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

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Abstract

Background: Ethylmalonic encephalopathy (EE) is a rare intoxication-type metabolic disorder with multisystemic involvement caused by *ETHE1* gene mutations playing a role in hydrogen sulfide (H2S) detoxification.

Results: This review focuses on the clinical, metabolic, genetic and neuroradiologic features of 70 reported cases, of which two are new cases. Included are eight cases of mild phenotype, demonstrating slow neurological progression with low levels of ethylmalonic acid (EMA) and C4 acylcarnitine. 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. Current age of mild phenotype cases was significantly higher compared to classical phenotype *(p=0.002).* Lowering the accumulation and inducing detoxification of H_2S 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: Samples of EMA and C4 acylcarnitine during metabolic attacks are critical to diagnose EE and treat early to prevent encephalopathic crises. Experience with liver transplantation, diet and CRRT, are currently limited. 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 sulphide (H_2S) detoxification pathway in mitochondria (Tiranti et al., 2009). Less than 100 cases have been reported worldwide since 1991, with the majority of patients being from Mediterranean and Arabic populations (Mineri et al., 2008) (A. B. Burlina et al., 1994). EE is a disorder of mitochondrial energy metabolism, which involves inhibition of short acyl-CoA dehydrogenase (SCAD) and cytochrome c oxidase deficiency. Deficiency in sulphur dioxygenase enzymatic activity results in the toxic accumulation of H_2S in body fluids and tissues, including the colonic mucosa, liver, muscle, and brain. 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, ethyl malonate and butyrilcarnitine (C4) and isovalerylcarnitine (C5) acylcarnitine in the brain and muscle tissues (Di Meo et al., 2011; Grosso et al., 2002; Tiranti et al., 2009).

Typical Magnetic Resonance Imagining (MRI) images for this disorder reveal symmetric T2 weighted signals throughout the periventricular and cerebellar white matter, dentate nuclei, and brain stem. Cases with an extensive disease can additionally exhibit cortical atrophy and diffuse leukoencephalopathy (Lim et al., 2021).

The course of the disease was originally thought to be universally aggressive and prematurely fatal early in life; onset in the first few months after birth, followed by progressive clinical deterioration. However, there are reports in the published literature of milder clinical phenotypes that resemble the 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 that have been documented to emphasise the importance of clinical suspicion in patients presenting with a milder phenotype.

Patient 1: A 13-years and 6 month 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 3 times previously. The preceding history included mucoid diarrhoea six times a day. These

symptoms also occurred 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, he acquired head control; he could sit without support at eight months of age. The patient could say mom and dad at 1.5 years of age and speak normally at 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. Eye examination was normal except for incidental right eye amblyopia, and hearing was intact. Urinary organic acid analysis revealed a high excretion of ethylmalonic acid (130 mg/g 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 umol/l (0 - 1.2) and C5 Carnitine 0.71 umol/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 mM/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 (Picture 1), together with the laboratory findings of elevation in C4, C5 and lactate and ethylmalonic acid elevation in urinary organic acid, EMA was suspected. *ETHE1* analysis by sanger sequencing demonstrated a homozygous mutation *ETHE1,* c.488G>A (p.R163Q), confirming EE. The patient was commenced on riboflavin (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-years and 8-month-old girl, the third child of consanguineous parents, presented to the clinic following a history of intellectual disability and spastic paraparesis (Picture 1b). 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. She has never been able to walk. She was followed up for chronic watery, mucoid diarrhoea, with seven episodes daily. She was managed for 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. Prior to this admission, the patient had four encephalopathic crises over the previous year. Urinary organic acids (urinary ethylmalonic acid: 15.37 mmol/mol, plasma amino acids and carnitine acylcarnitine profile (C4: 0,79 umol/ C5: 0.29 umol/) 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 mM/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, neuroradiological findings and clinical progress of patients were summarised.

RESULTS

In addition to our two 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 with EE by molecular analyse while twenty-five patients were diagnosed with laboratory and clinical analyses. Data of patients diagnosed without molecular analyses were collected from the 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) respectively. So far, 6 of the eight patients have been reported as having a mild phenotype in the literature with chronic, very slow neuromotor deterioration (Cavusoglu et al., 2018; Di Rocco et al., 2006; Ersoy, Tiranti, & Zeviani, 2020; Kitzler et al., 2019; Pigeon, Campeau, Cyr, Lemieux, & Clarke, 2009). 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). Gender distribution was as follows: 35 Females (48.6%), 36 Males (51.4%). 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 (Figure 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 (Figure 1b). gastrointestinal findings were failure to thrive in 42 patients, chronic diarrhoea in 49 patients, feeding difficulties in 34 patients and hepatomegaly in 6 patients (Figure 1c). Vascular manifestations were as follows 55 had petechiae, and 47 had orthostatic acrocyanosis (Figure 1e). Four patients exhibited renal involvement including grade 2 hydronephrosis, diffuse mesangial sclerosis, crescentic glomerulonephritis and renal failure (Dweikat, Naser, Damsah, Libdeh, & Bakri, 2012; Heberle, Al Tawari, Ramadan, & Ibrahim, 2006; Zafeiriou et al., 2007). Five infants demonstrated mild to moderate hematuria (Ozand et al., 1994). One patient had Arnold Chiari malformation type 1 (Kitzler et al., 2019), and two had tethered cords and cerebellar tonsillar ectopia (Nowaczyk, Blaser, & Clarke, 1998; Nowaczyk, Lehotay, et al., 1998). Nine patients had retinal vein tortuosity in the eye examination (Bulut et al., 2018;

Cavusoglu et al., 2018; Ozand et al., 1994; Pavlou et al., 2013; Peake & Rodan, 2017) (Figure 1d). Two patients who are twins with mild phenotypes had scoliosis and hip dislocation (Pigeon et al., 2009). Initially, Cow's milk protein intolerance, meningococcemia, septic shock, autoimmune disorders, celiac disease, coagulation defects, and mitochondrial disorders (Leigh Syndrome, MELAS) were suspected. Therefore, patients were put on a diet, but diarrhoea and gastrointestinal problems did not improve (Table 2).

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

MUTATIONS

A total of thirty different types of *ETHE1* gene variants were identified from these patients. 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, 3). 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) (Cavusoglu et al., 2018; Ersoy et al., 2020; Kitzler et al., 2019; Pigeon et al., 2009; Yis, Polat, Karakaya, Ayanoglu, & Hiz, 2015).

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 a restriction of sulfur-containing amino acids, methionine or protein. Half of the patients with liver

transplantation were reported to remain stable (Table 1). One patient was treated with continuous renal replacement therapy (CRRT) (Kitzler et al., 2019).

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 [3].

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. 7 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 (Figure 2d) ***(p=0.002***). Age of symptom onset was not different between classical and mild phenotypes ***(p>0.05).***

DISCUSSION

Ethylmalonic encephalopathy is recognised as a devastating, invariably fatal, multisystemic 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 [7, 8, 10, 11, 21] (Table 1).

Only 6 cases have been reported to date with a slow neurological deterioration and a slight increase in the metabolic profile, which is classified as 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.

Moreover, we share our experience of two patients suffering from EE with a milder clinical course than the prototypic cases and who presented with spastic paraparesis and acrocyanosis. Their clinical progression was slow, and they were admitted to the emergency department with neurological deterioration during episodes of infectious illnesses. Infection is a known precipitant factor of these encephalopathic crises, likely due to increased stress on body tissues and

associated catabolism. During an infectious period, the catabolic process brings about a metabolic decompensation with vascular brain changes, resulting in neurological deterioration. The current age of 7 patients with mild clinical phenotype was significantly higher compared to the classical phenotype (Figure 2d). One patient from the mild phenotype was deceased at 32 months (Di Rocco et al., 2006). We focus on this mild phenotype to raised awareness for the early diagnosis for future cases to give a chance for early treatment before neurological deterioration occurs.

Affected infants with EE typically have hypotonia, developmental delay, loss of neurological milestones, chronic diarrhoea, failure to thrive, malnutrition, petechia and orthostatic acrocyanosis. Recognised first most common symptoms in the literature were psychomotor regression and diarrhoea (Table 1).

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. Increased epileptic activity, including tonic-clonic, tonic, myoclonic, absence seizures, status epilepticus, and rarely infantile spasms, have been reported during metabolic attacks. Although presented cases with mild phenotype were investigated for spastic paraparesis as a prominent finding, spastic paraparesis was reported in three out of 5 patients with mild phenotype in the literature (Table 1).

