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Early-onset epileptic encephalopathy with migrating focal seizures associated with a *FARS2* homozygous missence variant

Dorothée Ville [1], Gaetan Lesca [2], Audrey Labalme [2], Vincent des Portes [1], Alexis Arzimanoglou [3], Julitta de Bellescize [3]

[1] Pediatric neurology Department and Reference Center of rare epilepsies, Hôpital Femme Mère Enfant, University Hospitals of Lyon,
[2] Genetics Department, Hôpital Femme Mère Enfant, Lyon University Hospital, Member of the ERN EpiCARE, Lyon
[3] Paediatric Clinical Epileptology and Functional Neurology Department, Reference Center of rare epilepsies, Member of the ERN EpiCARE, University Hospitals of Lyon (HCL), Lyon, France

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ABSTRACT – Epilepsy of infancy with migrating focal seizures (EIMFS) is now a well-recognized early-onset syndrome included in the ILAE classification of the epilepsies. *KCNT1* gain-of-function variants are identified in about half of patients. In the remaining cases, the underlying genetic component is far more heterogeneous with sporadic mutations occasionally reported in *SCN1A*, *SCN2A*, *SLC12A5*, *TBC1D24*, *PLCB1*, *SLC25A22*, and *KCNQ2*.
Here, we report, for the first time, a homozygous deleterious variant in the *FARS2* gene, identified using a 115-gene panel for monogenic epilepsies, in a patient with EIMFS. This boy was the second child born to healthy consanguineous parents. The first seizures occurred at six weeks of age. The patient rapidly developed severe epilepsy with focal discharges on EEG, migrating from one brain region to another, highly suggestive of EIMFS. At five months of age, he had daily multifocal clonic seizures and erratic myoclonic fits, which were not consistently related to spikes or spike-and-wave discharges. Neurological status was severely abnormal from onset and the patient died at 10 months of age from respiratory distress. Using the gene panel, a homozygous missense variant of *FARS2* was identified, at Chr6 (GRCh37):g.5404829C>T, c.667C>T (NM_001318872.1), inherited from both parents, leading to an arginine-to-cysteine substitution, p.(Arg223Cys).
FARS2 is a member of the mitochondrial aminoacyl tRNA transferase (ARS) enzymes. ARS variants are increasingly recognized causes of early-onset epileptic and neurodevelopmental encephalopathies, however, the associated epileptic phenotype is not completely described. This case shows that FARS2-related seizures can mimic EIMFS in the early stage of the

Correspondence:
Dr Dorothée Ville
Paediatric neurology Department and Reference Center of rare epilepsies,
Hôpital Femme Mère Enfant,
59 boulevard Pinel 69500 Bron,
Lyon University Hospital, France
<dorothee.ville@chu-lyon.fr>

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disease. Furthermore, in the setting of migrating focal seizures of infancy, *FARS2* should be considered as a further candidate gene, and increased lactate level and occurrence of refractory myoclonic seizures are possible key features to suspect FARS deficiency.

Key words: epilepsy of infancy with migrating focal seizures (EIMFS), *FARS2*, aminoacyl tRNA transferase, lactate

Early-onset epileptic and neurodevelopmental encephalopathies (EOEEs) are a heterogeneous group of rare and severe diseases characterized by a wide range of seizure types, EEG abnormalities and poor neurological outcome. In 1995, Coppola and Dulac first delineated a syndrome with multifocal and focal migrating seizures as the main seizure type, becoming the hallmark of epilepsy of infancy with migrating focal seizures (EIMFS), a now well-recognized early-onset syndrome included in the ILAE classification of the epilepsies and epilepsy syndromes (Engel, 2001; Scheffer, *et al.,* 2017).

