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CASE REPORT

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An atypically mild case of ethylmalonic encephalopathy with pathogenic *ETHE1* variant

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Abstract

Ethylmalonic encephalopathy (EE) is a rare, severe, autosomal recessive condition caused by pathogenic variants in *ETHE1* leading to progressive encephalopathy, hypotonia evolving to dystonia, petechiae, orthostatic acrocyanosis, diarrhea, and elevated ethylmalonic acid in urine. In this case report, we describe a patient with only mild speech and gross motor delays, subtle biochemical abnormalities, and normal brain imaging found to be homozygous for a pathogenic *ETHE1* variant (c.586G>A) via whole exome sequencing. This case highlights the clinical heterogeneity of *ETHE1* mutations and the utility of whole-exome sequencing in diagnosing mild cases of EE.

KEYWORDS
ETHE1 gene, ethylmalonic acid, gross-motor delay, speech delay

1 | INTRODUCTION

Ethylmalonic encephalopathy (EE; Online Mendelian Inheritance in Man #602473) is a rare, severe, autosomal recessive mitochondrial disorder with typical onset in infancy (di Meo et al., 2017; Tiranti & Zeviani, 2013). Clinically, affected patients exhibit early onset progressive encephalopathy, hypotonia evolving to dystonia, petechiae, orthostatic acrocyanosis, diarrhea, and elevated ethylmalonic acid in their urine (di Meo et al., 2017; Tiranti et al., 2006). Since the initial description in three unrelated Italian patients in 1991 (Burlina et al., 1991), more than 80 patients have been identified (di Meo et al., 2017; Tao et al., 2020).

The clinical manifestations of EE have been linked to pathogenic variants in the *ETHE1* gene leading to dysregulation of sulfur metabolism (Tiranti & Zeviani, 2013). *ETHE1* encodes the Ethe1 protein (Ethe1p), a 30 kDa polypeptide found in mitochondria involved in the catabolism of hydrogen sulfide (H_2S) and thiosulfate (Tiranti & Zeviani, 2013). Deficiency of Ethe1p activity leads to local accumulation of H_2S in brain, muscle, colonic mucosa, and liver as well as elevated thiosulfate levels detectable in blood and urine. In tissues of accumulation, H_2S acts as a signaling molecule leading to the clinical symptoms characteristic of EE. High local concentrations of H_2S also inhibits short-chain acyl-CoA dehydrogenase and cytochrome c oxidase activities leading to elevated lactate and C4/C5 acylcarnitines (Tiranti et al., 2009), lab abnormalities also seen in EE patients. Symptom onset is typically within the first several months of life and patients usually die within the first decade (Tiranti & Zeviani, 2013; Tiranti et al., 2006).

Certain pathogenic *ETHE1* mutations have been associated with findings such as joint hypermobility (di Rocco et al., 2006), genitourinary abnormalities (Heberle et al., 2006), or stroke-like episodes (Lim et al., 2021) in addition to the typical findings described above. This case report describes at patient exhibiting a mild case of EE despite being homozygous for *ETHE1* c.586G>A, a pathogenic variant previously identified as causal in a more severe case.

2 | CASE

A 19-month-old toddler boy presented for initial genetic evaluation for developmental delay and mild hyperammonemia (ammonia 40–

63, ref 13–37 μmol/L). This patient was the product of a consanguineous marriage (paternal great-grandfather is brother to maternal great-grandfather) and was born at 37 weeks and 4 days gestation via vaginal delivery. Pregnancy was uncomplicated with a normal 20-week anatomic ultrasound. Newborn screening was normal. During infancy, there were initial concerns for feeding difficulty requiring thickened feeds which improved over time. At the time of initial evaluation, our patient had a 5-word vocabulary with strong receptive language and a wide-based gait. There were no dysmorphic features. Lab work obtained notable for the following: plasma amino acids (within normal limits), plasma acylcarnitine profile (Iso-/Butyrylcarnitine, C4—1.41 nmol/mL [Ref <1.06]), and urine organic acids (trace methylmalonic acid; small ethylmalonic acid). The small amount of urine ethylmalonic acid was interpreted to be within the range of normal.