Petechia and orthostatic acrocyanosis were the other common manifestations at onset, being reported in 55 and 47 patients, respectively. They caused a diagnostic delay due to the suspicion of coagulation disorders and meningococcal infection. Petechiae and orthostatic acrocyanosis could be explained by the vasoactive and vasotoxic effects of hydrogen sulphide (Table 1). Furthermore, only one patient had petechiae out of 6 mild phenotype patients, and none of the previously reported cases had orthostatic acrocyanosis. 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 (Table 2) [3, 5-8, 19, 20, 29, 31, 32, 34, 37, 39, 41-44]. Although most patients were initially put on a diet due to the misdiagnosis of malabsorption syndromes and milk protein intolerance, their symptoms did not improve.

The biochemical profile consists of elevated lactate, plasma C4 and C5 acylcarnitines, and C4–6 acylglycines and increased urinary EMA. Thiosulfate is produced during H_2S catabolism and is also elevated in EE patients (Tiranti & Zeviani, 2013). Abnormal ethylmalonic acid excretion is a specific marker for the disease. It is proposed that EMA could arise from

methionine (McGowan et al., 2004) as a precursor or from abnormal isoleucine metabolism (Nowaczyk, Blaser, et al., 1998).

Urinary EMA levels range broadly between 45-730 mg/g creatinine (Tiranti et al., 2006). To date, normal ethylmalonic acid levels during an episode of decompensation have been reported only in two patients, of whom had a mild phenotype (Table 1) (Di Rocco et al., 2006; Ersoy et al., 2020). 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 (Figure 2a, Figure 2b), those might be accepted as important laboratory prognostic factors for the EE progression and treatment decision. Our second patient with 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 EMA; laboratory tests and imaging alone can miss the diagnosis.

H_2S has been shown to impair other Acyl-CoA dehydrogenases, including 2-Methylbutyryl-CoA dehydrogenase, Isovaleryl-CoA dehydrogenase and Isobutyryl-CoA dehydrogenase (Barth et al., 2010). As a result of that, high concentrations of C4-carnitine in plasma and EMA in urine are also detected in SCAD deficiency [44]. A build-up of H_2S as a consequence of the loss of activity of the key detoxification enzyme, sulphur dioxygenase, leads to its 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 [20, 23, 32, 45] (Table 1). Severe neurological symptoms, orthostatic acrocyanosis and petechia are essential clinical findings to distinguish SCAD deficiency from EE [20, 32].

Additionally, some patients with EE were misdiagnosed with multiple-acyl-CoA dehydrogenase deficiency (MADD) [32, 40] (Table 1). MADD can exhibit elevated C4, C6, C8, C10 and C12 in plasma and increased EMA in urine [46]. The lack of multiple biochemical elevations is essential to rule out MADD in these patients.

Nine patients demonstrated facial dysmorphic features (Cardelo Autero, Cordon Martinez, & Ramos-Fernandez, 2021; Garcia-Silva, Ribes, Campos, Garavaglia, & Arenas, 1997; McGowan et al., 2004; Ozand et al., 1994). Facial features of four out of 9 patients had broadened and depressed nasal bridge and epicanthic folds (Ozand et al., 1994). Mild hypertelorism and low nasal bridge were detected in 1 patient (Garcia-Silva et al., 1997). Two patients had prominent epicanthal folds, up slanting palpebral fissures, and a depressed nasal bridge (McGowan et al., 2004). Dolichocephaly, prominent forehead, retrognathia, low-set ears, and a small mouth with thin lips were detected in 1 patient (Cardelo Autero et al., 2021). Ozand et al.(Ozand et al., 1994)

hypothesised that mild facial dysmorphia and fronto-temporal 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) has been reported previously (Dweikat et al., 2012; Heberle et al., 2006; Ozand et al., 1994; Zafeiriou et al., 2007). 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 (Giordano et al., 2012). The renal disease might be a part of the findings, which is under-recognised due to the other severe clinical features of EE. Urinary tests should be performed in EE patients to detect hematuria secondary to renal vascular involvement.All patients with nephrological features presented with classical phenotypes in the literature.

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) (Heberle et al., 2006), articular hyperlaxity with suspicion of Ehlers-Danlos Syndrome (Di Rocco et al., 2006), scoliosis and hip dislocation (Pigeon et al., 2009). The patient with articular hyperlaxity showed normal cognitive development and normal ethylmalonic
acid excretion outside of decompensation episodes, with cerebrovascular involvement on MRI and was classified as a mild/atypical phenotype (Di Rocco et al., 2006). Scoliosis was detected in twins who exhibited clinical heterogeneity. They were alive at 10.5 years of age, and one of them demonstrated a milder clinical presentation (Pigeon et al., 2009). Neurological deterioration is an important reason for orthopaedic deformities in patients, such as scoliosis caused by postural instability.

Fundoscopic eye examination revealed tortuosity of retinal vessels in 9 patients (Bulut et al., 2018; Cavusoglu et al., 2018; Ozand et al., 1994; Pavlou et al., 2013; Peake & Rodan, 2017). 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 (Ozand et al., 1994). Fundus examination might be under-recognised in patients with EE, and vessel tortuosity must be a part of the diagnosis due to the vascular involvement of EE. Strabismus (Zafeiriou et al., 2007), esotropia (Yis et al., 2015), and abnormal visual and auditory evoked potentials were reported in one patient (Chen, Han, & Yao, 2020). One out of 8 patients had tortuosity of retinal vessels in fundus examination with mild phenotype (Cavusoglu et al., 2018). The diagnostic window of EE opens different perspectives from the view of clinicians, which is confusing due to multisystemic involvement.

The two most common mutations in the *ETHE1* gene were (p.R163Q) (c.488G>A) and exon 4 homozygous deletion. Mutations of mild phenotypes were (p.R163Q) (c.488G>A) (2), (p.R163W)(c.487C>T) (1)(Di Rocco et al., 2006), (p.M1I) (c. 3G>T) (3)(Cavusoglu et al., 2018; Ersoy et al., 2020; Yis et al., 2015), p.Q27K) (c.79C>A) (1) (Kitzler et al., 2019) and a compound heterozygous (p.Q27K) (c.79C>A), (p.L185R) (c.554T>G) mutation (1)(Pigeon et al., 2009). So far, p.R163Q and p.R163W have been reported in patients with both classical phenotypes (4 and 3 patients respectively) (Di Rocco et al., 2006) and one case of mild phenotype. To date, (p.M1I) (c. 3G>T) homozygous mutation has been reported in 3 patients with mild clinical phenotype (Cavusoglu et al., 2018; Ersoy et al., 2020; Yis et al., 2015). Still, however, the same mutation was also reported as a severe mutation by Tiranti et al (Tiranti et al., 2006).

Pigeon et al. (Pigeon et al., 2009) 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 use of a wheelchair. They were able to speak two languages, whilst the other twin had spastic quadriparesis and was non-verbal. The first twin did not have any attacks of petechiae, orthostatic acrocyanosis or diarrhoea (Pigeon et al., 2009). Even p.L185R was reported as a classical phenotype before, p.Q27K might alleviate the symptoms when located in the second allele of the patient. Western blot analysis showed the absence of ETHE1 protein-specific cross-reacting material in the missense mutations, including T136A, Y38C, and L185R. Whilst the R163W and R163Q mutations carrying the "catalytic" *ETHE1* protein mutations were associated with the presence of normal amounts of cross-reacting material (CRM) (Tiranti et al., 2006). Our presented cases have homozygous R163Q mutations, respectively, and they exhibit a milder clinical phenotype. Exon 4 deletion and exon 4 to 7 deletion might draw a severe phenotype. Above all, no obvious 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.

The pathophysiological mechanism of the brain MRI changes is cytotoxic oedema with the contributory factor of acute vascular injury (Giordano et al., 2012). The accumulation of H_2S causes direct injury of 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 (Barth et al., 2010; Kilic, Dedeoglu, Gocmen, Kesici, & Yuksel, 2017; Kitzler et al., 2019; Papetti et al., 2015; Peake & Rodan, 2017; Yis et al., 2015) (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 (Table 3). Lim et al. (Lim et al., 2021) 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. Two patients' cranial MRI with mild phenotype were normal, one of which was presented in case 2 (Ersoy et al., 2020) (Table 3).

Lowering the accumulation and inducing detoxification of H_2S is accepted as the primary strategy of treatment in the chronic management of EE. Metronidazole decreases the production of H_2S in the gut, and N-acetylcysteine (NAC) works as a glutathione donor and converts H_2S to a non-toxic form of glutathione persulfide (GSSH) (Viscomi et al., 2010). Riboflavin and carnitine were first used treatments of EE in 1991 (A. Burlina et al., 1991); however due to the early death in these patients, it was not possible to assess for meaningful clinical improvement. On the other hand, in 2002, riboflavin was used in a clinical trial to increase the activity of the acyl-CoA-dehydrogenases by Yoon et al. (Yoon et al., 2001), and this study demonstrated that riboflavin caused a slight improvement in clinical status and a decrease in C4 and C5 acylcarnitine levels in 1 out of three patients.