Since 2012, *KCNT1* gain-of-function variants have been identified in about half of patients fulfilling the electro-clinical criteria for EIMFS (Barcia *et al.,* 2012; Ishii *et al.,* 2013; Shimada *et al.,* 2014; Møller *et al.,* 2015; Ohba *et al.,* 2015; Lim *et al.,* 2016; Rizzo *et al.,* 2016; McTague *et al.,* 2013, 2018), suggesting that they can be considered as the core group of EIMFS. In contrast, in the remaining cases, the underlying genetic component is far more heterogeneous, with sporadic mutations occasionally reported in *SCN1A, SCN2A, SLC12A5*, *TBC1D24, PLCB1, SLC25A22,* and *KCNQ2* (Carranza *et al.,* 2011; Freilich *et al.,* 2011; Poduri *et al.,* 2012, 2013; Dhamija *et al.,* 2013; Milh *et al.,* 2013; Howell *et al.,* 2015; Stödberg *et al.,* 2015; Saitsu *et al.,* 2016; Saito *et al.,* 2017; Duan *et al.,* 2018). Here, we report, for the first time, a homozygous deleterious variant in the *FARS2* gene (identified using a 115-gene panel for monogenic epilepsies) in a patient diagnosed with EIMFS. *FARS2* encodes mitochondrial phenylalanyl tRNA synthetase, which catalyses the attachment of phenylalanine to its cognate mitochondrial tRNA, and has been recently recognized as a cause of EOEE (Cho *et al.,* 2016; Raviglione *et al.,* 2016; Walker *et al.,* 2016; Yang *et al.,* 2016; Vantroys *et al.,* 2017).

Case study

This boy was the second child born to healthy consanguineous parents of Somalian origin. He was born at term after an uneventful pregnancy, with birth weight of 2.680 kg (10-50th percentile), birth height of 46 cm (10-50th percentile), and head circumference of 34 cm (10-50th percentile).

His first seizures occurred at six weeks of age. They were first reported as right clonic fits, and then as clonic seizures of the left hand or arm. Frequency gradually increased up to multiple daily focal motor seizures. The patient rapidly developed severe epilepsy, with numerous focal, mainly clonic or tonic seizures. Initial EEG showed subnormal background activity with initially sporadic multifocal spikes (*figure 1*, *2*) increasing with age and more prominent in sleep (*figure 3*, *4*). Numerous asymptomatic ictal activities were recorded, of left or right temporal, posterior or right frontocentral origin. At two months of age, two successive ictal EEGs evidenced focal discharges, migrating from one brain region/hemisphere to another, highly suggestive of EIMFS (*figure 5*).

At five months of age, he had daily polymorphic seizures. Interictal EEG showed slow, high-amplitude background activity with multifocal spikes. Ictal EEGs revealed multifocal clonic seizures and erratic myoclonic fits, which were not consistently related to spikes or spike-and-wave discharges (*figure 6*). We did not record a pattern suggesting *epilepsia partialis continua*. Epilepsy was resistant to various drugs (vigabatrin, benzodiazepines, levetiracetam, topiramate, phenytoin, and phenobarbital), as well as the ketogenic diet and vitamins (pyridoxine, pyridoxal phosphate, and biotin).

Neurological examination was severely abnormal from onset with axial hypotonia, poor eye contact, limb hypertonia, and jerky gesticulation. Evolution was marked by severe developmental delay without any psychomotor acquisitions. The patient required enteral feeding. He died at 10 months of age from respiratory distress.

Broad aetiological screening was performed. Brain 1.5 T MRI, at 1.5 months of life, showed probable myelination delay but could not be repeated, as respiratory distress contraindicated sedation (*figure 7*). Fundus oculi was normal. Serum bicarbonate was decreased to 11-14 mmol/L, requiring supplementation, without any renal tubulopathy identified. Fasting serum lactate level increased to 3.2 mmol/L with pyruvate at 0.133 mmol/L (lactate/pyruvate=24), post prandial serum lactate level was 2.728 mmol/L with pyruvate at 0.119 mmol/L (lactate/pyruvate=23), and CSF lactate level increased to 2.420 mmol/L with pyruvate at 0.144 mmol/L (lactate/pyruvate=17). The organic acid profile in urine showed an increase in lactate level. Other metabolic screening (for serum and CSF amino acid profile, congenital disorders of glycosylation, very long chain fatty acids, and profile of neurotransmitter