At 3 years and 5 months of age, the patient was evaluated by his primary care provider who noted difficulty with articulation and had concerns for his gait. History obtained during a pediatric neurology evaluation at 3 years and 8 months of age was notable for articulation difficulty with <50% speech intelligibility and inability to jump with both feet. Neurologic exam was significant for paresis of lateral tongue movements and when asked to run, had right arm flexion and right leg out-swinging. Despite this, he had normal axial and appendicular tone, 5/5 and symmetric strength in all extremities with confrontational testing, no dysmetria, normal upper- and lower-extremity deep tendon reflexes, and down-going toes with plantar stimulation bilaterally. He was otherwise noted to have good social development without concern for seizures or regression. The right arm flexion and leg extension with running was most suspicious for a dystonia (potentially localizing to the left basal ganglia or its connections with the cerebellum), or less likely mild spasticity not detected during formal tone assessment (localizing to the corticospinal tract originating from the left motor cortex). The paresis of bilateral lateral tongue movements without atrophy or fasciculations could localize to the bilateral corticobulbar tracts as part of a pseudobulbar palsy. While a single localization in the absence of other brainstem or extremity symptoms seemed unlikely, given the potential multifocal localization at the level of the medulla or above, an MRI brain with and without contrast was pursued, which was normal (Figure 1). Chromosomal microarray was obtained revealing approximately 7.1% of single nucleotide polymorphism homozygosity consistent with known parental consanguinity. Subsequent neurology evaluation at 4 years and 2 months of age was notable for persistent expressive language deficit, difficulty with lateral tongue movement, and behavioral concerns for which audiology evaluation and re-evaluation by the genetics team was recommended. His hearing test was normal and whole-exome sequencing with mitochondrial genome sequencing was pursued by the genetics team. This revealed a homozygous pathogenic variant in the *ETHE1* (c.586G>A; p.D196N) consistent with a diagnosis of EE. No other likely causative variants were reported.

At 4 years and 8 months of age, the patient was speaking in full sentences with improved articulation. He could jump with 2 feet but could not hop on either foot. Neurologic exam was notable for low-normal tone without spasticity or dystonia, full range of tongue movements, and swaying and arm posturing with running without consistent laterality. He continued to have full strength of all extremities, no dysmetria, and normal deep-tendon reflexes. Laboratory workup included repeat acylcarnitine profile (Iso-/Butyrylcarnitine, C4—1.33 nmol/mL [Ref <1.06]), plasma thiosulfate—2.0 mcg/mL [Ref <2], and quantitative urine organic acids [mmol/mol Cr]: Pyruvate—29 [Ref 2–19]; Isobutyric—69 [Ref 4–64]; Malic acid—5 [Ref 0–4]; Isobutyrylglycine—18 [Ref 0–2]; Isovalerylglycine—25 [Ref 0–4]; Butyrylglycine—4 [Ref 0–0]; Ethylmalonic acid—16 [Ref 0–6]; 3-Methylglutaconic acid—2 [Ref 3–17]; 2-OH Glutaric acid—20 [Ref 1–14]; Random urine creatinine—8.88 mmol/L [Ref 0.18–11.49]. Cytochrome c oxidase activity has not been measured as the patient has not undergone muscle or skin biopsy. He was subsequently initiated on N-acetylcysteine and intermittent metronidazole to reduce sulfur burden. He remains without concern for seizures, developmental regression, or acrocyanosis. He did have a brief period of diarrhea with documented bacterial illness suggesting an infectious etiology. In support of an infectious etiology, symptoms have since completely resolved and not recurred.

3 | DISCUSSION

EE is a severe mitochondrial disease of infancy caused by pathogenic variants in the *ETHE1* gene leading to dysregulation of sulfur metabolism (di Meo et al., 2017; Tiranti & Zeviani, 2013). Resultant local tissue accumulation of H_2S leads to progressive encephalopathy, hypotonia evolving to dystonia, petechiae, orthostatic acrocyanosis, diarrhea, and ethylmalonic acid in urine (Tiranti & Zeviani, 2013). We describe a patient born from consanguineous parents homozygous for the *ETHE1* c.586G>A variant. Clinically, this patient had only mild findings which included expressive speech delay, gross motor delay, initial abnormal right-sided extremity movements with running, initial paresis of lateral tongue movements, low-normal muscle tone, and small elevation in urine ethylmalonic acid. Asymmetric extremity and restricted lateral tongue movements spontaneously improved. His brain MRI did not show abnormal findings. He remains without seizures, worsening weakness, petechiae, acrocyanosis, or diarrhea. The diagnosis of EE was made from whole exome sequencing and led to initiation of N-acetylcysteine and metronidazole to buffer serum sulfur burden and intestinal production of absorbable sulfur compounds, respectively (Tiranti & Zeviani, 2013). For more severe cases, orthotopic liver transplant has also been trialed to as an additional means to filter H_2S from the blood (Tam et al., 2019).

