

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

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Figure 1 Skin findings in the index patient



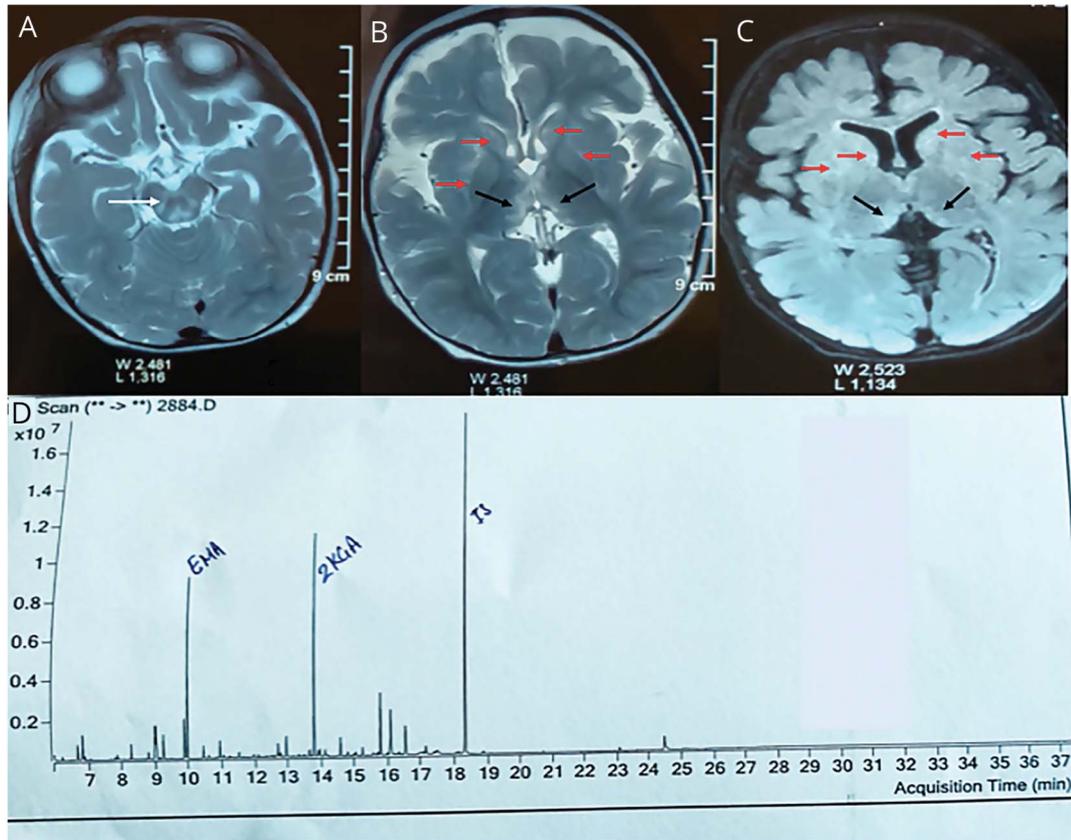
Note the spontaneous ecchymosis (black arrows; A, B, E), acrocyanosis (arrowheads; C, D), and mottled appearance of the forearm (red arrow; D).

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

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Figure 2 Brain MRI and urine gas chromatography mass spectrometry (GCMS) of the index patient



T2-weighted (A, B) and T2 fluid-attenuated inversion recovery (C) axial images show hyperintensities in midbrain (tegmentum; white arrow), bilateral caudate, putamen (red arrows), and thalamic pulvinar region (black arrows). Total ion chromatogram (D) of urine metabolites by GCMS shows increased excretion of ethylmalonic acid (EMA), 2-ketoglutaric acid (2-KGA), isobutyrylglycine, and isovalerylglycine.

hypotonia, acrocyanosis, mottled skin, and petechiae over extremities (figure 1). Neuroimaging revealed peculiar findings (figure 2). EEG revealed modified hypsarrhythmia (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