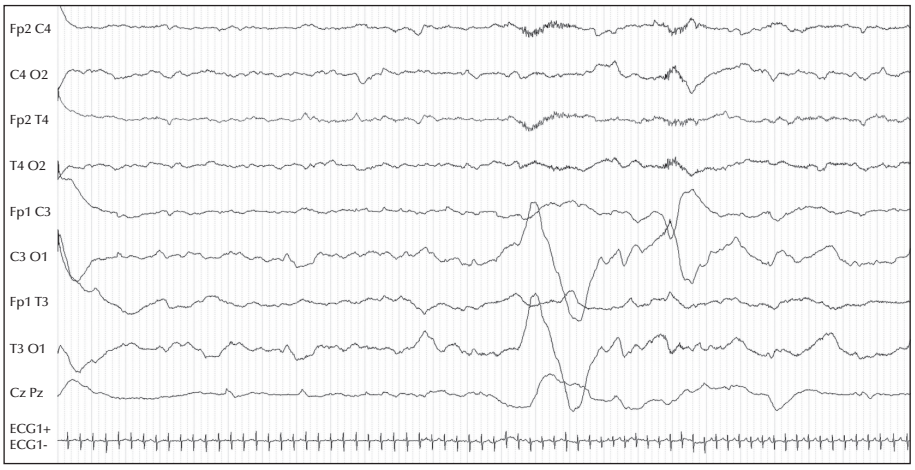

Figure 1. Awake recording at two months of life.

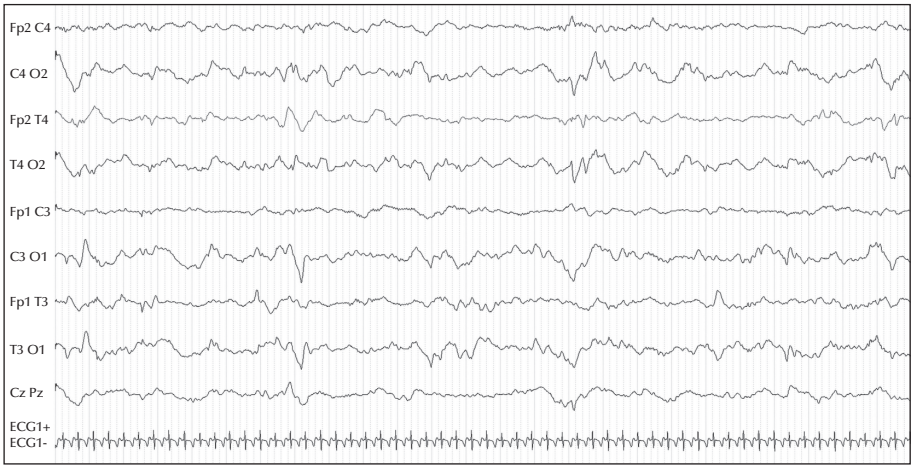

Figure 2. Asleep recording at two months of life with sporadic spikes in temporal and occipital areas.

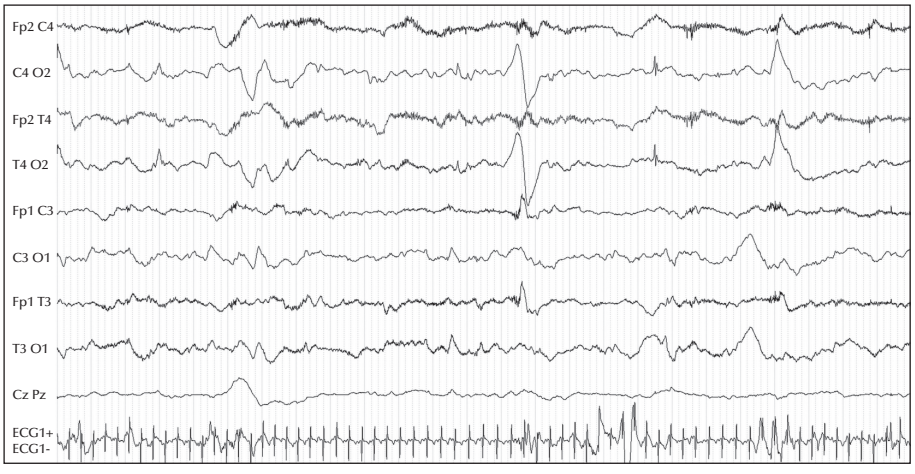

Figure 3. Awake recording at three months of life with moderate slowing of background activity and multifocal spikes.