In a study of 2004, restriction of the dietary intake of methionine showed a decrease in EMA excretion, but long-term follow-up could not be performed due to the early death of the patient at 8 months of age (McGowan et al., 2004). In 2010, a study of an isoleucine-restricted diet in one patient brought about partially corrected EMA, C4 and C5 acylcarnitine levels (Barth et al., 2010). Additionally, ascorbic acid, vitamin E, B1, biotin, vitamin B6 and coenzyme Q10 have been used as a treatment strategies (Table 1). In a study held in 2010 on 5 individuals with combined therapy of metronidazole and NAC, it was shown that neurological status improved and episodes of diarrhoea, petechia, and acrocyanosis disappeared. The urinary EMA, C4 acylcarnitines and thiosulfate levels also decreased (Viscomi et al., 2010). Kılıç et al, started intravenous NAC (100 mg/kg/day) infusion to a 10 month old girl in the intensive care unit with encephalopathic crises, and they reported that her clinical status improved (Kilic et al., 2017). We similarly started intravenous NAC on our second patient during their two encephalopathic

crises, and clinical status improved faster than during previous attacks. 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. The clinical outcome of the patient improved, and biochemical markers were also decreased. These results suggest earlier initiation of combined therapy, including diet, metronidazole and NAC, might result in imrpvoed clinical outcome in these cases.

Despite that, these treatment strategies are not entirely curative, therefore a couple of patients underwent liver transplantation with the aim to increase liver sulfur dioxygenase activity to increase clearance of toxic levels of H_2S through restoring liver sulfur dioxygenase activity. Biochemical abnormalities were reserved and demonstrated remarkable achievement in psychomotor development milestones in a patient following liver transplantation (Dionisi-Vici et al., 2016). However, debate continues regarding liver transplantation efficacy due to a further metabolic attack with stroke occurring afterwards in this patient. Although this patient's neurological status improved in the post-liver transplantation period, the patient died at two years of age during a severe encephalopathic crisis of viral gastroenteritis. The other reported patient exhibited a clear clinical improvement following transplant (Tam et al., 2019). Similarly, one out of the two patients had stroke-like episodes despite the clinical and metabolic improvements after liver transplantation (Lim et al., 2021). No obvious improvement was shown in the neurodevelopmental outcome of a liver-transplanted patient at 18 months of age (Zhou et al., 2020). It is shown that the disease course is stabilised or improved in 50% of patients, and it is recommended to continue metronidazole, carnitine and NAC after liver transplantation to protect vascular endothelium from potential H_2S accumulation (Dionisi-Vici et al., 2016; Lim et al., 2021; Olivieri et al., 2021; Tam et al., 2019; Zhou et al., 2020). It is necessary to take into account the benefit-risk ratio whilst considering liver transplantation in these cases. Reversibility of 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 should be considered a therapeutical option in these patients due to the potential for normal development and functioning.

The oldest reported mild atypical case 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. The

two patients we have described are currently treated with metronidazole and N-acetylcysteine. Patients with a milder clinical course may be suitable to undergo CRRT to achieve metabolic control during crises (Kitzler et al., 2019).

Conclusion:

We 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. Cow milk protein intolerance has been often first suspected in these patients due to chronic diarrhoea and gastrointestinal manifestations. Clinical variability of patients primarily affects age at diagnosis, chronic management and survival. Diagnosing in earlier stages and recognising the susceptibility of decompensation during periods of infection is essential. Individualised treatment strategies need to be considered according to the frequency and nature of metabolic decompensation attacks, clinical phenotype, metabolic profile, MRI results and genotype. NAC and metronidazole should be started as soon as EE is diagnosed. More detailed studies are required to evaluate the clinical efficacy of sulfur 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 made by the multidisciplinary team.

Data availability:

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

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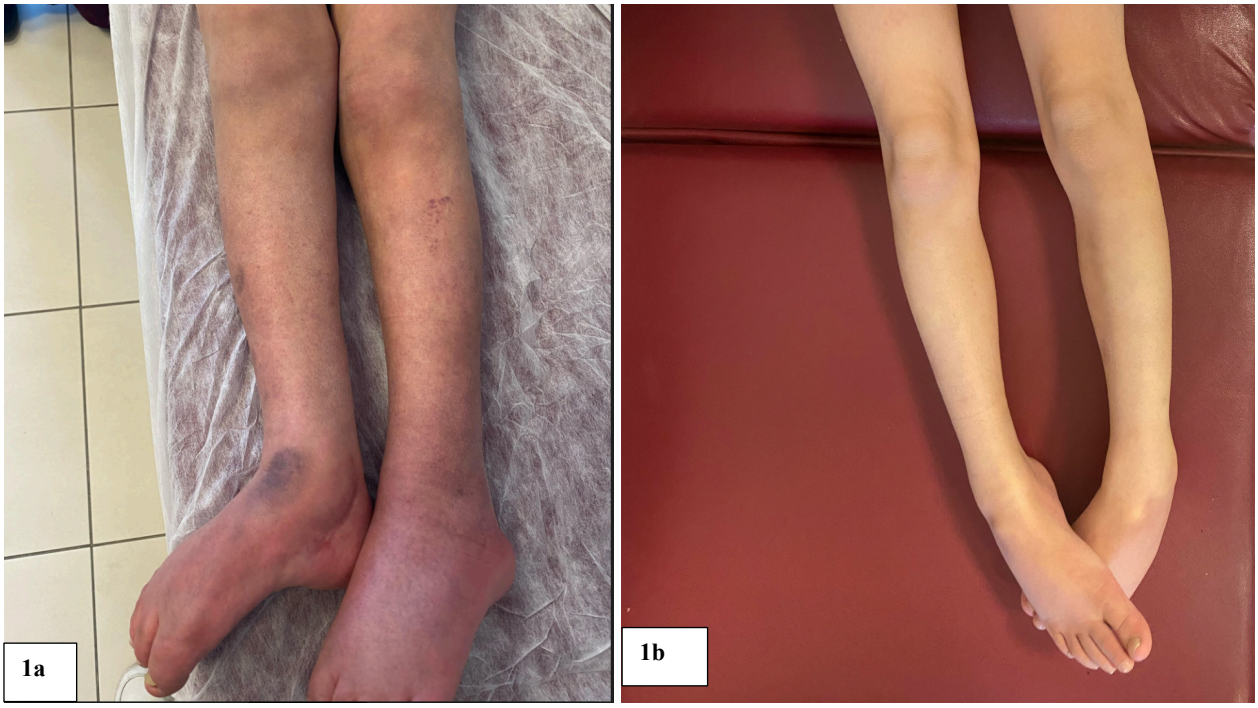

Picture 1a: Acrocyanosis of patient 1. **Picture 1b**: Spastic paraparesia of patient 2