Homozygosity for the *ETHE1* c.586G>A variant has been previously described (Mineri et al., 2008). In contrast to our patient, the previously reported patient was born from non-consanguineous parents and developed classic/more severe findings of EE (Mineri et al., 2008). Specifically, they had frequent vomiting and diarrhea within the first year of life followed by proximal muscle weakness, axial hypotonia, and poor trunk control (Mineri et al., 2008). By 5 years of age, there were pyramidal signs and distal acrocyanosis.

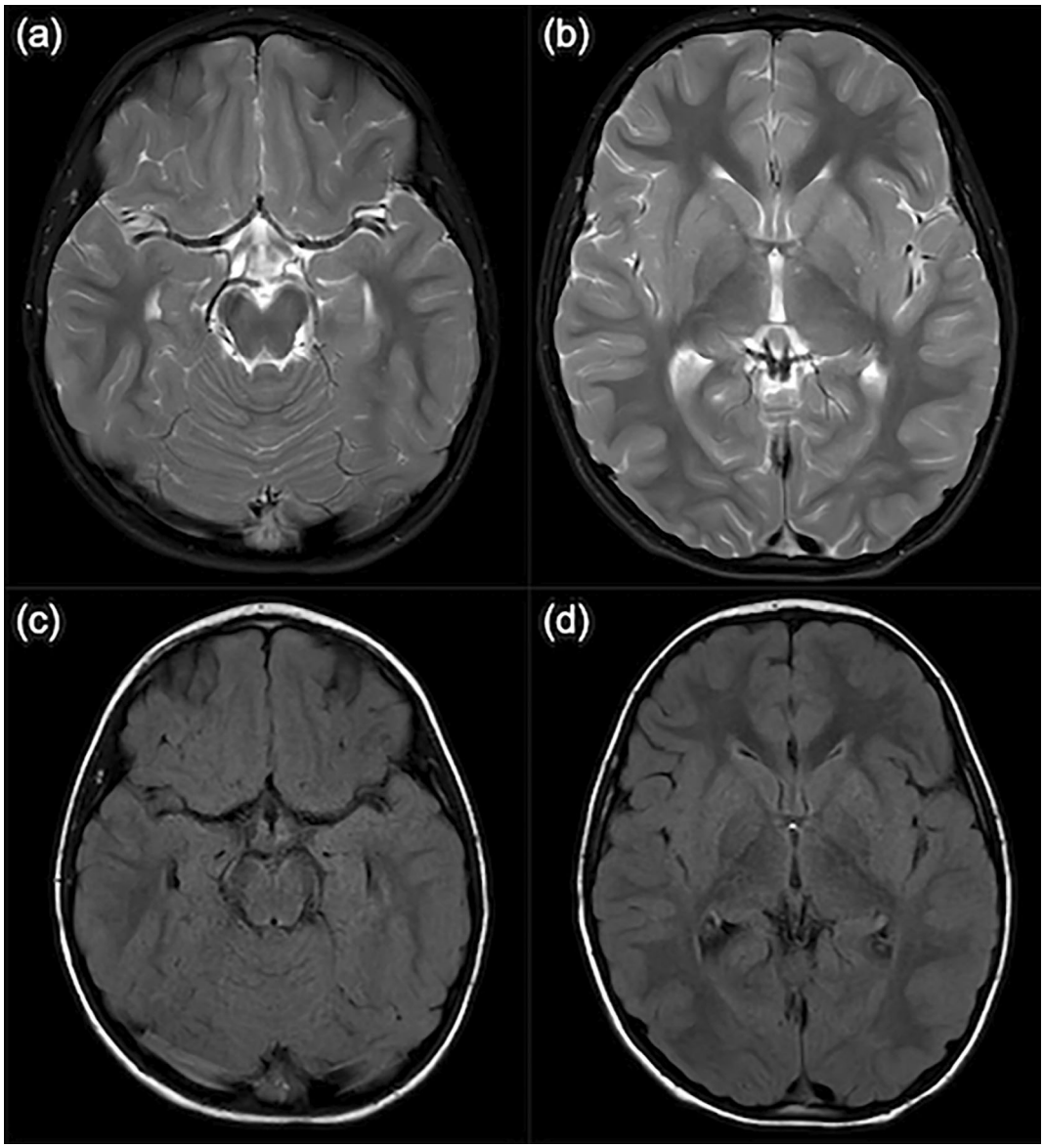

FIGURE 1 Axial MRI images of patient's brain. Scan performed when patient was 3 years and 9 months of age. (a) T2-weighted image at the level of the midbrain which includes amygdala. (b) T2-weighted image at the level of the thalamus, caudate, putamen, globus pallidus, and external capsule. Small foci of T2 hyperintensity in basal ganglia not evident on corresponding FLAIR sequences likely represent Virchow–Robin spaces (c, d).

