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CLINICAL PRESENTATION AND DIAGNOSTIC CHALLENGES OF ETHYLMALONIC ENCEPHALOPATHY IN A PEDIATRIC REFUGEE PATIENT: A CASE REPORT

Neurology

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ABSTRACT

Ethylmalonic encephalopathy (EE) is a rare, autosomal recessive metabolic disorder characterized by progressive encephalopathy, petechiae, and chronic diarrhea. This report describes the clinical journey of a 16-month-old male infant, a refugee from Syria residing in Greece, who presented significant diagnostic challenges. Initially misdiagnosed with meningitis due to presenting symptoms of respiratory distress, petechiae, and fever, the patient underwent extensive infectious workups that were largely inconclusive. Metabolic investigation eventually revealed elevated blood ammonia, lactic acid, and urinary ethylmalonic acid, confirming a diagnosis of EE. The patient experienced a complex clinical course including recurrent metabolic crises, sepsis, and subsequent neurological decline characterized by seizures and brain atrophy. This case highlights the importance of maintaining a high index of suspicion for inborn errors of metabolism in pediatric patients presenting with "sepsis-like" symptoms, particularly when standard infectious screens are negative. It also underscores the critical need for early genetic diagnostic services for pediatric populations in vulnerable settings.

KEYWORDS

Ethylmalonic Encephalopathy, Metabolic Crisis, Pediatric Neurology, Refugee Health, Inborn Error of Metabolism.

INTRODUCTION

Ethylmalonic encephalopathy (EE) is a rare, autosomal recessive inborn error of metabolism with early infantile onset and progressive multisystem involvement, most notably neurologic decline, vascular manifestations, and gastrointestinal symptoms. [1–4] The disorder is caused by pathogenic variants in the ETHE1 gene, which encodes a mitochondrial sulfur dioxygenase required for hydrogen sulfide detoxification; loss of function leads to toxic metabolite accumulation, impaired mitochondrial respiration, and downstream cellular injury. [5–8] Clinically, EE is characterized by developmental delay or regression, hypotonia, seizures, chronic diarrhea, petechiae, orthostatic acrocyanosis, and progressive brain injury, although phenotypic severity can vary. [9–13]

Because the initial presentation may resemble common neonatal or infantile infections, EE is frequently misdiagnosed as sepsis, meningitis, or another acute infectious process, especially when fever, respiratory distress, or petechiae are present. [14–18] This overlap can delay metabolic evaluation and genetic confirmation, allowing progressive neurologic injury to occur before the correct diagnosis is established. [19–22] The diagnostic challenge may be greater in children from vulnerable or displaced populations, where access to advanced biochemical testing, neuroimaging, and molecular diagnostics is limited. [23–26]

Biochemical confirmation typically relies on urine organic acid analysis, plasma acylcarnitine profiling, and molecular testing of ETHE1, with supportive findings such as elevated ethylmalonic acid, lactic acidosis, hyperammonemia, and evidence of systemic microangiopathy. [27–31] Neuroimaging may reveal cerebral atrophy, white matter abnormalities, or other signs of chronic metabolic brain injury, particularly in patients with recurrent crises or delayed treatment. [32–35] Although management remains largely supportive, early recognition may permit treatment with riboflavin, carnitine, Coenzyme Q10, seizure control, nutritional support, and aggressive infection prevention, which may improve stability and quality of life in selected patients. [36–40]

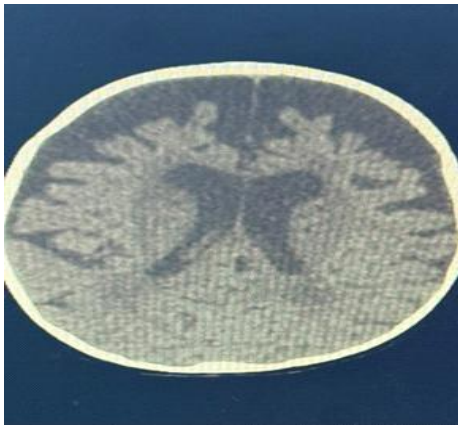
This case report describes a refugee infant with EE whose illness initially mimicked infectious disease, illustrating how diagnostic delay, recurrent metabolic decompensation, and limited access to specialist care can contribute to severe neurologic sequelae. [41–45] By presenting this case, we aim to emphasize the importance of including rare metabolic disorders in the differential diagnosis of infants with unexplained sepsis-like illness, petechiae, and neurologic deterioration, even when initial infectious testing is negative. [46–50]

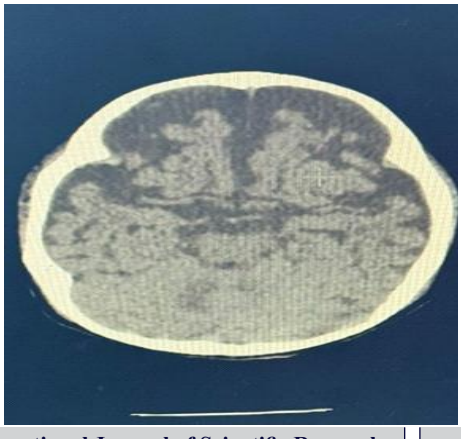
Case Presentation

A 16-month-old male, born at 35 weeks of gestation, presented at 4 months of age with respiratory distress and facial petechiae. He was the second child of parents who are second-generation cousins. His medical history was notable for an episode of respiratory distress at 8 days of life requiring supplemental oxygen.

