenzyme Q10, vitamin E, riboflavin, thiamine, and L-carnitine; Metronidazole, NAC	Liver transplantation NAC, Metronidazole, L-carnitine	Liver transplantation NAC, Metronidazole, L-carnitine	Riboflavin , coen-zyme Q10, L-carnitine, NAC intravenous, Metronidazole, and a low protein diet	Riboflavin, coenzymeQ10 Metronidazole NAC intravenous
Outcome Alive	2.5 years	7 years	1. 7years 8 months 2. 5 years 3. 59 months		1 . 13 years 6 months 2. 11 years
Age of Death					
Death Reason					

NA: not available, *MNZ*: Metronidazole, *NAC*: N-acetylcysteine, *CRRT*:Continious Renal Replacement Therapy, *Hom*: Homozygous, *CH*: Compound Heterozygous, *SCADD*: Short chain acyl-co A dehydrogenase deficieny, *GTCS*: Generalise tonic clonic seizure, *HMG*: Hepatomegaly, SMG: Splenomegaly, MADD: Multiple Acyl-co-A Dehydrogenase deficiency

*:Mild phenotype

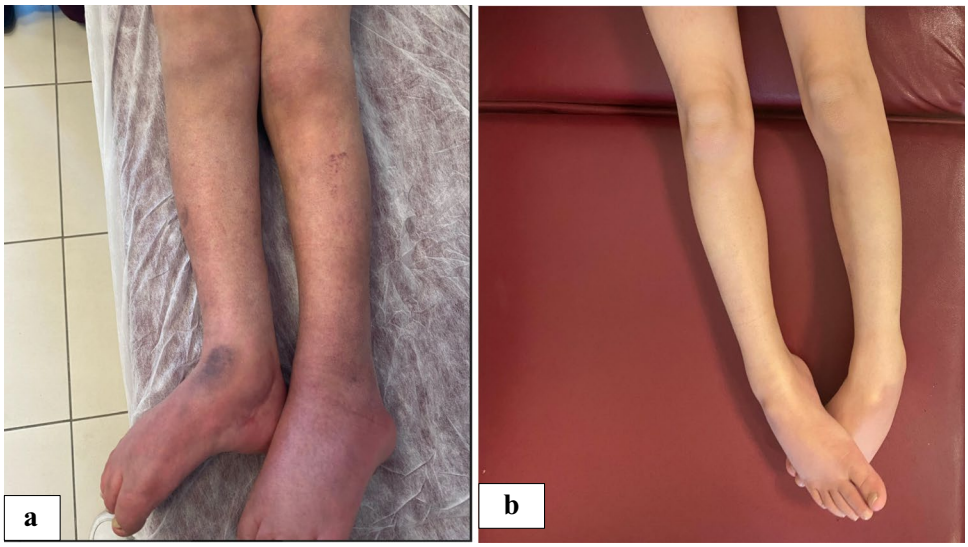


Fig. 3 Picture 1 **a** Acrocyanosis of patient 1. **b** Spastic paraparesia of patient 2