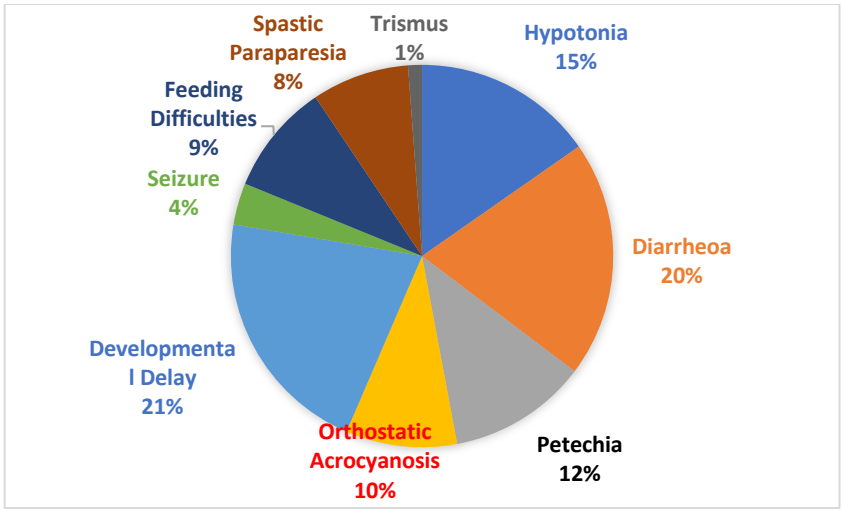

Figure 1a: First clinical manifestations of patients

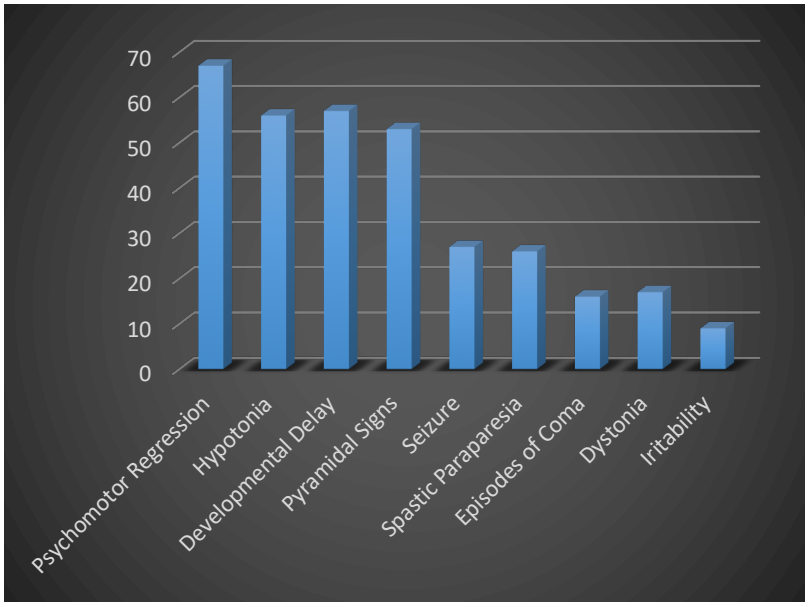

Figure 1b: Neurological manifestations of EE cases.

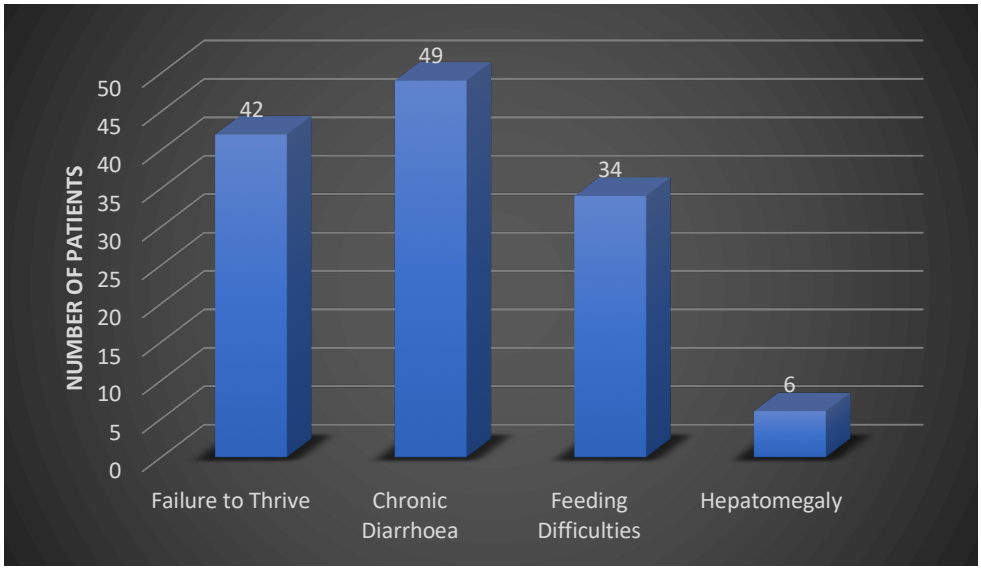

Figure 1c: Gastrointestinal manifestations of EE cases

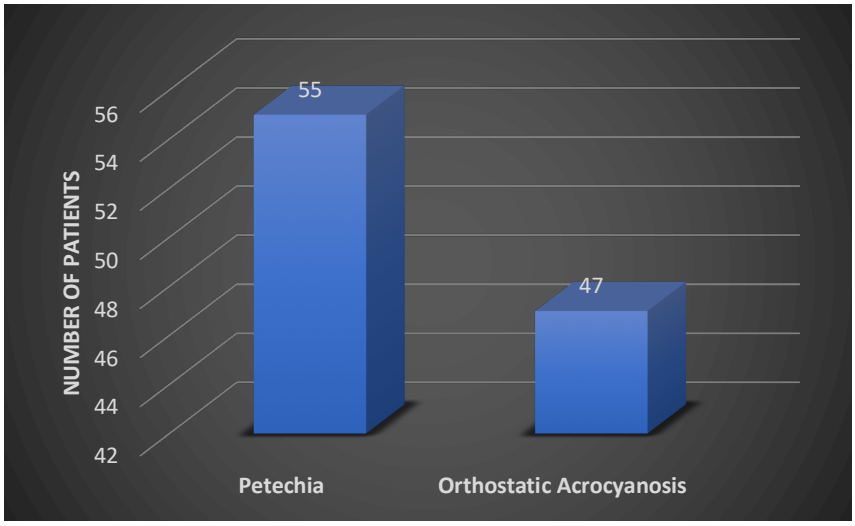

Figure 1d: Vascular manifestations of EE cases

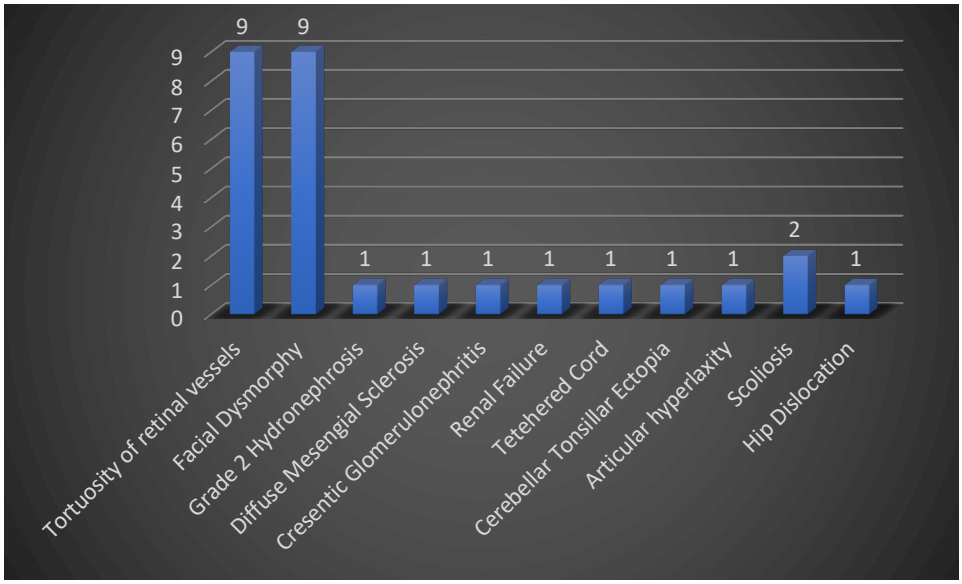

Figure 1e: Other manifestations of EE cases

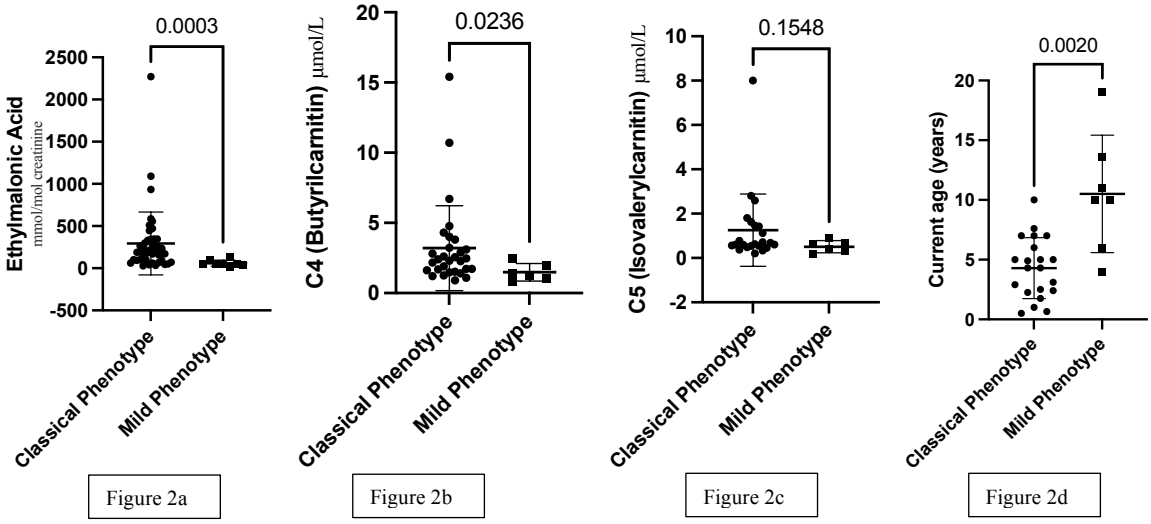

Figure 2a, 2b, 2c, 2d. Comparison of metabolic profile and current ages of classical and mild phenotype. Statistically significant at $p < 0.05$.

