Case Report

FARS2 (Phenylalanyl-tRNA Synthetase 2) Deficiency: A Novel Mutation Associated with EEG Phenotype of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

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Abstract

Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare devastating infantile epileptic encephalopathy that is characterized by a unique electroencephalography (EEG) signature of multifocal simultaneous seizures. Although no definite etiology is understood for EIMFS, mutations in certain ion channels, are implicated. Similarly, phenylalanyl-tRNA synthetase 2 (FARS2) deficiency is a rare, autosomal recessive disorder of dysfunctional mitochondrial translation causing refractory seizures, lactic acidosis, and developmental regression with a variety of EEG findings. However, an EIMFS-like pattern on EEG in FARS2 deficiency has only recently been reported once. Herein, we describe a seven-week-old male with seizures where whole exome sequencing (WES) revealed pathogenic FARS2 variants and an EIMFS pattern on EEG. This case provides an insight on a novel genetic mechanism for EIMFS. We encourage early consideration of WES when EIMFS is detected to evaluate for FARS2 deficiency, especially in the setting of profound lactic acidosis.

Keywords: Alpers Huttenlocher Syndrome (AHS), EIMFS, epileptic encephalopathy, FARS2

Introduction

EIMFS is a rare syndrome that is characterized by refractory seizures, early developmental arrest, and death. On an EEG, it appears as continuous, random focal seizures with simultaneous, albeit independent involvement of both hemispheres.[1] Despite its unknown etiology, EIMFS is more commonly associated with several genetic mutations, including KCNT1, SCN1A, SCN2A, and SLC12A5.[2] FARS2 deficiency is a severe multisystem disorder due to a mutation of the FARS2 gene on chromosome 6p25.1, which encodes for mitochondrial phenylalanyl-tRNA synthetase, an enzyme that is essential for protein synthesis.

We aim at expanding on the genetic mutations that are associated with EIMFS by describing its association with FARS2 deficiency and highlighting its clinical, electroencephalographic, and imaging features.

Case History

A seven-week-old, healthy, full-term, Caucasian male, the firstborn to healthy non-consanguineous parents, presented with a four-day history of seizures. Seizures involved clonic movements of either the upper or lower extremities, bilateral or unilateral (affected alternate sides of the body)—lasting one to two minutes, up to six episodes per hour and often associated with behavioral arrest and brief unresponsiveness.

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Systemic examination was unremarkable without neurocutaneous markers or malformations. His head circumference was 38.1 cm (33rd percentile; Nellhaus chart). The neurodevelopmental exam was unremarkable for age.

Initial laboratory studies revealed an anion gap metabolic acidosis of 22 and a markedly elevated lactate of 10.14 mmol/L (0.4–2.3). The lactate to pyruvate ratio was elevated at 54 (normal <30). Further studies were notable for transaminitis, with aspartate aminotransferase 971 U/L (20–67) and alanine aminotransferase 233 U/L (5–33). His birth history and newborn screening were reportedly normal, with no evidence of peripartum infections in either the child or the mother. An EEG confirmed several clinical and subclinical, independent, and simultaneous seizures from different cortical regions (midline, bilateral central/temporal/occipital regions) and the pattern was suggestive of EIMFS [Figure 1]. Clinical seizures subsided with levetiracetam and phenobarbital; however, electrographic seizures persisted. Because of the profound lactacidosis, a mitochondrial disorder was suspected and multiple supplements were maintained through the hospital course, including arginine, levocarnitine, coenzyme Q10, leucovorin, and pyridoxine. The ketogenic diet was not initiated.

Magnetic resonance imaging (MRI) of the brain without contrast showed diffusion restriction in the occipital lobes, thinning of the corpus callosum, and bilateral thalamic T2 signal intensities [Figure 2]. Magnetic resonance spectroscopy (MRS) was suggestive of a lactate peak in the right basal ganglia. The radiographic findings were not typical of hypoxic–ischemic injury or perinatal infections and were concerning for a metabolic encephalopathy. The MRI also ruled out an underlying congenital structural brain abnormality. The WES revealed that the patient was a compound heterozygote