Table 2 ETHE1 gene mutations

Homozygous		
[13]	(p.N77fsX144)(c.230delAA)	1
[18],[8],[6],[33]	(p.R163W) (c.487C>T)**	4
[14]	(p.R163G) (c.487C>G)	1
[40] [38] [43],[20] + Presented Cases	(p.R163Q) (c.488G>A) **	6
[2]	(p.D169N)(c.586G>A)	1
[2]	(p.L55P) (c.164T>C)	1
[2]	Homozygous deletion from exon 4 to exon 7	1
[44],[45],[46],[19],[33]	Exon 4 homozygous deletion	5
[12]	(IVS4DS) (c.505+1G>T)	1
[7],[9],[29]	(p.M1I) (c. 3G>T)**	3
[31] [41] [42]	(p.Glu44ValfsTer62)(c.131_132delAG)	3
[32]	(p. L185R)(c.554T> G)	1
[10]	(p.Q27K) (c.79C>A)**	1
[23]	(p.Q99*) (c.295C>T)	1
[34]	(p.D165H) (c.493G>C)	1
[37]	(p.Cys189PhefsTer2) (c.505+1G>A)	1
Compound Heterozygous		
[2]	(p.Y74X)(c.221-222insA)//(p.T164K) (c.491C>A)	1
[2]	(p.R163W)(c.487C>T) //(p.T152I) (c.455C>T)	1
[45]	(p.L185R) (c.554T>G) // deletion of exon 4	2
[28]	(p.E208del)(c.622_624delGAG)//(p.I114F)(c.340A>T)/ (p.R163Q) (c.488G>A).	1
[30]	(p.R163Q) (c.488G>A)/(c.375+5G>T)	1
[37]	(c.566delG) / (p.Glu44ValfsTer62) (c.131_132delAG)	1
[39]	(p.D196H)(c.586G>C) / (c.595C + 1G>T)	1
[35]	(c.375+5G>A) (splicing)/ (p.D154E) (c.462T>A)	1
[6]	(p.Ser88Leu)(c.263C>T) / (p. Thr136Ile) (c.407C>T)	2
[11]	(p.Q27K) (c.79C>A), (p.L185R) (c.554T>G)**	2

**: Patients with mild phenotype.

Table 3 Cranial Imaging of Patients

Authors	Cranial Imaging
[21]	MRI: Hyperintensity of the cerebellar white matter and bilateral hyperintensity of caudate and lenticular nuclei.
[26]	CT: Normal
[3]	1. MRI :Bilateral symmetric hyperintensity and swollen dishomogeneous areas with small, hypotense polymorphic structures affecting the head of the caudate nuclei and putamen, but sparing the thalamus. Other MRI's are similar.
[22]	1. Brain MRI: Bilateral hyperintensity of the cerebellar white matter, and of the basal ganglia. 2. CT scan and MRI showed bilateral lesions involving the head of caudate and putamen.
[15]	1. Small areas of high T2 intensity bilaterally within the heads of caudate nucleus, putamen and posterior fossa. Frontotemporal hypoplasia 2. Symmetric anterior and posterior infarcts in watershed distribution, as well as symmetric hypodense lesions in basal ganglia and caudate nuclei. Frontotemporal hypoplasia. 3. Increased subarachnoid spaces. Low density lesions bilaterally in the heads of caudate nuclei. Frontotemporal hypoplasia 4. Diminished density of the white matter in both cerebral hemispheres. 5. Mild frontal atrophy, somewhat widened sylvian fissure and subarachnoid spaces. Frontotemporal hypoplasia.
[27]	1. Prolongation of the relaxation times involving many structures, including both lenticular and caudate nuclei, periaqueductal region, bilateral scattered subcortical areas, hemispheric white matter foci, and brainstem.
[25]	1. Hypoxic ischemic encephalopathy 2. Multifocal nodular high signals in both basal ganglia with enhancement, patchy high signals in periventricular white matter, centrum semiovale and cerebellum. 3. Multiple acute and subacute haemorrhagic lesions in the both parietal areas, with increased signals in the bilateral putamen, medial part of cerebellum, posterior portions of C-spines, medulla, bilateral cerebellar peduncles and pons.