Table

Authors	(A. Burlina et al., 1991)	(Christensen et al., 1993)	(A. B. Burlina et al., 1994)	(Garavaglia et al., 1994)	(Ozand et al., 1994)	(Garcia-Silva, Ribes, Campos, Garavaglia, & Arenas, 1997)	(Nowaczyk, Blaser, & Clarke, 1998; Nowaczyk, Lehotay, et al., 1998)	(Yoon et al., 2001)	(Grosso et al., 2002)	(McGowan et al., 2004)	(Heberle, Al Tawari, Ramadan, & Ibrahim, 2006)	(Di Rocco et al., 2006)*	(Mineri et al., 2008)	(Merinero et al., 2006)	(Zafeiriou et al., 2007)	(Pigeon, Campeau, Cyr, Lemieux, & Clarke, 2009)*	(Ismail, Seoudi, Morsi, & Ahmad, 2009)	(Barth et al., 2010)	(Drousiotou et al., 2011)	(Dweikat, Naser, Damsah, Libdeh, & Bakri, 2012)	(Pavlou et al., 2013)
Country	Italy	Denmark	Italy	Italy	Saudi Arabia	Spain	Canada	Japan	Italy	USA	Kuwait	Italy	Italy	Spain	Greece	Canada	Kuwait	France	Cyprus	Israel	Greece
Year of publication	1991	1993	1994	1994	1994	1997	1998	2001	2002	2004	2006	2006	2008	2006	2006	2008	2009	2010	2011	2012	2013
Number of Cases	3	1 M	4 M	2 M	5 (2M,3F)	1 M, 1 F (sister)	2 (1M, 1F)	3 (3 F) 2nd patients is sister of first patient	2 (2F)	2 (1F, 1M)	2 (2 M)	1M	5 (2F,3M)	3 (na)	1 M	2 (2F) Twins	1 F	1 M	3 (2F,1M)	1 (F)	1 (M)
Parental consanguinity	NA	-	-/-/-/-	-/+	+/+/+/+/+	-/-	NA	NA, NA, -	+/-	+/+	+/+	-	-/ -/ - /	-	-	- / -	NA	+	-	+	-
First symptom	Hypotonia	Hypotonia	Hypotonia,diarrhea, petechia	1. Diarrhoea, distal limb acrocyanosis and diffuse petechiae. 2.Diarrhea, petechia 3.Failure to thrive, psychomotor development al delay and 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	na	1. Developmental delay, spastic quadriplegia and diarrhoea 2.Acrocyanosis, petechiae and spastic quadriplegia 3. Diarrhoea	1. Petechiae, diarrhea, orthostatic acrocyanosis, and failure to thrive 2. Feeding difficulties, irritability, abdominal distension and diarrhea	1.Psychomotor delay 2.Irritability	1.Diarrhea 2.Purpuric skin rash	1.Petechia and echimoses	1.Frequent vomiting, diarrhea 2. Hypotonia, pyramidal signs, psychomotor delay, difficulties in swallowing and poor growth 3. Seizure, psychomotor delay, hypotonia without vomiting or failure to thrive/ 4. Neonatal screening 5.Psychomotor delay, lactic acidosis, acrocyanosis and petechiae	1. Neurological involvement affected 2. Asymptomatic	1.Diarrhea	1.Hyperbilirubinemia,psychomotor delay 2.Gastroesophaial reflux	1.Diarrheoa psychomotor delay	1.Diarrhea	1.Floppy with severe head lag and microcephaly 2.Failure to thrive, diarrheoa 3.Intrauterin growth retardstion	1.Diarrhea	1.Petechia
Age at Symptom onset	na	4 m	1.3 m 2.1 m 3.45 days 4.<6m	1.45 days 2.1st day	1.2m/ 2.birth 3.7-8m 4. <1 y 5. 22m	1.45 days	1.3m 2. 2m	1.na 2.na 3.Few days after birth	1.7m 2.1m able to sit and walk	na	1.4 m 2. na	1.3m Head control, could not sit alone	1.6m 2.First weeks 3.6m 4.6m 5.First weeks	na	2 m	15 m /able to speak	4 months	2 m	2 ½ m , 6m ,6 m	1 mo	4m
Psychomotor Retardation	+/+/+	+	+/+/+/+	+/+	+/+/+/+/+	+/+	+/+	+/+/+	+/+	+	+/+	+ Mental normal	+/+/-/-/+	+	+	+/+ Severe MR /mild-moderate MR	+	+	+/ + /+	+	+
Hypotonia	+/+/+	+	+/+/+/+	+/+	+/+/+/+/+	+/+	+	+	+/+	+/+	+/+	+	+/+/+/+/+	na	+	+/+	+	+	+/ - /+	+	+
Spastic parapareasia	+/+/+	NA	+/+/+/+	+/-	-/+/NA/NA/NA	+/+	NA	+/+	-/+	NA	NA/NA	NA	NA	NA	NA	NA	NA	NA	-	NA	-
Seizure	-	+	-/-/-/-	-	+/+/+/-/-	-	-	NA	+/+	+/+	-/+	-	-/+/+/+/-	NA	+	+/-	+	NA	+/+/+	NA	+

Seizure Type	-	NA	-	NA	GTCS/Tonic/GTCS / Tonic and Gelastic seizure	-	-	-	Sporadic tonic/infantil spasm	Infantile spasm, absence seizure// myoclonic seizure	NA	-	-	Status mycoclonicus	NA	Status Epilepticus	Myoclonic Epilepsy	-	-	-	Extensor spasms
EEG	-	Abnormal	-	-	Multifocal discharges/ bilateral independent spikes	NA	-	-	Generalized polyspike-waves activity/ Hypsaritmia	Hypsarythmia/	NA	-	-	NA	NA	NA	NA	-	-	-	Hypsarythmia/
Dystonia	-	-	-	+	-	+/+	+	-	+/-	NA	-	-	+/+/-/+/+	NA	-	+/+	-	+	-	+	-
Pyramidal signs	+/+/+	+	+/+/+/+	+ /+	+/+/+/+/+	+/+	NA	+/+/-	+ /+	+/+	+/-	+	+/+/	NA	+	+/+	+	+	+/ -/-	+	+
Muscle wastng	NA	NA	NA	+/-	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA	-	NA	NA	NA	NA	NA
Eisodes of coma				NA	+/+	+/+		+/+/+	NA	+/+		+		NA		+/-				+	
Microcephaly	-	-	-/-/-/+	NA	+/-/-/+/-	+/+	-	-	+/-	+/	+	-	-	NA	-	-	-	+	+/-/-	+	-
Skin (Petechiae)	+/+/+	+	+/+/+/+	+/+	+/+/+/+/+	+/+	+	+/+/+	+/+	+/+	+/+	+	-/+/+/-/+	+	+	-/-	+	+	+/-/+	+	+
Orthostatic acrocyanosis	+/+/+	NA	+/+/+/+	+/+	+/+/+/-/-	-/-	+/+	+/+/+	++	+/	NA	NA	+/+/+/-/+	NA	-	-/-	+	+	+/-/-	+	+
Chronic Diarrheoa	+/+/+	NA	+/+/+/+	+/+	+/+/-/-/-	+/+	++	+/+/+	++	NA	+/-	+	+/+/-/-/+	+	+	-/-	+	+	+/+/+	+	-
Failure to Thrive	NA	+	+-/-/+	+/+	-/+/-/-/-	+/+	NA	NA	+/+	+/-	NA	+	+/+/+/+/+	NA		+/+	+	+	+/+	+	+
Feeding difficulties	NA	NA	Tube feeding/+ /+/+	+/+	NA	+/+	-	+/+/+	+/+	NA	-	-	-	NA	-	+/-	-	-	+ Gastrostomy	+	-
Irritability	NA	NA	NA	NA	+	+/+	NA	NA	+/-	NA	NA	NA	NA	NA	NA	NA	NA	NA	+/+/+	NA	NA
Developmental Delay		+	+/+/+/+	+/+	+/+/+/+/+	+/+		+/+/+	+/+	+/+			+/+/+/+/+		+	+/+			+/ + /+	+	+
Other Malformations	NA	NA	-	NA	-	-	1.Tethered cord, 2.Cerebellar tonsillar ectopia (Chiari I malformation)	-	NA		Grade 2 hydronephrosis /	Articular hyperlaxity	-	Enlarged kidneys, diffused mesangial sclerosis	-	Scoliosis Hip Dislocation// Scoliosis	-	-	NA	Cresentic glomerulonephritis, renal failure	-
Eye	NA	NA	NA	NA	Retinal vessel tortuousity, left pale optic disc// Retinal vessel tortuousity/ Retinal vessel tortuosity/ Retinal vessel tortuosity// Retinal vessel tortuosity	-	NA	NA	NA	NA	NA	-	NA	NA	Strabismus	NA	NA	NA	NA	NA	Retinal vessel tortuosity

