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Infantile epileptic spasms syndrome in a child with lissencephaly associated with *de novo PAFAH1B1 v*ariant and coincidental CMV infection

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ABSTRACT

Type 1 lissencephaly is a brain malformation characterized by agyria and pachygyria and is known to be caused by congenital infections and genetic variations. Here we present a case of a 4-month-old female with new onset infantile epileptic spasms syndrome (IESS) with initial etiology concerned for congenital cytomegalovirus (cCMV) due to a positive urine CMV PCR and maternal viral syndrome during pregnancy. Her brain MRI was significant for type 1 lissencephaly without other radiographical features of cCMV. The patient initially responded to high dose Prednisolone but had relapse of spasms at 9-month-old and required an ACTH course. She later developed generalized tonic seizures and focal impaired awareness seizures. Subsequent whole exome sequencing (WES) trio revealed a *de novo PAFAH1B1* (c.405G > A, p.W135*) heterozygous nonsense variant which is pathogenic and thus solved the diagnostic puzzle. This case demonstrates that the absence of cCMV stigmata should raise concern for alternative etiology in cases of lissencephaly and the importance of genetic evaluation for subsequent management and family counseling.

1. Introduction

Classic lissencephaly or type 1 lissencephaly presents with decreased or absence of gyri and thickened cortex and is on the "agyri-pachygyria-band" spectrum with subcortical band heterotopia (SBH) due to migration arrest during early fetal development [1–3]. This is also commonly associated with congenital CMV [4]. Severity of lissencephaly can be classified from 1(mild) to 3(severe) based on subtypes including the gradient and grade of gyral malformation, cortical thickness, and other brain malformations [5]. More than 90 % of patients with isolated lissencephaly have seizures in the first 2 years of life, with 80 % being infantile spasms [2]. Patients tend to have a poor prognosis due to various development delays and risk for developing status epilepticus in their life [2]. Here we present a case with new onset IESS with type 1 lissencephaly investigated for both an infectious and genetic etiology.

2. Case report

A 4-month-old female infant presented to Hasbro Children's Hospital with worsening abnormal movements that began at 3-months of age. She had also developmental delay in rolling, visual tracking and fixation. Movements were described as rhythmic with increased tone of the bilateral upper or lower extremities for 1–2 s per episode and in clusters for less than 30 s initially, later increased to 5 min. On examination, she was non-dysmorphic with a head circumference at 38.9 cm (<5th percentile) and hypotonic with significant head lag. There was no neurocutaneous stigmata except for extensive hypopigmentation over her whole body. Video EEG during admission confirmed evolving hypsarrhythmia (a BASED score of 3) and a diagnosis of infantile spasms (Fig. 1).

The mother had good prenatal care and no abnormalities were noted on her prenatal US and negative prenatal labs including HBsAg, Trep Ab, VZV Ab, Chlamydia and Gonorrhea, TB quant, and HIV and Rubella immune. Around 24–25 weeks of gestational age (GA), mother had a flu-like illness consisting of cough, rhinorrhea, wheezing, weakness, and malaise and this self-resolved in ~ 2 weeks. The infant was born full term via spontaneous vaginal delivery (SVD). She passed the newborn hearing screen and did not require neonatal ICU stay. Investigative work-up included an MRI of the brain which revealed type 1

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lissencephaly (Fig. 2). Her urine CMV qPCR was positive at 1,200 IU/mL (assay range 475——1.88E + 8 IU/ml, *Eurofins Viracor*), raising concern for congenital versus perinatal acquired CMV infection. However, there was no intracranial calcification appreciated on the brain MRI to suggest a symptomatic cCMV infection (Fig. 2). Her ophthalmologic evaluation revealed no findings of chorioretinitis.

The infant received two doses of 100 mg Pyridoxine intravenously, 10 min apart, without electrographic or clinical improvement. She was started on Topiramate and then high-dose Prednisolone course following the UKISS protocol [6]. Infectious disease (ID) was consulted regarding the positive urine CMV qPCR. Due to risk for disseminated CMV in the setting of immunosuppression, the infant was treated with oral Valganciclovir for prophylactic therapy during the duration of steroid course.