[13]	1. Symmetric T2-weighted hyperintensities in the basal ganglia. showed multiple areas of low and high signal (T1W & T2W) in the basal ganglia and prominent frontal and temporal subarachnoid spaces. 2. Revealed asymmetry of the frontal horns, prominent sulci of the right hemisphere and areas of altered signal in the lentiform and caudate nuclei.
[8]**	Multiple patchy areas of abnormal signal intensity involving the striate nuclei bilaterally with inhomogeneous contrast enhancement, an appearance consistent with cerebrovascular lesions with attendant blood–brain barrier breakdown. MR angiography showed irregular margins of the right anterior cerebral artery and prominent perforating arteries.
[2]	1. Bilateral asymmetrical high T2-weighted signal intensity in the globus pallidus, capsula extrema and amygdala 2.-- 3. Abnormal signal in the white matter with Leigh-like lesions 4. -- 5. Brain atrophy
[14]	CT: fronto-temporal atrophy, enlargement of the subarachnoid spaces and basal ganglia involvement MRI: At the age of 8 months: Fronto-temporal atrophy, enlargement of the subarachnoid spaces and basal ganglia involvement. At the age of 2 years demonstrating more extensive atrophy involving fronto-temporal and parietal regions bilaterally with ventricular dilatation and subarachnoid space enlargement, basal ganglia and periventricular white matter involvement, as well bilateral subdural hygromas.
[11]**	1. Increased signals on T2-weighted images in the frontoparietal white matter in the form of lines and rosaries, while the basal ganglia were normal. During the episode of coma, MRI showed diffuse anomalies on T2-weighted images in the white matter (partly sparing the occipital lobes and U-fibers), the lentiform nuclei and caudate nuclei. The cerebellum and pons were mostly spared. 2. Increased white matter signals on T2-weighted images in the peri-ventricular area and adjacent to the right formix. A small focus of increased signal on T2-weighted images was seen the right putamen. A 2.8 cm x 0.8 cm cavity was seen next to the right fornix, the latter being atrophied. At 8 years of age, MRI showed increased signals on T2-weighted images diffusely affecting the white matter of the centrum semiovale, sparing the U-fibers
[46]	MRI: Basal ganglia and white matter changes
[44]	Symmetric patchy high T2-weighted areas in caudate nuclei and thalami with global brain atrophy. Proton MR spectroscopic imaging detected high levels of lactate in basal ganglia and in dentate nuclei.
[45]	1. MRI of the brain revealed multiple loci of high intensity on the T2-weighted images and low-signal intensity on the Flair and T1W/SE images of the basal ganglia bilaterally. 2. MRI of the brain showed evidence of high-signal foci at the basal ganglia and thinning of the corpus calosum.
[19]	MRI: Symmetrical frontotemporal atrophy, diffuse T2 hyperintensity of the periventricular white matter, and high signal in the heads of the caudate nuclei on fluid-attenuated inversion recovery images