Liver involvement	NA	NA	NA	NA	Mild HMG+SMG/HMG/	HMG/ HMG		HMG /-/-	NA		Increased liver echogenecity / + (HMG)	-		NA		NA			NA		
Facial dysmorphy	-	NA	-	-	+/+/+/+/+	+/-	-	-	NA	+/+	-	-	-	NA	-	NA	-	-	-	-	-
Misdiagnosis	Food intolerance (gluten, cow's milk proteins, lactose), bacterial or parasitic infections, or inflammatory bowel disease.	MADD deficiency	Cow milk protein intolerance	Haemorrhagic disorders, malabsorption,autoimmune disorders, and chromosome abnormalities Coagulation factor deficiency		Peripheral dysautonomia, autoimmune disorder, coagulopathy, or platelet dysfunction		Lactose, cow's milk proteins), bacterial or parasitic infections, or inlammatory bowel disease	Celiac disease/ Cow milk protein intolerance	Hematological investigation// Leigh disease		Hematological disorder Ehler Danlos Syndome		NA		-			NA		
LABORATORY																					
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	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	NA	1. 2.67 2. 3.1 3. 7.2 4. NA 5. NA	NA	NA	1. 3.5-5 2. 3.69-4.4	NA	1. 3 2. 4	1. 6.47 2. 16.74 3. 3.93	NA	NA
Ethylmalonic Acid (acute) **mmol/mol creatinine**	**62-933**	⇑⇑⇑	**1. 446-1090** **2. 180-264** **3. 272** **(Acute State)** **1. 73-120** **2. 96-209** **3. 195 (Steady state)**	⇑⇑⇑⇑	**54-2270**	**1. 196** **2. 343**	**1. 92.5** **2. NA**	**1. 93.1** **2. 158.4/** **3. 234.9**	⇑⇑⇑⇑	**1. 276** **2. NA**	**NA**	**1. 49.2**	**1. 170** **2. 345** **3. 189** **4. 147** **5. 100**	⇑⇑⇑⇑	**1.258-512**	**1. 50-250** **2. 47-60**	**NA**	**1. 99** **2. NA**	**1. 331** **2. 213** **3. ⇑**	⇑	**1. 470**
C4 mmol /L	NA	NA	NA	NA	NA	NA	NA	1. 15.4 2. 10.7 3. 2.6	NA	⇑	NA	1. 2.48	1. 1,2 2. 4.7 3. 2.8 4. 1.9 5. NA	⇑⇑⇑⇑ NA	1. 3.81	NA	NA	1.3.1 2. 4.3	⇑ , NA, NA	NA	NA
C5 mmol /L	NA	NA	1.0.2 2. 8	NA	NA	NA	NA	1. 2.6 2. 1.8 3. 2.8	NA	⇑	NA	1.0.67	1.na/ 2. 0.37 3. 0.6 4. 0.55 5. na	NA	1. 0.34	NA	NA	(0.54–0.62	NA	NA	NA

Carnitine mmol /L	NA	NA	NA	Normal	NA	NA	NA	51.8	1. 19 (24-76) 2. 11	14	NA	NA	NA	NA	1. 51	NA	NA	NA	NA	NA	NA
***ETHE1* gene mutation**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.(p.N77fsX144)(c.230delAA), Hom 2. na	1.(p.R163W) (c.487C>T) , Him	1.(p.D169N)(c.586G>A), Hom 2. (p.Y74X), (c.221-222insA) (p.T164K) (c.491C>A), CH 3.(p.L55P) (c.164T>C), Hom 4.(p.R163W) (c.487C>T) (p.T152I) (c.455C>T), CH 5. Hom deletion from exon 4 to exon 7	NA	1.(p.R163G) (c.487C>G), Hom	1 (p.Q27K) (c.79C>A), (p.L185R) (c.554T>G)CH 2. (p.Q27K) (c.79C>A), (p.L185R) (c.554T>G)CH	1.Exon 4 Hom deletion	1.Exon 4 Hom deletion (c.3758505del130)	1.(p.L185R) (c.554T>G), /deletion of exon 4 CH 2. (p.L185R) (c.554T>G), /deletion of exon 4 CH 3. Deletion of exon 4/ Deletion of exon 4	1.(IVS4D (c.505+1G>T)	1. Exon 4 Hom deletion
Others	-	NA	-	-	Mild-to-moderate hematuria (5 patients)	-	-	-	NA	-	Grade II hydronephrosis . mild tricuspid regurgitation and dilatation of the pulmonary artery// Undescended testes, small penis, nystagmus	-	-	-	Enlarged kidneys, diffuse mesengial sclerosis	-	-	-	-	-	-
Treatment	Riboflavine and carnitine	NA	MNZ L-carnitine and riboflavin - L-carnitine and riboflavin	NA	L-carnitine 200 mg/kg/d, riboflavin 100 mg/kg/d, phenobarbital, Tegretol, and on pregestemil// Riboflavin, ascorbic acid, vitamin E, glycine, or carnitine. Prolonged large doses of methylprednisolone	L-carnitine 100 mg/kg/day, riboflavin 100 mg/day, thiamine 100 mg/day, and vitamin C 900 mg coenzyme Q10	L-carnitine (100 mg/kg per day), riboflavin (100 mg/day), and coenzyme Q10 (50 mg/kg)	L-Carnitine (100 mg/kg per day), riboflavin (100 mg/day), and coenzyme Q10 (50 mg/kg) // Riboflavin (100 mg/day) and coenzyme Q10 (50 mg/kg) // L-Carnitine (100 mg/kg per day), riboflavin (50 mg/kg per day), thiamin (100	1.Valproic Acid 2.Vigabatrin, Valproic Acid, Vigabatrin and ACTH	Methionine restricted diet	Vitamins B1, B2 , B6 , C, E, biotin, Q10 and carnitine/ Vitamin B1, B2, B6, Q10, carnitine, sodium bicarbonate and -/ Phenobarbitale	NA	NA	Sodium valproate	Sodium valproate	Topiramate, clobazam, and carnitine	NA	**İsoleucine restricted diet**	NA	MNZ, NAC, Coenzyme Q10	NA

								mg/day), pyridoxine (30 mg/day), vitamin B12 (1 mg/day) and a low-protein diet													
Outcome Alive	1 patient is alive 6 years of age		6 years of age	7 years of age alive	-		7 years alive 5 years alive	7 years alive	+	8 months alive			6 months, 7 years and 13 years (In total of 14 cases)	na		**10 years 10 years**			5 years (1 patients alive)		
Age of Death	2 years 23 months 20 months	13 months	2 years 23 months - 20 months	5 years	16 months 7 months 2 years 4 years	20 months 7,5 months	-	46 months 23 months	10 years	8 months	8 months	32 months	Age of death ranged from 18 months to 3 years (In total of 14 cases) 17 m 2 years (1/3) (2 severely mentally retarded)	na	3 years	-	14 months		Alive 6 months 8 months	8 months	18 months
Death Reason		Bronchopneumonia e	Respiratory tract infection (3 patients)	Acute respiratory failure	Septicemia	Bronchopneumonia e/ bronchopneumoniae		Alive// Apnea // intractable metabolc asidosis	Respiratory tract infection / -		Leigh disease	Diarrheoa	Acute respiratory failure	na	Bronchopneumonia e	-	Bronchopneumonia e		Alive// Respiratory tract infection //Cardiopulmonary arrest	Renal impairement	Unknown