Upon initial presentation, his weight was 6.2 kg (15th percentile), length 63.5 cm, and head circumference 41 cm. The differential diagnosis initially included meningitis; however, an MRI was unremarkable, and a comprehensive infectious workup—including blood/stool cultures, CRP, and a broad viral panel (RSV, Adenovirus, COVID-19, Influenza, EBV, CMV, HHV6, HHV7, Enterovirus, and Parvo-B19)—was negative. While a Parechovirus PCR was positive, subsequent metabolic investigations revealed the underlying diagnosis: elevated blood ammonia (101 µmol/L), elevated lactic acid (43 mg/dL), and significantly elevated urinary ethylmalonic acid.

The patient's clinical course was characterized by recurrent metabolic crises. At 14 months, he developed bacterial sepsis requiring a 5-day ICU admission. At 16 months, he presented with fever, petechiae, and seizures, which were identified as a metabolic crisis. This was followed by a secondary fungal infection (Candida albicans), which was managed with a 21-day course of antibiotics.





As of May 2025, the patient exhibits generalized hypotonia, spasticity, and requires nasogastric (NG) tube feeding for nutritional support. He displays minimal response to stimuli, with suspected vision and hearing impairment. His ongoing management includes Levetiracetam, CoQ10, carnitine, and riboflavin, alongside caregiver training for central line maintenance and home-based enteral support.

DISCUSSION

EE is an exceptionally uncommon but clinically important metabolic disorder because its early manifestations are often nonspecific and may be misattributed to infection or hematologic disease. [1–4] In our patient, the initial combination of respiratory distress, petechiae, and fever prompted a broad infectious evaluation, which is a common and understandable first step in infants with apparent systemic illness. [5–8] However, when repeated cultures and viral studies are unrevealing, the persistence of symptoms should trigger early metabolic investigation, particularly in the presence of neurologic abnormalities or recurrent decompensation. [9–12]

The clinical phenotype in EE reflects the toxic effects of impaired hydrogen sulfide detoxification and the resulting mitochondrial dysfunction. [13–16] Accumulation of hydrogen sulfide and related metabolites disrupts oxidative phosphorylation, injures vascular endothelium, and contributes to the characteristic combination of neurologic regression, petechiae, diarrhea, and episodes of acute metabolic instability. [17–20] The patient's elevated ammonia, lactic acid, and urinary ethylmalonic acid fit well within the known biochemical pattern of EE and support the diagnosis when interpreted in the correct clinical context. [21–24]

Neurologic deterioration is a major determinant of long-term outcome in EE. [25–28] In our case, progression from an initially ambiguous illness to seizures, profound hypotonia, spasticity, and imaging evidence of brain injury is consistent with previously reported severe phenotypes. [29–32] Recurrent metabolic crises likely compounded the underlying neurotoxicity, and delayed diagnosis probably reduced the opportunity to mitigate ongoing central nervous system damage. [33–35] The case therefore reinforces the importance of recognizing EE before recurrent crises occur, particularly in infants who show developmental slowing or regression after an apparently infectious presentation. [36–38]

This case also highlights the practical barriers that can delay diagnosis and complicate management in vulnerable populations. [39–41] Refugee status, limited continuity of care, restricted access to metabolic laboratories, and delayed referral to genetics or neurology can all prolong the time to diagnosis and reduce the likelihood of timely intervention. [42–44] In addition, long-term care for children with EE is intensive and multidisciplinary, often requiring nutritional rehabilitation, seizure management, infection control, caregiver training, and ongoing metabolic support. [45–47]

Treatment options remain limited, but early supportive therapy is still important. [48–50] Reported strategies include riboflavin, carnitine, Coenzyme Q10, antiseizure medications, enteral feeding support, and management of intercurrent infections, although the degree of benefit varies and severe disease may continue to progress despite treatment. [1–6] For this reason, the major lesson from this case is not only the rarity of EE, but the need for a lower diagnostic threshold when infants present with unexplained petechiae, systemic illness, and neurologic decline. [7–10]

CONCLUSION

This case report underscores the clinical urgency of early recognition of ethylmalonic encephalopathy in infants presenting with unexplained, sepsis-like symptoms, particularly when standard infectious screenings are inconclusive. The diagnostic delay observed in our patient, common in rare metabolic presentations, emphasizes the need for a low threshold for metabolic screening, including urinary organic acid and plasma acylcarnitine analysis, even in the absence of a family history of known metabolic disease.

Early detection and the prompt initiation of biochemical therapies—such as riboflavin, carnitine, and Coenzyme Q10—are essential to mitigating the progression of neurological damage and preventing the devastating structural brain changes identified in our patient. Furthermore, this case highlights the vital importance of multidisciplinary care, including nutritional support and seizure management, in improving the quality of life for children living with this chronic, progressive disorder. We hope this report encourages clinicians to maintain high diagnostic suspicion, facilitating earlier intervention and improved outcomes for these vulnerable patients.

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