Table 3 (continued)

Authors	Cranial Imaging
[28]	Multiple patchy areas of abnormal signal intensity involving the lenticular and caudate nuclei bilaterally as well as the brainstem and cerebellar dentate nuclei. The corpus callosum was significantly thinned especially in the trunk and the splenium. Brain proton MR spectroscopy showed a lactate peak in the areas of altered MRI signal and a significant increase in choline peak with a slight reduction in the peak of N-acetylaspartate.
[29]**	Bilateral punctuate hyperintense T_2 signals in the basal ganglia with minor lactate peak on spectroscopy.
[30]	MRI brain showed abnormal hyperintense signals in T2W/FLAIR in bilateral putamen and caudate nuclei. Subtle hyperintensities were also noted in bilateral peritrigonal regions.
[32]	Abnormal hyperintense tiny areas involving corpus striatum bilaterally a as well as bilateral middle cerebellar peduncle lesions. These lesions shows no abnormal diffusion restriction on diffusion weighted imaging. Proton MR spectroscopy with lactate peak at on the corpus striatum, shows a small lactate peak on the bilateral middle cerebellar peduncle lesion
[20]	Magnetic resonance imaging scan demonstrated volume loss and increased T2 signal in the periventricular white matter and dorsal brainstem, and abnormal foci of increased T2 signal in the basal ganglia bilaterally with decreased diffusion. Spectroscopy demonstrated a lactate peak.
[37]	1. T2 at 10 weeks of age: Cavitary lesions within bilateral putamina and head of the caudates. 1b. T2 at 25 months of age showed new increased T2 hyperintensity seen diffusely in the caudate and putamina. On diffusion-weighted imaging (DWI) at 25 months of age, several scattered areas of cortical restricted diffusion 2. T2 and other imaging sequences at 4 weeks of age were unremarkable. T2 at 21 months of age showed increased heterogeneous patchy T2 hyperintensity involving caudate and putamina. Some small cystic areas were developing. DWI at 21 months of age; no restricted diffusion noted in cortical areas, subtle signal changes were seen in bilateral putamen.
[7]**	Revealed bilateral hyperintensity in the head of the caudate nucleus, subcortical and deep white matter, and cerebellar white matter. It also showed multiple cavitation foci; diffusion-weighted MRI showed diffusion-restricting lesions. CT: Calcification of the posterior occipital area
[18]	Symmetrical hyperintense signals on T-2 weighted images in basal ganglia
[39]	Abnormal signal shadows in the temporal horn of the left lateral ventricle, revealing demyelination in the brain.
[10]	Bilateral and symmetric increased T2 signaling in the basal ganglia and cerebellum. Magnetic resonance spectroscopy (MRS) of the basal ganglia demonstrated a corresponding high lactate peak not shown
[9]**	MRI: Normal
[23]	Bilateral frontal and temporal subarachnoid space dilatation, and enlarged interhemispheric fissure.
[34]	Bilaterally symmetrical, patchy hyperintensity in caudate and putamina, without evidence of diffusion restriction or bleed and subtle hyperintensity in the dorsal pons. A small focus of enhancement is noted in the right caudate head. Bilaterally symmetrical hyperintensity is also noted in the periventricular white matter. Brain MRI at 60 months of age shows the persistence of hyperintensity in caudate and putamina and subtle hyperintensity in the dorsal pons. The extent and intensity of enhancement in postcontrast sequences has increased.
[35]	Fronto-temporal atrophy with multiple bilateral symmetrical abnormal low and high signal intensity involving caudate nucleus and lentiform nucleus in T1- and T2-weighted sections, respectively. Twenty months after transplantation, brain magnetic resonance imaging shows lesions remained but ameliorated.
[40]	Bilateral signal alterations in the putamen and head of the caudate nucleus; hyperintense lesions on T2- weighted and FLAIR sequences. No globus pallidus or internal capsule involvement were observed. No loss of parenchymal volume was observed at the supra or infratentorial levels.
[41]	A mild brain atrophy and initial bilateral involvement of basal ganglia.
[6]	T2 hyperintense and T1 hypointense focus in the left caudate with general volume loss. demonstrates normal appearance of the brain parenchyma at the level of the basal ganglia. During the acute presentation, T2 weighted FLAIR MRI demonstrates increased signal intensity involving the head of the caudate and putamina bilaterally. This correlates with increased signal in DWI sequence and decreased ADC signal demonstrating diffusion restriction in these areas. A 3-month follow-up MRI after the acute presentation demonstrates the development of T2-hyperintense areas indicative of cavitation in the caudate and putamina with associated volume loss seen as widening of the ventricles and sulci.

Table 3 (continued)

Authors	Cranial Imaging
[42]	Apparent diffusion coefficient (ADC) map and diffusion-weighted image (DWI) show multiple punctate lesions in the thalami and globi pallidi that are associated with true diffusion restriction consistent with small acute (likely <7 d old) infarcts. SWI showing signal loss in a few of the right thalamic lesions consistent with microhemorrhage, T2-weighted image demonstrating numerous T2 hyperintense periventricular punctate lesions that have no corresponding restricted diffusion consistent with nonacute infarcts. T2-weighted axial image demonstrating subtle widening of the left frontoparietal subarachnoid space (arrows) likely due to reduced left hemispheric volume consequent upon microscopic remote ischemic white matter/subplate injury postnatally or prenatally.
Presented Cases	1. Increased signal in bilateral basal ganglia, dentate nuclei and peridental areas, and substantia nigra in the level of cerebral peduncles in addition to diffusion restrictions. 2. Normal

compared to the classical phenotype (Fig. 2d). Patients with mild phenotypes were found to live longer and do not demonstrate severe encephalopathic findings.