	(Papetti et al., 2015)	(Yis, Polat, Karakaya, Ayanoglu, & Hiz, 2015) **Mild**	(Bijarnia-Mahay et al., 2016)	(Dionisi-Vici et al., 2016)	(Kilic, Dedeoglu, Gocmen, Kesici, & Yuksel, 2017)	(Peake & Rodan, 2017)	(Boyer et al., 2018)	(Kasapkara, Aksoy, Polat, Kılıç, & Ceylaner, 2017)	(Cavusoglu et al., 2018)* **Mild**	(Bulut et al., 2018)	(Chen, Han, & Yao, 2020)	(Kitzler et al., 2019)* **Mild**	(Tam et al., 2019)	(Ersoy, Tiranti, & Zeviani, 2020)* **Mild**	(Tao et al., 2020)	(Govindaraj et al., 2020)	(Zhou et al., 2020)	(Cardelo Autero, Cordon Martinez, & Ramos-Fernandez, 2021)	(Olivieri et al., 2021)	(Lim et al., 2021)	(Horton et al., 2022)	Presented Cases* **Mild**
Country	Italy	Turkey	Japan	Italy	Turkey	USA	USA	Turkey	Turkey	Turkey U	China	Canada	USA	Turkey	China	India	China	Spain	Italy	USA	Australia (Afganian patient)	Turkey
Year of the Article	2015	2015	2016	2016	2017	2017	2018	2018	2018	2018	2019	2018	2019	2020	2020	2020	2020	2021	2021	2021	2022	2022
Number of Cases	1 (F)	1 (F)	1 (M)	1 F	1 F	1 F	1 F, 1M	1 M	1 F	1 (M)	1 (M)	1 (M)	2 (1F, 1 M)	1 M	1 (M)	1 M	1 M	1 M	1 F	3 (1 F, 2 M)	1 F	2 (1 F, 1 M)
Parental consanguinity	-	+	-	-	+	na	-/-	+	-	+	-	-	+/+	+	-	+	-	-	na	-	+	+/+
First symptom	1.Sudden bilateral and symmetrical spasms of the neck, trunk and	1.Tip toe walking	1.Developmental delay, hypotonia	1.Psychomotor delay, mild drowsiness and axial hypotonia	1.Fever, rash, poor feeding, respiratory difficulty, shock,	1.Developmental delay, hypotonia, and infantile spasms	1.Newborn screening 2.Poor feeding and hypoglycemia	1.Acrocyanosis	1.Diarrheoa, severe lactic acidosis, and encephalopathy	1.Irritability	1.Diarrheoa	1.Long-standing spastic paraplegia, dysarthria	1.Diarrhea 2.Hypotonia	1.Diarrhoea.	1.Poor feeding, diarrhea,	1.Poor feeding ,sepsis	1.Diarrhea, petechia, echymosis	1.Developmental delay, mild language regression with the loss of the 3		1.Psychomotor delay 2.Psychomotor delay 3.Enteropathy	Acute deterioration, involving depressed conscious state, hypotonia, reduced	1.Encephalopatic crises, diarrheoa spastic parapare sia 2. Diarrheo

	extremities			with spasticity of lower limbs	encephalopathy							(Trismus during first hospitalisation)						words, hypotonia, and failure to thrive			peripheral perfusion with only central pulses palpable, and a rapidly evolving widespread purpuric rash	a spastic paraparesia
Symptom onset age	3 months	2 years	Infancy	7 months	na Unable to sit	10 months	Newborn	3 y 9m	na	na	At birth	16 years	Birth na	6 months 5 years Spastic paraparesia diarrhoa	Birth Can not sit	Birth	Birth	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	+	NA	+	+	+	+	+/+	+	+	+	+	-	+/+	+	+	+	+	+	+	+++	+	+/+
Hypotonia	+	-	+	+	+	+	+/+	+	NA	+	-	-	+	-	+	+	+	+	+	-/-/+	+	-/-
Spastic paraparesia	NA	+	NA	+	NA	NA	NA	NA	NA	NA	-	+	-/+	+	NA	+	+	NA	+	+/+/+	NA	+/+
Seizure	+	-	+	-	-	+	+/+	NA	NA	+	-	-	-/-	-	+	+	-	-	-	-	-	-/+
Seizure Type	Infantile spasms		NA			Infantile spasms	NA			NA					During attack	NA						NA
Ataxia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	-/-
EEG	High voltage slow waves and spikes, hypsarrhythmia		NA			Hypsarrhythmia	1.Normal 2.Hypsarrhythmia								Normal							-/NA
Dystonia	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	NA	NA	-	+	NA	NA	NA	NA	NA	+;/+
Pyramidal signs	NA	+	+	+	+	+	+/+	NA	+	NA	-	+	NA	NA	+	+	+	+	+	-/+	+	+/+
Eisodes of coma	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	-	+	+	-	NA	+	NA	NA	NA	NA	+	+/+
Microcephaly	-	-	+	-	-	-	-/-	NA	NA	+	NA	Macrocephaly	-	-	Macrocephaly	+	-	-	-	-	-	-
Skin (Petechiae)	+	-	+	+	+	+	-/-	+	NA	+	+	-	+/-	-	+	+	+	+	+	-/-		+/+
Orthostatic acrocyanosis	+	+	+	+	+	+	+/+	+	NA	+	-	-	+/-	-	+	NA	+	NA	+	-/-/+	+	+/+
Chronic Diarrhoa	+	-	+	NA	-	+	-/-	+	+	+	+	-	+/+	+	+	NA	+	+	+	-/-/+	NA	+/+
Failure to Thrive	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	+	+		-/-/+	+	+/+
Feeding difficulties	NA	NA	NA	NA	+	NA	Gastrostomy/ +	NA	NA	NA	NA	NA	+ /+gastrostomy	NA	+	+	NA	NA	NA	-/-/+	NA	+/+
Irritability	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA
Developmental Delay	+	NA	+	NA	+	+	+/+	+	+	+	+	+	+/+	NA	+	NA	+	+	+	+//+//+	+	+/+
Other Malformations	-	-	-	-	-	-	-	-	-	NA		Arnold-Chiari malformation type I	-	-	-	-	-	Dolichocephaly, prominent forehead, retrognathia,	-	-	-	-

																		low-set ears a small mouth with thin lips				
Eye	-	Esotropia	-	NA	NA	Retinal vessel tortuosity	NA	NA	Retinal vessel tortiosity	Retinal vessel tortiosity	Abnormal VEP Abnormal auditory potencial	-	NA	NA	-	NA	NA	NAN	NA	NA	NA	NA
Liver involvement	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	NA	NA	NA	NA	NA	NA	-
Facial dysmorphy	-	-	NA	-	-	-	-	-	-	NA	NA	-	-	-	-	-	-	+	-	-	-	-
Misdiagnosis	NA	NA	NA	NA	Meningococcemia and septic shock	Mitochondrial disorder	- /Meningococcemia	Rheumatologic disorder	Leigh syndrome	SCAD deficincy	Superficial gastritis, cholitis	NA	NA	Food allergies or malabsorption syndromes	SCADD or MADD	NA	NA	NA	NA	MELAS	Meningoccemia	-
Laboratory																						
Lactat mmol/L	NA	2.92	NA	8.1	NA	3.1	5.8/	NA	⇑ (mild)	NA	9.05	1-14.8	1. 4.2 2. NA	1.4	NA	3.8-5.3	NA	NA	6.4 -2.8	1. 6.2 2. 9.3	6.6	8-9.9/4-8
Ethylmalonic Acid (acute) mmol/mol creatinine	NA	41	⇑⇑⇑	169-210		299	1. 556 2. 585	93.63	96	⇑⇑⇑	28.86-71.84	20-100 (min-max) 29, 42, 72	1. NA 2. 177	46	34.6	⇑⇑⇑	74.93-142.53	NA	205.8-66.2	⇑⇑⇑	⇑⇑⇑	1.130 2.15.37
C4 µmol/L	1.72	NA	3.22	1.47-1.53	NA	1,69	1. 1.62-1,73 2. 1.09-2.55	2.89	⇑ (mild)	⇑⇑⇑	0.91	(0.71-6,71)	1. 2,31 2. 2,17	1.26	2.28	⇑⇑⇑	2.4	NA	NA	1.1.53 2. 1.17 3. 2.17	⇑⇑⇑	1. 1.95 2. 0.79
C5 µmol/L	0,71-1.62	NA	1.12	0.45-0.6	NA	NA	1. 0.56 2. 0.48	NA	⇑ (mild)	⇑⇑⇑	NA	(0.17-0.92)	1. 0,59 2. 0.77	0.39	1.47	⇑⇑⇑	1.42	NA	NA	-/-/0.77	⇑⇑⇑	1.0.61 2.0.29
Carnitine µmol/L	247.4	NA	NA	NA	NA	NA	N/low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	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)	1. (p.R163Q) (c.488G>A Hom	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	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.295 C>T) Hom	1. (p.D165H) (c.493 G>C) Hom	1. (c.375+5G>A) a novel mutation (c.462T>A) (p.D154E) CH	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
Others																						