Figure 1: Ictal EEG using a neonatal/double distance montage shows independent seizure foci with epileptiform discharges of different frequency, morphology, and amplitude over the two hemispheres, thus demonstrating a pattern seen in migrating focal seizures. Top: left occipital seizure manifesting as high-amplitude rhythmic delta activity (white arrow) with simultaneous, independent right central seizure with rhythmic sharp-slow wave complexes (black arrow). Bottom: Seizure over the midline comprising sharp waves (white arrow) with concurrent right temporal seizure characterized by high-amplitude rhythmic delta activity (black arrow)
for the p.D62N, p.P108L, and p.D265TfsX29 variants in the FARS2 gene. None of the three variants were previously reported as pathogenic or benign variants. Moreover, the WES did not reveal other pathogenic variations in the known mutations associated with EIMFS. In silico analyses of the p.D62N (de novo and classified as a likely pathogenic variant) and p.P108L (paternally inherited and classified as a variant of uncertain significance) variants supported deleterious effects due to changes in secondary protein structure. The p.D265TfsX29 variant was maternally inherited, classified as a likely pathogenic variant, and led to a frameshift starting with aspartic acid 265, changed to a threonine residue and creating a premature stop codon at position 29 of the new reading frame, resulting in loss of normal protein function, predicted through either protein truncation or non-sense mediated mRNA decay. Of note, the variants were classified based on the American College of Medical Genetics (ACMG) system. Mitochondrial DNA sequence analysis and deletion testing was normal.

Despite aggressive management efforts, the patient exhibited poor feeding, failure to thrive, and persistent lactic acidosis. Per parents’ request, he was transferred to another tertiary care center that specialized in mitochondrial disorders where, unfortunately, he passed away after a week.

**Discussion**

This patient supports an association between FARS2 deficiency and EIMFS. He manifested with EIMFS pattern on EEG, as well as marked lactic acidosis, hepatic dysfunction, hypothermia, and failure to thrive. EIMFS typically presents around seven weeks of age, with a range of four days to five months whereas infantile-onset FARS2 deficiency with epileptic encephalopathy typically presents from birth to six months. Both portend a dismal outcome, with early death. FARS2 deficiency, a rare autosomal recessive disorder, has been reported in 38 individuals from 26 different families of various ethnic groups. Though multiple pathogenic gene variants have been described, to the best of our literature review our patient’s variants have yet to be reported.[3] There are two major clinical phenotypes: a later-onset, less severe spastic paraplegia and an infantile-onset, more severe phenotype of epileptic encephalopathy, characterized by refractory seizures, developmental regression, and lactic acidosis.[3]

FARS2 has also been rarely implicated as a cause of Alpers Huttenlocher Syndrome (AHS), a rare, autosomal recessive disorder typically caused by a polymerase gamma (POLG) mutation on chromosome 15q26.1 that presents with the classic triad of refractory epilepsy, liver disease, and developmental regression.[4,5] FARS2-related Alpers-like epileptic encephalopathies are rare, with seizure onset typically seen within the first three months and death typically by 24 months. One case has been reported to survive into adolescence.[3]

Our patient’s brain MRI demonstrated thinning of the corpus callosum, as seen in EIMFS, FARS2 deficiency, and AHS alike.[6,7] Moreover, he exhibited thalamic T2 signal intensities, which have also been reported in FARS2 deficiency and AHS.

The EIMFS on EEG is notable for simultaneous, random focal seizures independently involving both hemispheres. Although a characteristic ictal EEG pattern in FARS2 epileptic encephalopathy and AHS is not established, interictal findings have been previously reported to include hypsarrhythmia, multifocal spike-slow wave complexes, absent or slow posterior dominant rhythm, and rhythmic high-amplitude delta activity with superimposed spikes.[8] Only one recent case in the literature highlights an association between EIMFS and FARS2.[9]

Our patient showed both, clinical and radiologic, characteristics that correlate with FARS2 deficiency and AHS. The case supports an association between FARS2 deficiency and an EEG pattern seen in EIMFS. We suggest that clinicians consider FARS2 as a genetic etiology in infantile-onset epileptic encephalopathy with EIMFS characteristics on EEG, especially in
the setting of marked lactic acidosis and elevated transaminases.

Overall, it is important to consider that despite the rarity of not only FARS2 deficiency, but also that of EIMFS, these disorders have poor outcomes and can have genetic implications to patients’ families. Though the literature surrounding these topics is scarce, further reports of EIMFS and FARS2 alike will assist clinicians in earlier identification of these disorders and hopefully inspire further research into the treatment and management of these uncommon, yet devastating conditions.

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Conflicts of interest
There are no conflicts of interest.

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