The most common symptoms of EE were psychomotor regression and diarrhoea (Table 1) (Fig. 1a). Hydrogen sulfide accumulation results in vasotoxicity and damages vascular endothelial and mucosal cells of the intestines, which is associated with chronic diarrhoea. Hypotonia, psychomotor regression, developmental delay, pyramidal signs, and spastic paraparesis result from vasculopathy-associated necrotic lesions in the brain [47]. Increased epileptic activities especially have been reported during metabolic attacks [34]. Petechia and orthostatic acrocyanosis could also be explained by the vasoactive and vasotoxic effects of hydrogen sulfide were the other common manifestations at onset, being reported in 55 and 47 patients, respectively [20, 47] (Fig. 1d). These symptoms caused a diagnostic delay due to the suspicion of coagulation disorders and meningococcal infection.

Five out of 8 (62.5%) patients with mild phenotype exhibited spastic paraparesis, a higher ratio compared to classical phenotype (35.4 %). The mental status of two patients in the literature was normal [9, 10, 29] (Table 1).

The biochemical profile of EE patients consists of elevated lactate, plasma C4 and C5 acylcarnitines, and C4–6 acylglycines and increased urinary EMA. Thiosulfate is produced during sulfide catabolism and is also elevated in EE patients [47]. Urinary EMA levels range broadly between 45-730 µmol/mmol creatinine [24]. To date, normal ethylmalonic acid levels during an episode of decompensation have been reported only in two patients with a mild phenotype (Table 1) [8, 9]. Urinary EMA, C4 and C5 levels can also exhibit normal values in milder cases in the attack-free periods and only slight elevations in the steady phase. In suspected cases of EE, it is critical to take samples during metabolic attacks. Since EMA and C4 levels were higher in the classical phenotype than the mild phenotype (Fig. 2a,b), these have prognostic value for EE progression and future treatment decisions. Our second patient with a mild phenotype demonstrated normal urinary organic acid levels of EMA and cranial MRI. Therefore, a detailed physical examination of patients is required to guide the diagnosis in milder cases of EE,laboratory tests and imaging alone can miss the diagnosis.

Sulfide has been shown to impair other Acyl-CoA dehydrogenases, including 2-Methylbutyryl-CoA dehydrogenase, Isovaleryl-CoA dehydrogenase and Isobutyryl-CoA dehydrogenase [44]. As a result, high concentrations of C4-carnitine in plasma and EMA in urine are also detected in SCAD deficiency [48]. Sulfide accumulation in body tissues above a limit at which toxicity occurs and inhibits SCAD,as a result, a few patients were diagnosed with SCAD deficiency of whom laboratory results mimicked EE [18, 23] (Table 1). Severe neurological symptoms, orthostatic acrocyanosis and petechia are essential clinical findings to distinguish SCAD deficiency from EE [18, 43].

Additionally, some patients with EE were misdiagnosed with multiple-acyl-CoA dehydrogenase deficiency (MADD) [23, 26] (Table 1). MADD can exhibit elevated C4, C6, C8, C10 and C12 in plasma and increased EMA in urine [49]. The lack of multiple biochemical elevations is essential to rule out MADD in these patients.

Nine patients demonstrated facial dysmorphic features [15, 27, 36, 40]. Facial features of four out of 9 patients had broadened and depressed nasal bridge and epicanthic folds [15]. Mild hypertelorism with a depressed nasal bridge was detected in 1 patient [27]. Two patients had prominent epicanthal folds, up-slanting palpebral fissures, and depressed nasal bridges [36]. Dolichocephaly, prominent forehead, retrognathia, low-set ears, and a small mouth with thin lips were detected in 1 patient [40]. Ozand et al. [15] hypothesised that mild facial dysmorphia and frontotemporal lobe hypoplasia suggest a prenatal onset for the disease. None of the mild cases was reported with facial dysmorphic features, and this might prove the theory of the late influence and late-onset pathogenesis in mild phenotype.