Laboratory findings included a significant elevation urine ethylmalonic acid (170 mmol/mol creatinine [Ref <20]), faintly elevated lactate, and slightly elevated C4 acylcarnitine on a single measurement. Brain imaging showed asymmetric T2 hyperintensities surrounding the basal ganglia (globus pallidus, external capsule, and amygdala). This clinical description led to the classification of the *ETHE1* c.586G>A variant as being pathogenic.

Comparatively mild clinical presentations have been described for several other pathogenic *ETHE1* variants. One patient was homozygous for the *ETHE1* c.487C>T variant who exhibited recurrent petechiae/ecchymosis, diarrhea, and cognitive delay as well as atypical joint hyperlaxity in the setting of abnormal brain MRI. This patient had normal urine organic acids during a random collection but died at 32 months of age following a metabolic crisis (di Rocco et al., 2006). A second patient was homozygous for the *ETHE1* c.3G>T variant and had spastic paraparesis and intractable diarrhea in the setting of normal cognitive development. This patient had normal brain MRI and spectroscopy and an elevation of urine ethylmalonic acid of 46 mmol/mol creatinine [ref <8.8] (Ersoy et al., 2020). A third patient was compound heterozygous for *ETHE1* c.595+1G>T and c.586G>C who had chronic diarrhea, global developmental delay, and consistently elevated urine ethylmalonic acid 28.96–71.84 μM/L [ref <4.70] but was without acrocyanosis, hypotonia, or pyramidal signs (Chen et al., 2020). MRI brain for the third patient showed evidence of

demyelination and during follow-up, developmental delay was restricted to language delay. A fourth patient who was homozygous for the *ETHE1* c.79C>A variant exhibited developmental delay, intellectual disability, dysarthria, spastic paraplegia requiring a baclofen pump, Chiari I malformation, and T2 hyperintensities in the cerebellum and basal ganglia on brain MRI (Kitzler et al., 2019). This fourth patient did not have diarrhea or acrocyanosis and did not require hospitalization at until 16 years of age. Urine ethylmalonic acid levels ranged from 29 to 100 mmol/mol Cr [ref <11]. He had a metabolic crisis with fever, seizures, elevated lactate, and elevated urine ethylmalonic acid at 17 years of age which was successfully treated with continuous renal replacement therapy (Kitzler et al., 2019).

Our patient's mild clinical presentation in the setting of homozygosity for a different pathogenic variant, *ETHE1* c.586G>A, underscores the clinical heterogeneity of this condition. Our patient differs from these other less severe EE cases in that the mild developmental delay without other clinical sequelae, mild biochemical abnormalities, and normal brain imaging did not raise suspicion for EE. It is possible other genes impact the presentation of patients with EE, perhaps altering sulfur burden. Our patient does not have prominent encephalopathy as has been previously described, and as the full spectrum of EE is delineated, it is possible that a more accurate nomenclature may be *ETHE1*-related disorder. Of course, it is also impossible to predict if this patient will develop other symptoms over time. He remains closely followed in our neurology and genetics clinics.

Our patient's atypical clinical and biochemical presentation also highlights the utility of whole exome sequencing to provide a genetic diagnosis in otherwise nonspecific abnormalities. In this case, it affected management in that therapies to reduce sulfur burden were initiated. Further natural history studies are needed to determine if patients with mild cases of EE are at the same risk for acute decompensation/metabolic crisis.

4 | CONCLUSION

This case report details a patient with a mild form of EE despite homozygosity for *ETHE1* c.586G>A, a variant previously found in a separate patient with more classic/severe features. It is likely the full spectrum of this disorder is not yet fully recognized, and other patients may be identified with *ETHE1*-related disorders over time through use of whole exome and whole genome sequencing. Further research into the spectrum, natural history, and possible treatments of this disorder is needed.

AUTHOR CONTRIBUTIONS

Daniel T. Kashima, Christina M. Sloan-Heggen, Rachel J. Gottlieb-Smith, and Amanda Barone Pritchard contributed to the literature review, diagnostic workup, test result interpretation, and clinical care of the patient. Daniel T. Kashima wrote the manuscript. Christina M. Sloan-Heggen, Rachel J. Gottlieb-Smith, and Amanda Barone Pritchard revised the manuscript. All authors approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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