Parents reported significant reduction in spasms with the last episode occurring 2 days following hospital discharge. A follow-up video EEG around 2 weeks after discharge also showed significant improvement with a BASED score of 1. She was enrolled in early intervention with slow improvement of motor skills and receptive language but continued to have poor tracking without signs of regression.

The infant had a relapse of spasms at 9-month age and was admitted to initiate ACTH treatment. At this admission, serum CMV viral load was below the detection range (96 IU/mL to 1.88E + 08 IU/mL). ID team recommended against anti-CMV treatment but weekly monitoring for serum CMV viral load while on ACTH therapy. Epileptic spasms resolved soon after ACTH was initiated. At 16-months of age, the child was re-admitted due to a prolonged focal seizure and Levetiracetam was added. Given irritability and moodiness despite Pyridoxine supplementation, Levetiracetam was subsequently tapered off with improved calmness and alertness. More recently, the child had drastic seizure

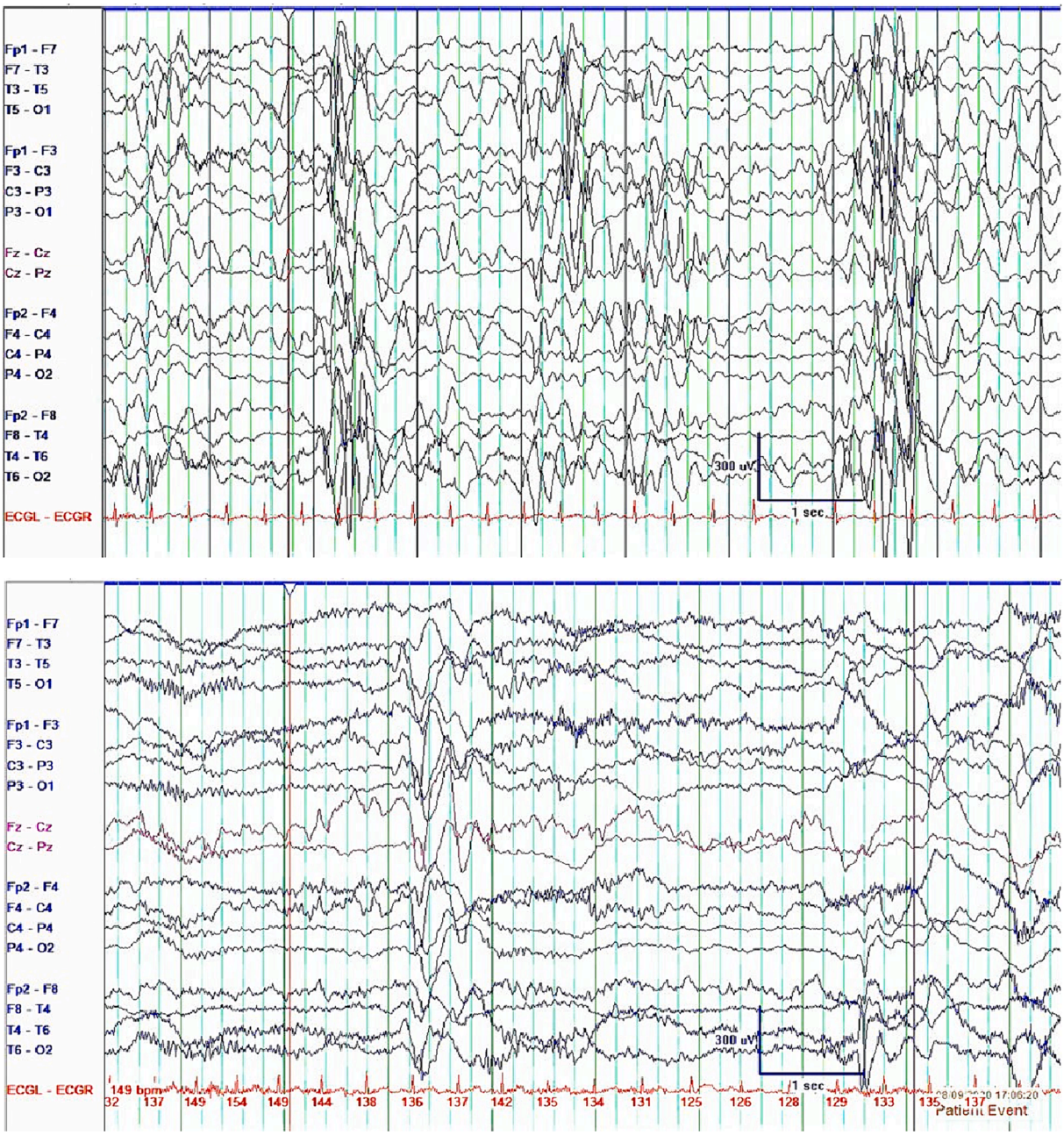

Fig. 1. EEG during initial admission at 4-month of age showing interictal epileptiform abnormalities (top) and ictal electro-decrement correlated with epileptic spasms (bottom).

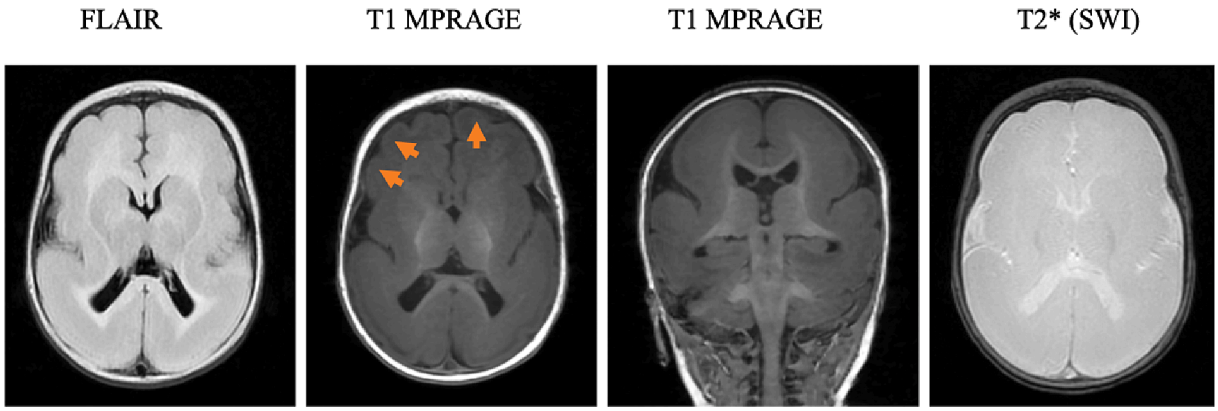