Renal involvement of EE patients (grade 2 hydronephrosis, diffuse mesangial sclerosis, crescentic

glomerulonephritis, renal failure, mild to moderate hematuria) with classical phenotype has been reported previously [12–15] (Table 1). It is hypothesised that the accumulation of hydrogen sulfide is responsible for the diffuse vascular damage of renal vessels as a part of systemic vasculitis [50]. This renal disease may have been previously underrecognised due to the other severe clinical features of EE. Therefore, urinary tests should be performed in EE patients to detect hematuria secondary to renal vascular involvement.

Cardiac and skeletal involvements were ultra-rare in EE. Only one patient was reported with cardiac involvement (mild tricuspid regurgitation and dilatation of the pulmonary artery) [13]. Scoliosis and hip dislocation were reported in twins who were alive at 10.5 years of age [11]. Neurological deterioration is an important reason for orthopaedic deformities in patients, such as scoliosis caused by postural instability.

A patient with articular hyperlaxity with suspected Ehler Danlos syndrome showed normal cognitive development and ethylmalonic acid excretion outside of decompensation episodes, with cerebrovascular involvement on MRI, was classified as a mild/atypical phenotype [8].

Fundoscopic eye examination revealed tortuosity of retinal vessels in 9 patients [7, 15, 18–20]. Four out of 9 patients' eye findings had appeared after 3-4 months of life. None of them received oxygen therapy or had a history of prematurity [15]. Fundus examination has been previously underutilised in the diagnosis of EE, with vessel tortuosity being diagnostic of the vascular involvement of EE. Strabismus [14], esotropia [29], and abnormal visual and auditory evoked potentials were reported in one patient [39]. One out of 8 patients had tortuosity of retinal vessels in fundus examination with the mild phenotype [7].

The pathophysiological mechanism of the brain MRI changes is cytotoxic oedema with the contributory factor of acute vascular injury [50]. The accumulation of sulfide causes direct injury to endothelial cells. Symmetrical T_2-weighted signals are the typical changes in the basal ganglia, dentate nuclei, brain stem, cerebellar and periventricular white matter in the MRI of patients. In some cases, frontotemporal atrophy, enlargement of the subarachnoid spaces, cortical or global atrophy and diffuse leukoencephalopathy were presented. Magnetic resonance spectroscopy (MRS) of 6 patients showed a high lactate peak of the basal ganglia [10, 20, 28, 29, 32, 44] (Table 3). Symmetrical hyperintensities in the basal ganglia and increased lactate levels in MRS are also typical findings of Leigh Syndrome, which is suspected in some patients with EE [2, 7, 13, 36] (Table 3). Lim et al. [6] presented three cases whose mental status deteriorated with subsequent developmental regression with suspicion of stroke-like episodes. Their Cranial MRI typically demonstrated stroke-like lesions, diffusion restriction of basal ganglia and involvement of cerebellum or white and deep grey matter. Cranial MRI shows a classical Leigh Syndrome appearance in most patients following disease progression, white matter and deep grey matter could also be affected together with stroke-like lesions depending on the vascular endothelial damage. Interestingly, two patients' cranial MRIs with mild phenotype were normal, one of which was presented in case 2 [9] (Table 3).