Treatment	Metronidazol, NAC	Riboflavine (100 mg/day) and Coenzyme Q10 (20 mg/kg/day)	Riboflavin (50 mg/day	MNZ (30 mg/kg/day) and NAC (100mg/kg/day **Liver transplantation**	Riboflavine (10 mg/kg), coenzyme Q10 (10 mg/kg), MNZ (30 mg/kg), NAC (20 mg/kg)	Oral MNZ, NAC Vigabatrin	NAC, MNZ alternating neomycin Ascorbic acid, **restricting the sulfur containing** amino acids (not compatible) 1 years of age // MNZ or neomycin and NAC. Ascorbic acid, restricting **sulfur containing amino acids** Adrenocorticotropic hormone (ACTH) and phenobarbital, felbemate	Oral MNZ 30 mg/kg/day, NAC 100 mg/kg/day, coenzyme Q10 5 mg/kg/day and riboflavin 100 mg/day	NA	L-carnitine,MNZ NAC	L-carnitine ,vitamin B1 and vitamin B2, NAC, MNZ, Clostridium butyricum tablets	MNZ, NAC, carnitine, baclofen CRRT CVVV HDF	At 19m and 13 m **Liver Transplantation** MNZ and NAC	NAC-MTZ, coenzyme Q10 and riboflavine Achile tendon strengthening	Carnitine (100 mg/kg daily), NAC (20 mg/kg twice daily), coenzyme Q10 (20 mg daily), and multivitamins (500 µg vitamin B12 once every other day; 30 mg vitamin B1, 10 mg vitamin B2, 1500 IU vitamin A and 500 IU vitamin D daily)	Baclofen , biotin, L-carnitine, coenzyme Q , multivitamins Levatiracetam	**Liver transplantation** A sulfur-containing amino acids restricted diet and the combined use of MNZ (30 mg/kg/d) and NAC	Biotin, coenzyme Q10, vitamin E, riboflavin, thiamine , and L-carnitine ; MNZ and NAC	Liver **transplantation** NAC MNZ 1 NAC (100 mg/kg/day), MNZ (30 mg/kg/day) and carnitine (100 mg/kg)	**Liver transplantation** MNZ (30mg/kg/d), NAC(105 mg/kg/d), L-carnitine (60 mg/kg/d)	Riboflavin , coen-zyme Q10, and carnitine enterally on day 5, with intravenous NAC, MNZ, and a low protein	Riboflavin (10 mg/kg), coenzyme Q10 (10 mg/kg), MNZ (30 mg/kg) and NAC (20 mg/kg). Moreover, NAC100 mg/kg/day intravenous (iv)
Outcome Alive		**4 Years**		1 years very much improved	NA		NA		6 years	21 months	29 months	19 years	1. 27 months 2.35 months	11 years Walking without support IQ normal		52 months	38 months	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	9 months		4.5 years				NA		-	-		-										
Death Reason	Respiratory infection		Infection				NA	NA	-			-										

Table 1. **Clinical, genetic and biochemical data from previously reported patients with EE**. NA: not available, MNZ: Metronidazole, NAC: N-acetylcysteine, CRRT:Continious Renal Replacement Therapy, Hom: Homozygous, CH: Compound Heterozygous, *:Mild phenotype

Table 2. Suspected Diagnoses

1. Cow's milk protein intolerance
2. Meningococcemia
3. Septic shock
4. Autoimmune disorders
5. Coeliac diseae
6. Food allergies or malabsorption syndromes
7. Coagulation defects
8. Bacterial or parasitic infections
9. Inflammatory bowel disease
10. Rheumatologic Disorders
11. SCAD (Short Chain Acyl Co A Dehydrogenase Deficiency)
12. Multiple Acyl co-A Dehydrogenase Deficiency
13. Mitochondrial disorders (Leigh Syndrome,MELAS)

Table 3. *ETHE1* gene mutations

	Homozygous	
(Heberle et al., 2006)	(p.N77fsX144)(c.230delAA)	1
(Bulut et al., 2018; Di Rocco et al., 2006; Lim et al., 2021; Tam et al., 2019)	(p.R163W) (c.487C>T)**	4
(Zafeiriou et al., 2007)	(p.R163G) (c.487C>G)	1
(Cardelo Autero et al., 2021; Kasapkara et al., 2017; Merinero et al., 2006; Peake & Rodan, 2017) + Presented Cases	(p.R163Q) (c.488G>A) **	6
(Mineri et al., 2008)	(p.D169N)(c.586G>A)	1
(Mineri et al., 2008)	(p.L55P) (c.164T>C)	1
(Mineri et al., 2008)	Homozygous deletion from exon 4 to exon 7	1
(Barth et al., 2010; Drousiotou et al., 2011; Ismail et al., 2009; Pavlou et al., 2013; Tam et al., 2019)	Exon 4 homozygous deletion	5
(Dweikat et al., 2012)	(IVS4DS) (c.505+1G>T)	1
(Cavusoglu et al., 2018; Ersoy et al., 2020; Yis et al., 2015)	(p.M1I) (c. 3G>T)**	3
(Dionisi-Vici et al., 2016; Horton et al., 2022; Olivieri et al., 2021)	(p.Glu44ValfsTer62)(c.131_132delAG)	3
(Kilic et al., 2017)	(p. L185R)(c.554T> G)	1
(Kitzler et al., 2019)	(p.Q27K) (c.79C>A)**	1
(Tao et al., 2020)	(p.Q99*) (c.295C>T)	1
(Govindaraj et al., 2020)	(p.D165H) (c.493G>C)	1
(Boyer et al., 2018)	(p.Cys189PhefsTer2) (c.505+1G>A)	1

	Compound Heterozygous	
(Mineri et al., 2008)	(p.Y74X)(c.221-222insA)//(p.T164K) (c.491C>A)	1
(Mineri et al., 2008)	(p.R163W)(c.487C>T) //(p.T152I) (c.455C>T)	1
(Drousiotou et al., 2011)	(p.L185R) (c.554T>G) // deletion of exon 4	2
(Papetti et al., 2015)	(p.E208del)(c.622_624delGAG)//(p.I114F)(c.340A>T)/ (p.R163Q) (c.488G>A).	1
(Bijarnia-Mahay et al., 2016)	p.R163Q) (c.488G>A)/(c.375+5G>T)	1
(Boyer et al., 2018)	(c.566delG) / (p.Glu44ValfsTer62) (c.131_132delAG)	1
(Chen et al., 2020)	(p.D196H)(c.586G>C) / (c.595C + 1G>T)	1
(Zhou et al., 2020)	(c.375+5G>A) (splicing)/ (p.D154E) (c.462T>A)	1
(Lim et al., 2021)	(p.Ser88Leu)(c.263C>T) / (p. Thr136Ile) (c.407C>T)	2
(Pigeon et al., 2009)	(p.Q27K) (c.79C>A), (p.L185R) (c.554T>G)**	2

**: Patients with mild phenotype.

Table 4. Cranial Imaging of Patients

Authors	Cranial Imaging
(A. Burlina et al., 1991)	MRI: Hyperintensity of the cerebellar white matter and bilateral hyperintensity of caudate and lenticular nuclei.
(Christensen et al., 1993)	CT: Normal
(A. B. Burlina et al., 1994)	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.
(Garavaglia et al., 1994)	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.
(Ozand et al., 1994)	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.
(Garcia-Silva et al., 1997)	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.
(Yoon et al., 2001)	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.
(Heberle et al., 2006)	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.
(Di Rocco et al., 2006)**	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
(Mineri et al., 2008)	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
(Zafeiriou et al., 2007)	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.
(Pigeon et al., 2009)**	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
(Ismail et al., 2009)	MRI: Basal ganglia and white matter changes
(Barth et al., 2010)	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.
(Drousiotou et al., 2011)	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.
(Pavlou et al., 2013)	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
(Papetti et al., 2015)	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.
(Yis et al., 2015)**	Bilateral punctuate hyperintense T_2 signals in the basal ganglia with minor lactate peak on spectroscopy.
(Bijarnia-Mahay et al., 2016)	MRI brain showed abnormal hyperintense signals in T2W/FLAIR in bilateral putamen and caudate nuclei. Subtle hyperintensities were also noted in bilateral peritrigonal regions.
(Kilic et al., 2017)	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
(Peake & Rodan, 2017)	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.
(Boyer et al., 2018)	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.
(Cavusoglu et al., 2018)**	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
(Bulut et al., 2018)	Symmetrical hyperintense signals on T-2 weighted images in basal ganglia
(Chen et al., 2020)	Abnormal signal shadows in the temporal horn of the left lateral ventricle, revealing demyelination in the brain.
(Kitzler et al., 2019)	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
(Ersoy et al., 2020)**	MRI: Normal
(Tao et al., 2020)	Bilateral frontal and temporal subarachnoid space dilatation, and enlarged interhemispheric fissure.
(Govindaraj et al., 2020)	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.

(Zhou et al., 2020)	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.
(Cardelo Autero et al., 2021)	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.
(Olivieri et al., 2021)	A mild brain atrophy and initial bilateral involvement of basal ganglia.
(Lim et al., 2021)	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.
(Horton et al., 2022)	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

**:Mild phenotype

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Video