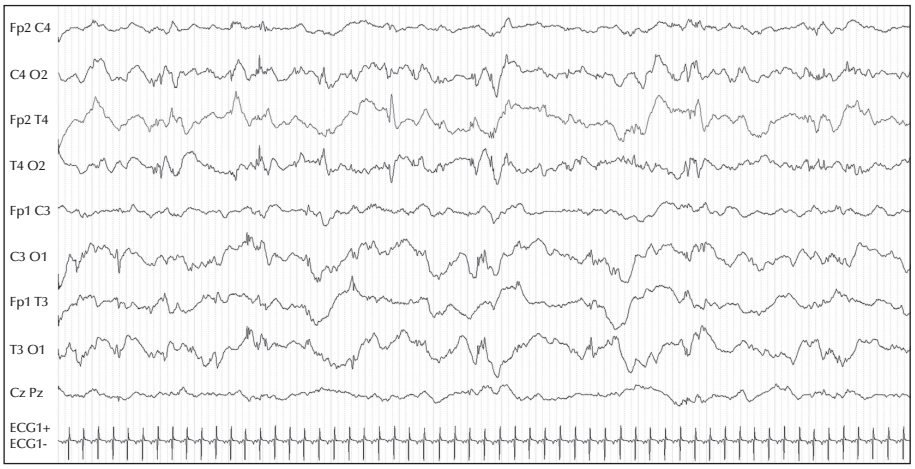

Figure 4. Asleep recording at three months of life with more abundant multifocal spikes.

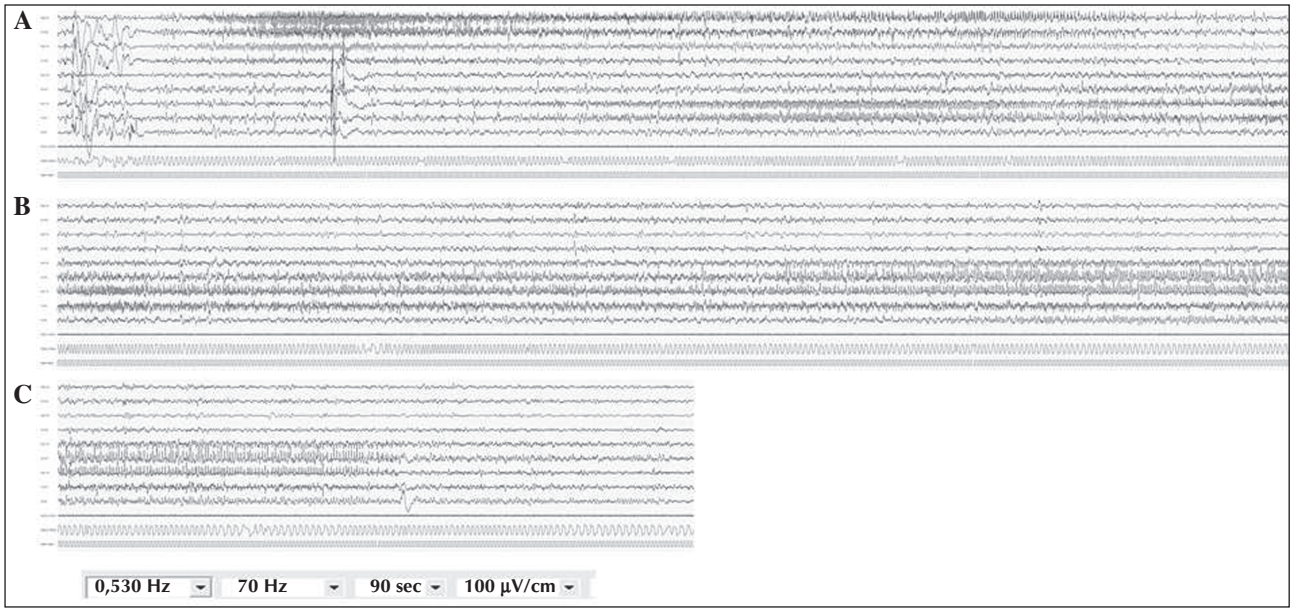

Figure 5. Pattern of migrating focal seizures at two months of age.

in CSF) was normal. There was neither renal nor hepatic involvement, nor other abnormal features.

Array-CGH was normal. Sequencing using a 115-gene panel for monogenic epilepsies (Roche, Madison, WI, USA) was performed with a NextSeq500 sequencer (Illumina, San Diego, CA, USA). A homozygous missense variant of *FARS2* was found, Chr6(GRCh37):g.5404829C>T, c.667C>T (NM_001318872.1), inherited from both parents, leading to the arginine-to-cysteine substitution, p.(Arg223Cys). *In silico* prediction tools (DIFT, Polyphen2, and Mutation Taster) were in favour of a deleterious effect. This mutation was reported in 18 control individuals from the gnomAD database, but not in the homozygous state, and has been reported twice in the ClinVar database as likely pathogenic (RCV000650594.1 and RCV000196357.2).