So far, missense, nonsense, pathogenic variants and deletions have been identified in the *ETHE1* gene. Whilst the most frequent missense mutation in our review was (p.R163Q) (c.488G>A), with the most frequent large deletion being an exon 4 homozygous deletion (Table 2). Mutations in the cases of mild phenotype were (p.R163Q) (c.488G>A) (2), (p.R163W)(c.487C>T) (1)[8], (p.M1I) (c. 3G>T) (3) [7, 9, 29], (p.Q27K) (c.79C>A) (1) [10] and a compound heterozygous (p.Q27K) (c.79C>A), (p.L185R) (c.554T>G) mutation (1) [11]. So far, (p.R163Q) and (p.R163W) have been reported in patients with both classical phenotypes (4 and 3 patients, respectively) [8] and one case of a mild phenotype. To date, (p.M1I) (c. 3G>T) homozygous mutation has been reported in 3 patients with mild clinical phenotype [7, 9, 29]. However, the same mutation was also reported as a severe mutation by Tiranti et al [24].

Pigeon et al. [11] reported two monochorionic twins with the same (p.Q27K/ p.L185R) compound heterozygous mutation with divergent clinical courses. The twin sister exhibited a mild phenotype with limited symptoms confined to the lower extremities with the use of a wheelchair, language was intact and they were bilingual. Contrastingly the other twin had spastic quadriparesis and was non-verbal. The first twin did not have any attacks of petechiae, orthostatic acrocyanosis or diarrhoea [11]. Despite reports of the p.L185R mutation being associated with the classical EE phenotype previously [45], this indicates when p.Q27K is the second allele, it might modify the phenotype severity [11, 32]. Our presented cases have homozygous R163Q mutations, respectively, and they exhibit a mild clinical phenotype. Exon 4 deletion and exon 4 to 7 deletion might draw a severe phenotype [2, 19, 33, 44–46]. Our review of these cases illustrates that no clear genotype-phenotype correlations have been recognised for pathogenic *ETHE1* variants. These phenotypic differences may reflect the influence of environmental factors such as metabolic decompensation attacks, epigenetic or modifier gene influences, suppressor genes or genetic factors which is not related to th*e ETHE1* gene on the extent of clinical presentation.

Lowering the accumulation and inducing detoxification of sulfide is accepted as the primary treatment strategy in the chronic management of EE currently. Combination therapy of metronidazole and N-acetylcysteine (NAC) is used from diagnosis to attempt to achieve this. Metronidazole decreases the production of sulfide in the gut, and NAC works as a glutathione donor, which is involved in the conversion of

sulfide to a non-toxic form of glutathione persulfide (GSSH) [51]. In a study held in 2010 on five individuals with metronidazole/NAC combination therapy, the results showed neurological status improvement, with a reduction or resolution in episodes of diarrhoea, petechiae and acrocyanosis. The urinary EMA, C4 acylcarnitines and thiosulfate levels also decreased [51]. NAC has been shown to be beneficial during acute episodes of metabolic decompensation, with Kılıç et al initiating intravenous NAC (100 mg/kg/day) infusions to a 10-month-old girl with encephalopathic crisis, resulting in neurological improvement [32]. We similarly started intravenous NAC for our second patient during his two encephalopathic crises, and clinical status recovered faster than during previous attacks.

Other previously trialed treatments in EE have been Riboflavin and L-carnitine [21], however, due to the early mortality in these patients, it was not possible to assess for meaningful clinical improvement. Further use of riboflavin was revisited in 2002 when Yoon et al investigated its potential for increasing the activity of acyl-CoA-dehydrogenases. [25]. This study demonstrated only a slight improvement in clinical status despite a reduction in C4 and C5 acylcarnitine levels in a third of patients. Dietary modification has been investigated as a treatment for EE. A study by McGowan et al in 2004 investigated restriction of dietary methionine, which lead to a subsequent measured decrease in EMA excretion however, long-term follow-up could not be performed due to the early death of the patient at 8 months of age [36]. In 2010, a study of an isoleucine-restricted diet in one patient resulted in partially corrected EMA, C4 and C5 acylcarnitine levels [44]. Additionally, ascorbic acid, vitamin E, B1, biotin, vitamin B6 and coenzyme Q10 have been used as treatment strategies (Table 1). In 2018 one patient identified through newborn screening was commenced on a methionine and cysteine-restricted diet at 8 months of age, combined with metronidazole and NAC at 10 weeks of age. Both the clinical outcome and biochemical markers improved. These results suggest earlier initiation of combined therapy, including diet, metronidazole and NAC, might result in improved clinical outcomes in these cases [37].