Fig. 2. Initial brain MRI without contrast showing diffuse lissencephaly with scattered shallow gyri predominately in the frontal region (denoted by arrows). Note the normal ventricular sizing on the T1 sequence and lack of intracranial calcifications on the SWI sequence.

reduction on a regimen of clobazam, oxcarbazepine, and vigabatrin, most notably after the addition of vigabatrin at 3 years of age. The child needed a gastrostomy tube placement at 3-year 2-month-old. A follow-up EEG at age of 3-year and 3-month captured only one tonic seizure during a 6-hour recording and still showed abundant generalized versus bilateral periodic epileptiform discharges (Fig. 3). Ketogenic diet was discussed but was deferred by parents' choice. Vigabatrin was titrated up to 76 mg/kg/day.

The child underwent comprehensive metabolic and genetic evaluation. Serum metabolic studies, plasma pipecolic acid and urine alpha-aminoadipic semialdehyde returned negative. Chromosomal microarray was normal. Brain malformation panel was denied by insurance. Subsequent whole exome sequencing (WES) trio including mitochondrial genome revealed a *de novo* pathogenic variant c.405G > A (p. W135*) in *PAFAH1B1*gene as both parents tested negative for this variant. A variant of unknown significance (VUS) was identified in the mitochondrial gene *MT-CYB* m.15299 T > A (p.L185M). Therefore, a genetic diagnosis was established at 17-month of age, which explained the developmental and epileptic encephalopathy (DEE) as well as her brain malformation. Subsequently, the parents had another child born healthy.