Discussion

This is the first report of a patient fulfilling the electroclinical criteria for EIMFS with a homozygous deleterious variant in the *FARS2* gene, based on a 115-panel of epilepsy genes. FARS2 belongs to the group of aminoacyl tRNA transferase (ARS) enzymes, responsible for aminoacylation, *i.e.* the process of attaching amino acids to their cognate tRNA, essential

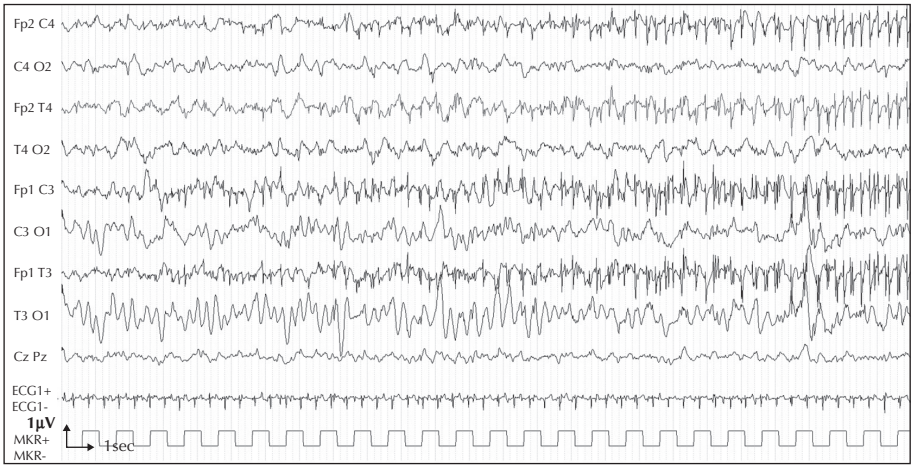

Figure 6. Status of erratic myoclonic fits at five months of age.

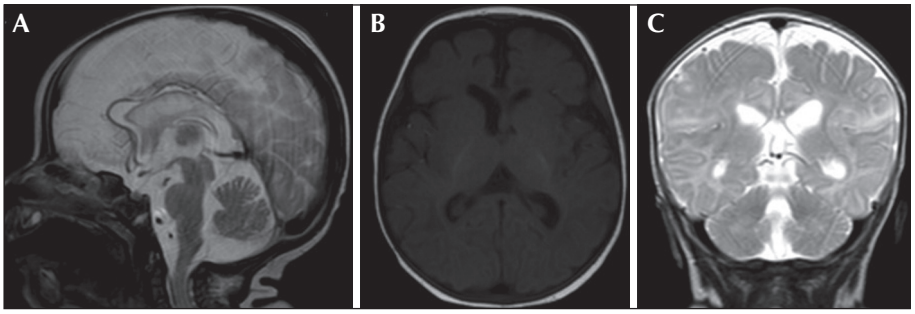

Figure 7. MRI at 1.5 month of age with myelination delay.

for the translation of RNA. Deleterious variants of different genes encoding ARS have been identified, associated with a wide range of neurological manifestations. In particular, *QARS* and *AARS* variants are recognized to be involved in early-onset epileptic encephalopathy (Zhang *et al*., 2014; Kodera *et al*., 2015; Simons *et al*., 2015; Nishri *et al*., 2016; Ngoh *et al*., 2016; Leshinsky-Silver *et al*., 2017). The phenotypes associated with variants of the respective ARS genes are not fully elucidated, and to date, only small series have been reported with *AARS*, *QARS*, and *FARS2* variants (*summarised in table 1*). Severe psychomotor delay, progressive marked cerebral atrophy and hypomyelination seem to be hallmarks of these pathologies. Severe progressive microcephaly, which is one of the main features associated with *AARS* and *QARS* variants, does not appear as a prominent trait in patients with *FARS* mutation.

To date, about 20 patients with *FARS2* pathogenic variants have been reported. Despite variable clinical presentations, almost all, including our patient, showed increased lactate levels. Only five cases were reported with muscular biopsy, revealing no abnormalities suggestive of a mitochondrial respiratory chain defect based on microscopic and histochemical examination of skeletal muscle. Nonetheless, it is now well established that pathogenic variants of *FARS* cause mitochondrial diseases; *FARS*-related mt-aaRS defects result in disturbed intramitochondrial translation and affect OXPHOS complexes containing mitochondrially-encoded subunits (complexes I, III, IV and V) (Elo *et al.,* 2012; Almalki *et al.,* 2014; Vernon *et al.,* 2015; Vantroys *et al.,* 2017).

