Mystery Case: An infant with developmental delay, epileptic spasms, and acrocyanosis

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Figure 1 Skin findings in the index patient

Note the spontaneous ecchymosis (black arrows; A, B, E), acrocyanosis (arrowheads; C, D), and mottled appearance of the forearm (red arrow; D).

A 10-month-old girl presented with global developmental delay, epileptic spasms, and easy bruisability. She was fourth-born of third-degree consanguineous parents with 3 healthy siblings. The perinatal period was uneventful. Examination revealed microcephaly, central
hypotonia, acrocyanosis, mottled skin, and petechiae over extremities (Figure 1). Neuroimaging revealed peculiar findings (Figure 2). EEG revealed modified hypersrrhythmia (Figure 3). Epileptic spasms resolved with oral prednisolone therapy (given at 3 mg/kg/d for 2 weeks followed by tapering over 6 weeks). She had elevated C4-acylcarnitines on tandem mass spectrometry (TMS) and urinary ethylmalonic acid on urine gas chromatography mass spectrometry (GCMS). The diagnosis of ethylmalonic encephalopathy (EE) was confirmed genetically (c.487C > T; p.Arg163Trp homozygous variation in ETHE1). She was initiated on N-acetyl cysteine, metronidazole, and mitochondrial cocktail but died of an acute crisis at 14 months of age.

Discussion

EE is a rare infantile-onset metabolic encephalopathy with an abysmal prognosis. It is characterized by chronic diarrhea, recurrent petechiae, acrocyanosis, developmental delay or regression, and an unusual metabolic signature in plasma and urine. ETHE1 codes for mitochondrial sulfur dioxygenase, abnormalities that lead to accumulation of hydrogen sulfide (H2S) in gut and tissues. Accumulated sulfides subsequently inhibit several enzymes such as short-chain acyl-CoA dehydrogenase (SCAD) or cytochrome oxidase, resulting in vasotoxic and neurologic effects.

Other manifestations of EE include epilepsy, sensory neuropathy, and crescentic glomerulonephritis. Epileptic spasms have also been reported in the literature and are usually refractory to adrenocorticotropic, vigabatrin, and steroids. The index child, however, responded to steroids. Although the mechanism of action of oral steroids in epileptic spasms is unclear, the inhibition of corticotropin-releasing hormone overexpression may be responsible.

TMS and GCMS are widely used screening investigations for various inborn errors of metabolism, including EE. They are based on the principles of mass spectrometry (for identification and quantification of metabolites based on mass to charge ratio) and gas chromatography (for separation of various metabolites based on their volatility). The metabolic abnormalities in EE include lactic acidemia, elevated plasma C4 and C5 acyl-carnitines, and ethylmalonic aciduria. A similar metabolic profile may also be seen in SCAD deficiency, Jamaican vomiting sickness, and glutaric aciduria.
acidemia type 2 but classical clinical phenotype in EE may provide a diagnostic clue.1

Treatment aims at reducing H$_2$S accumulation. Metronidazole and N-acetyl cysteine are thought to be useful.4 Besides this, orthotopic liver transplantation corrects the metabolic defect and improves psychomotor outcomes.5,6 Thus early recognition and referral to liver transplant centers may significantly improve outcomes.

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Disclosure
The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Figure 3 EEG of the index patient

Ten-second EEG epoch (pediatric montage; sensitivity 70 $\mu$V; sweep speed 30 mm/s) shows bursts of polyspike wave discharges followed by attenuation and posterior-dominant high-amplitude slow waves, which is consistent with modified hypsarrhythmia.

Appendix Authors

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Microcephaly is defined as an occipitofrontal circumference of more than 2 SD below the mean. Primary microcephaly is caused by a fetal brain insult leading to an impairment of neurogenesis and most severely affects the forebrain (correctly noted by 39% of responses). Genetic disorders (including monogenic disorders, genetic syndromes, and chromosomal abnormalities) and prenatal brain injury (such as teratogenic exposure) account for just under a third of primary cases each and nearly 50% are underdetermined. Second microcephaly occurs when an insult to a previously normal brain causes a reduction in dendritic processes and synaptic connections (e.g., postnatal TORCH [toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes] infections, hypoxic-ischemic insults, or severe malnutrition). Metabolic disorders can also be associated with microcephaly but the coexistence is low (~1–5%)..

The final diagnosis was EE, correctly made by 67% of respondents. SCAD deficiency and glutaric academia type 2 share the same metabolic profile (lactic acidemia, elevated plasma C4 and C3 acyl-carnitines, and ethylmalonic aciduria) and were therefore the most appropriate differential diagnoses, chosen by 62% and 50% of respondents, respectively.

Metabolic disorders are characterized by the deficiency or dysfunction of essential metabolites and cause neurologic symptoms due to impaired brain development or functioning. Although a child with a metabolic disorder typically presents with global neurodevelopmental delay and accumulating disability, acute encephalopathy, ataxia, childhood epilepsy, or movement disorders are increasingly recognized presentations. Only one respondent correctly answered all questions; this highlights how such cases are considered challenging. However, having a structured approach focusing on the presenting age, developmental progression, and peculiar examination findings and obtaining a basic metabolic screen and neuroimaging should significantly narrow the differential diagnosis and ease discussions with specialists.

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References
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