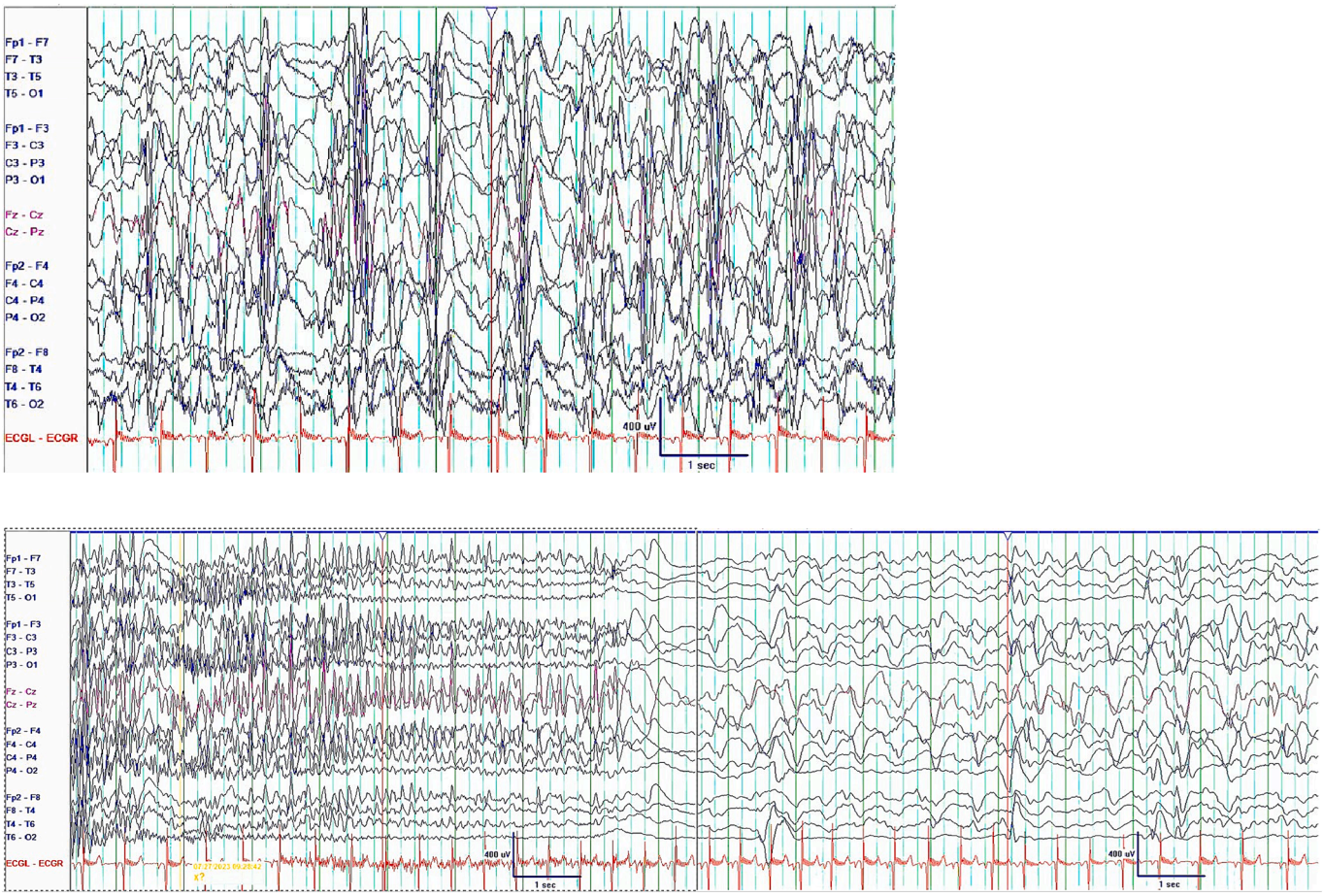

Fig. 3. The most recent 6-hour video EEG at age of 3-year and 3-month revealing interictal high amplitude slow spike-wave epileptiform discharges (top) and one electro-clinical tonic seizure (bottom).