Vantroys *et al*. defined two distinct *FARS2* phenotypes based on predominant clinical findings:

– epilepsy;

– and spastic paraplegia.

The phenotype with epilepsy is the most severe, and more than half of subjects die before the age of two years. Fifteen of the 20 cases reported in the literature presented with seizures ranging from a single episode to severe neurodevelopmental and epileptic encephalopathy. Ten were classified as early-onset epileptic encephalopathy. Seizure semiology was heterogeneous with myoclonic fits described in six cases, infantile spasms in three, and *epilepsia partialis continua* in two. Epilepsy was qualified as refractory in eight cases (Vantroys *et al.,* 2017). To our knowledge,

Table 1. Phenotypic data of patients with *AARS*, *QARS*, and *FARS2* variants.

	AARS **Nakayama *et al.* (2017) (n=5)**	***QARS*** **Leshinsky-Silver *et al.* (2017) (n=10)**	***FARS 2*** **Vantroys *et al.* (2017) (n=20)**
Epilepsy	*n*=5/5	*n*=7/10	*n*=15/20
Age at onset	2 to 5 months	Early (before one month of life)	2 days to 5 months
Characteristics of epilepsy	Various types of seizure: infantile spasms, Lennox-Gastaut, myoclonic seizures	with various types of seizure, EIMFS (2 cases)	Various types: from single seizure to EOEE (spasms, myoclonic fits, epilepsy partialis continua)
Microcephaly	Progressive microcephaly	Progressive microcephaly	Not reported
Cognitive outcome	Profound developmental delay	Severe or profound	Developmental delay most often severe with possible regression
Other neurological manifestations	Increased tone and spasticity, dystonia	No characteristic neurological manifestation reported	Spastic paraplegy
MRI	Hypomyelination, progressive white matter cerebral and cerebellar volume diminution	Cerebral and cerebellar atrophy Hypomyelination	Cortical atrophy =/- hypomyelination
Other features	No other features reported	No other features reported	Increased lactate and pyruvate level
Other phenotypes	Charcot-Marie-Tooth type 2	Less severe phenotype (3 cases) Mild or moderate deficiency Progressive microcephaly Severe growth deficiency Morphological features (midface retrusion, high, broad forehead, prominent metopic ridge, laterally sparse eyebrows, short nose, long philtrum, widely spaced abnormal teeth, long fingers, and partial cutaneous syndactyly of T2-3. No epilepsy	Progressive spastic paraplegy with no epilepsy

EOEE: early-onset epileptic encephalopathy; AARS: alanyl-tRNA synthetase; QARS: glutaminyl yRNA synthase; FARS 2: phenylalanyl-tRNA synthetase 2.

migrating focal seizures have not previously been associated with *FARS2* variants. Most of the cases in the review of Vantroys *et al*. (2017) showed progressive cerebral +/- cerebellar atrophy, but this was not assessable in our case. No other characteristic abnormal features were reported in patients with *FARS2* variants. The core features of EIMFS, formerly named "migrating partial seizures of infancy" (MPSI), are: epilepsy onset in the first semester of life, predominantly focal seizures, characteristic three-phase evolution, striking drug resistance and developmental arrest with very poor outcome, and a death rate of between 20 and 50% (Coppola *et al*., 1995; Caraballo *et al*., 2008; Coppola, 2009, 2013; McTague *et al*., 2013). In the first stage, focal seizures are sporadic. EEG shows normal background activity or diffuse slowing with focal or multifocal interictal abnormalities. After weeks to several months, the child enters the second and very distinctive stage of the disease, referred to as the "stormy phase". Frequent focal polymorphous seizures are organized in clusters. Seizure clusters occur several times a day and may form an almost continuous seizure activity over days. During this period, focal EEG discharges typically migrate, starting from one cortical area and expanding to contiguous regions, whereas others independently develop in the same or opposite hemisphere, forming a complex pattern of multifocal status epilepticus (Coppola, 2009). The ictal EEG morphology is very characteristic of the syndrome, showing prominent overlapping rhythmic theta activity, but delta-, alpha-,

or rhythmic focal spikes are also described. The third phase, occurring between one and five years of age, is a relatively seizure-free period, although intercurrent illnesses may easily trigger clusters of seizures or occasionally status epilepticus. The amplitude of ictal discharges tends to increase with age, and frontal areas are more frequently affected (Coppola *et al*., 1995). This particular seizure organization and the fact that, over time, seizures remain principally focal, distinguishes EIMFS from other entities categorised under EOEE, usually characterized by the coexistence of multiple seizure types and accordingly by more variable EEG presentation. In Coppola's historical series of EIMFS, no burst-suppression pattern was mentioned and only one patient developed epileptic spasms.