The oldest patient reported with a mild phenotype was a 19-year-old male with a homozygous p.Gln27Lys mutation presenting with atypical features including ataxia, spastic paraparesis, macrocephaly and Arnold Chiari Malformation type 1 without any attacks of diarrhoea or acrocyanosis. During episodes of decompensation, continuous renal replacement therapy (CRRT) was successfully performed to regain his metabolic control and lower sulfide levels. Patients with a milder clinical course may be suitable to undergo CRRT to achieve metabolic control during crises [10].

As these discussed treatment strategies are not entirely curative, two patients underwent liver transplantation intending to increase liver sulfur dioxygenase activity, resulting in increased clearance of toxic levels of H_2S. Following transplantation biochemical abnormalities were reversed, with a remarkable progression of psychomotor developmental milestones [31]. Although this patient's neurological status improved in the post-liver transplantation period, the patient died at two years of age during this severe encephalopathic crisis of viral gastroenteritis. This has resulted in the continued debate regarding the efficacy of liver transplantation given this further metabolic decompensation in this patient. The other reported cases of liver transplantation exhibited similar improvements in psychomotor development in the post-transplant period [33], with another reported case developing stroke-like episodes despite the initial improvements after liver transplantation [6]. The age at transplantation also appears to influence the outcome, with a patient undergoing liver transplantation at 18 months of age showing no clear clinical improvement [35]. Overall, of those who underwent liver transplantation, 50% either stabilised or improved, and it is currently recommended that post-transplantation metronidazole, carnitine and NAC all continued to protect vascular endothelium from potential sulfide accumulation [6, 31, 33, 35, 41]. It is necessary to take into account the benefit-risk ratio on an individual case-by-case basis whilst considering liver transplantation. The potential reversibility of the existing neurological disability, peri and postoperative morbidity, transplant-related complications, and immunosuppression should be kept in mind during decision-making. Patients with milder phenotypes are neurologically intact during earlier stages,therefore, liver transplantation could be considered a therapeutical option in these patients due to the greater likelihood for normal development and functioning.

Conclusion

We have reported two patients with mild clinical phenotype and reviewed 68 patients from the literature presenting with a variety of clinical, biochemical, genetic and neuroradiological features. Eight out of 70 patients were classified as having a mild phenotype. Patients with EE are often first suspected to have Cow milk protein intolerance due to chronic diarrhoea and other gastrointestinal manifestations. The diverse clinical variability of EE patients impacts the age at diagnosis, chronic management and survival. Early diagnosis and recognition of susceptibility to acute metabolic decompensation are essential to minimise the neurological decline in these patients. Individualised treatment strategies need to be considered according to the frequency and nature of metabolic decompensation, clinical phenotype, metabolic profile, imaging results and genotype.

NAC and metronidazole should be started as soon as EE is diagnosed. Further studies are required to evaluate the clinical efficacy of sulphur and methionine-restricted diets and CRRT. Although liver transplantation may not resolve the occurrence of metabolic attacks, it must be considered in each case as a potential component of combined therapy. The process of diagnosis and initiation and maintenance of therapies should be conducted via a multidisciplinary team approach.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Declarations

Ethics approval Ethical committee approval is not required for review article and case presentations. Patient consent statements were obtained from all the legal guardians of the patients. Consent for the use of patient pictures was also obtained.

Consent to participate and consent to publish Written informed consent was obtained from the parents of the patients described in the study. The authors affirm that human research participants provided informed consent for publication of the images.

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