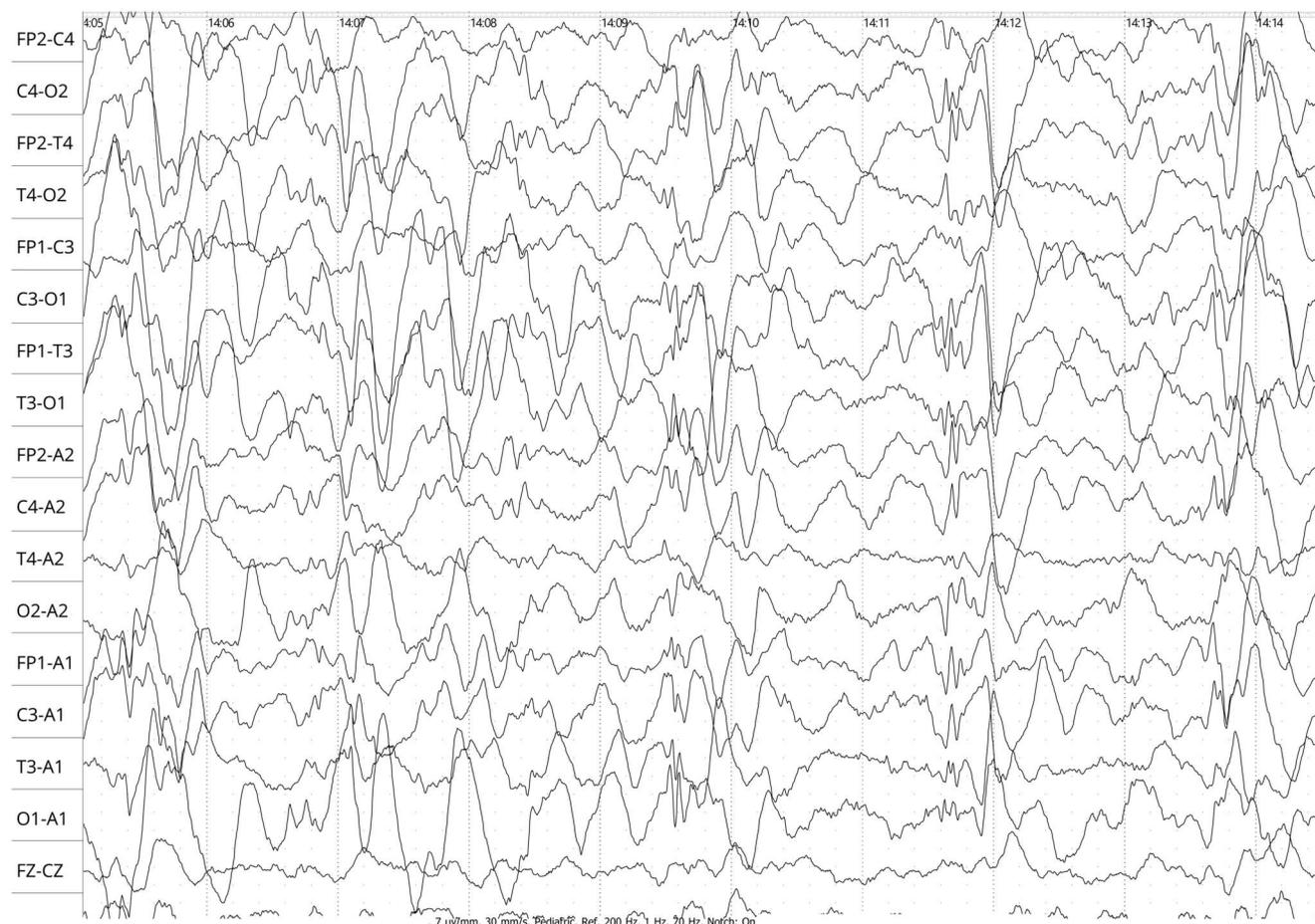
EE is a rare infantile-onset metabolic encephalopathy with an abysmal prognosis.¹ It is characterized by chronic diarrhea, recurrent petechiae, acrocyanosis, developmental delay or regression, and an unusual metabolic signature in plasma and urine. *ETHE1* codes for mitochondrial sulfur dioxygenase, abnormalities that lead to accumulation of hydrogen sulfide (H₂S) in gut and tissues.^{1,2} Accumulated sulfides subsequently

inhibit several enzymes such as short-chain acyl-CoA dehydrogenase (SCAD) or cytochrome oxidase, resulting in vasotoxic and neurologic effects.¹⁻³

Other manifestations of EE include epilepsy, sensory neuropathy, and crescentic glomerulonephritis.⁴ Epileptic spasms have also been reported in the literature and are usually refractory to adrenocorticotropin, vigabatrin, and steroids.⁴ 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

Figure 3 EEG of the index patient



Ten-second EEG epoch (pediatric montage; sensitivity 70 µV; 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.

acidemia type 2 but classical clinical phenotype in EE may provide a diagnostic clue.¹

Treatment aims at reducing H₂S 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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Appendix Authors

Name	Location	Contribution
Priyanka Madaan, DM	Postgraduate Institute of Medical Education and Research, Chandigarh; CSIR, New Delhi, India	Patient management, literature review, initial draft manuscript, preparation and final approval of the version to be published
Lokesh Saini, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Patient management, critical review of the manuscript, final approval of the version to be published
Sameer Vyas, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Analysis of the radiologic data, critical review of manuscript, final approval of the version to be published
Savita Verma Attri, MD	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Analysis of metabolic tests, critical review of manuscript, final approval of the version to be published

Continued

Appendix (continued)

Name	Location	Contribution
Jitendra Kumar Sahu, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Patient management, critical review of manuscript for important intellectual content, final approval of the version to be published

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Mystery Case responses

The Mystery Case series was initiated by the *Neurology*[®] Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses to multiple choice questions formulated using this case were solicited through a group email sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media. We received 123 responses. The majority of respondents (77%) had been in practice for 1–4 years; 58% were residents or fellows, while 26% were faculty/board-certified physicians; the remainder were medical students or advanced practice providers. Fifty-eight percent resided outside the United States. A wide range of practice settings was represented.

The 10-month-old patient, born of consanguineous parents, presented with global developmental delay, epileptic spasms, and easy bruising. She was found to have microcephaly, central hypotonia, acrocyanosis, mottled skin, and limb petechiae on examination and an EEG revealed hypsarrhythmia. Hypsarrhythmia is a disorganized pattern of high-amplitude asynchronous slow waves, multifocal spikes, and polyspikes,¹ suggestive of significant cortical dysfunction. The triad of hypsarrhythmia, epileptic spasms, and developmental impairment is called West syndrome. Most respondents correctly identified rhythmically repetitive spikes (70%), paroxysmal generalized 4-Hz to 6-Hz polyspike and wave discharges (63%), and low voltage, fast waves and spikes originating from the same cortical area (72%) as not being features of hypsarrhythmia.

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.² Secondary 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%).³

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 C₅ 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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