The epilepsy course in our patient could also be divided into three distinctive phases:

– Seizure onset at the age of six weeks with essentially isolated focal or multifocal seizures.

– A second phase, at the age of two months, with an extremely high frequency of multifocal seizures, evolving into a migrating pattern, highly resistant to any antiepileptic therapy.

– A third stage in which seizures frequently involved the central regions and were mostly clonic, in contrast to the reported EIMFS cases.

This third stage was particularly severe. At the age of five months, myoclonic fits appeared, without any consistent electro-clinical correlations. To the best of our knowledge, this was not reported in the classic series of Coppola *et al*. (1995) or Barcia *et al*. (2012), or in the follow-up study reported by Caraballo *et al*. (2008), but was mentioned in two patients in the series of McTague *et al*. (2013).

As the genetic basis for EIMFS becomes more apparent, a broader electro-clinical spectrum has been described, as well as cases lacking the characteristic three-stage evolution. Selioutski *et al*. (2015) reported in detail the evolution of EEG abnormalities in neonates with transient burst-suppression features in a EIMFS patient with a *KCNT1* variant and another with a *SCN2A* variant. Lee *et al*. reported an infant who first presented, at three months of life, with a pattern of migrating partial seizures that evolved into West syndrome at the age of nine months; the genetic status was not known. Recently, Duan *et al*. (2018) described a patient with a *de novo KCNQ2* deleterious variant, who presented with seizure onset at eight days of life with burst-suppression, followed by a pattern of EIMFS at one and a half months, and infantile spasms at eight months. In the case series reported by McTague *et al*. (2013), burst-suppression was mentioned in two of 14 patients, and two children experienced hysarhythmia with epileptic spams during the course of the disease. At present, EIMFS phenotype/genotype correlations are not well established despite the expansion of the genetic background associated with the disease, mainly due to the small number of patients reported. There may be a trend towards an earlier age at onset in cases with *SCN2A* gain-of-function variants, as seizures occurred within the first 10 days of life in six of the seven patients reported by Howell *et al*. (2015). All reported observations indicate seizure onset before the age of six months, a pattern of focal migrating seizures during the course of evolution, drug-resistant epilepsy, and poor neurological outcome. We agree with Lee *et al*. (2012) and McTague *et al*. (2013) who postulated that the pattern of migrating focal seizures is characteristic of the syndrome, but should not be the only hallmark of such a specific and unique disease. Rather, it would appear that the pattern of this particular electroclinical seizure reflects age-specific changes associated with an epileptic disorder with various underlying aetiologies. Lee *et al*. (2012) hypothesized that EIMFS may constitute a "continuum of infantile epileptic encephalopathy, probably sharing a common pathophysiology with maturation-related hyperexcitability". Conversely, features of EIMFS that evolve into other distinctive epileptic encephalopathies represent very rare conditions.

Conclusion

This case demonstrates that *FARS2*-related seizures can closely mimic EIMFS in the early stage of the disease, however, in the later stage, the epilepsy profile is different. FARS2 is an ARS, and ARS variants are becoming increasingly recognized causes of EOEE, however, the associated epileptic phenotype has not been fully described. This case therefore demonstrates that *FARS2* should be considered as a further candidate gene involved in EIMFS, along with the large group of genes associated with early-onset developmental and epileptic encephalopathy. Moreover, increased lactate and the occurrence of myoclonic seizures in the setting of early-onset multifocal migrating seizures should point to a *FARS*-related mitochondrial respiratory chain disorder.

In addition, this case illustrates how ongoing genetic dissection of historically well-delineated epilepsy syndromes, such as EIMFS, may modify our investigation methods (based on panel/exome sequencing). Further carefully described cases are needed to delineate phenotype-genotype correlations. A better understanding of gene variants underlying pathophysiological mechanisms will progressively lead to better genetic counselling and hopefully offer new treatment strategies. □

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