3. Literature review

3.1. Congenital cytomegalovirus (cCMV) infection

CMV is a neurotropic virus and continues to be a major cause for neurodevelopmental impairment through infection and inflammatory infiltration of the fetal brain [7]. Approximately 1 % of all newborns from developed countries are still affected by CMV. Early infection can lead to damage of the germinal matrix causing neuronal tissue loss [8]. Affected neonates can have a range of anomalies including microcephaly, sensorineural hearing loss, hepatomegaly and/or splenomegaly, chorioretinitis, petechiae, and/or thrombocytopenia [8–10]. Infants can also have asymptomatic congenital infection at birth and still be at risk for neurodevelopmental sequelae later in life [11].

Classically, MRI findings such as periventricular/basal ganglia calcifications, periventricular cysts or pseudocysts in occipital horns, cerebellar hypoplasia or dysplasia should warrant further investigation for cCMV. Ventriculomegaly can also be present in mild to moderate forms with 10–15 mm of ventricle enlargement but can have severe cases of $>$ 15 mm [7,10]. Lesions found in the polar temporal regions as well as white matter abnormalities have also been detected in cCMV associated MRIs, though the latter may be more difficult to detect during the first year of life due to incomplete myelination [8]. Pachygyria-lissencephaly and polymicrogyria can both be seen in early injury due to cell loss and abnormal migration [8,10]. Children with symptomatic and asymptomatic cCMV can develop epilepsy later with various seizure types including IESS, focal seizures, and generalized tonic-clonic seizures [12].

3.2. PAFAH1B1 haploinsufficiency syndrome

IESS, or formerly West Syndrome, is associated with *ARX, CDK5, PAFAH1B1 (also known as LIS1), DCX, TUBA1A, DYNC1H, RELN,* and *14–3-3-ε* gene mutations with many of them also as causes for type 1 lissencephaly [3]. Chromosome 17p13.3 contains a high amount of low-copy repeats, making it a common area for deletions and duplications. Genes located in this area including *CRK*, *PAFAH1B1*, and *YWHAE* are involved in neuronal migration causing neurodevelopmental diseases [13]. Large contiguous deletions of 17p13.3 can cause Miller-Dieker Syndrome, characterized by agyria and facial dysmorphisms [1,13,14]. Isolated lissencephaly sequence (ILS) in contrast is commonly associated with an intragenic variation or deletion of *PAFAH1B1* and does not present with craniofacial deformities [13].

Platelet-activating factor acetyl hydrolase IB subunit alpha (*PAFAH1B1)*, plays an important role in neuronal migration through the regulation of mitosis, microtubules, and dynein-mediated motility as well as cell proliferation during neurodevelopment [13,15]. Critical impairment of neuronal migration during 10–14 weeks of gestation causes defective cortical laying and gyri formation [1,16]. Mouse models with heterozygous deletion have been shown to cause lissencephaly as well as GABAergic neuronal loss [15]. *PAFAH1B1*-related lissencephaly can be distinguished phenotypically for its more severe involvement of the posterior brain regions as opposed to other genetic variations such as *DCX* mutation on Xq23 which has an anterior greater than posterior gradient [13,14].

PAFAH1B1-related lissencephaly patients can present with an array of neurological clinical features including axial hypotonia, poor visual tracking, motor delay, opisthotonos, spastic quadriparesis [2,17]. Seizure onset often occurs within 6 months of age commonly as IESS [18,19]. *PAHFAH1B1*-related IESS may not show the classic hypsarrhythmia pattern on EEG and instead have characteristic high-amplitude fast rhythms [2,19]. Seizures are also frequently refractory to antiepileptic drugs despite initial response to ACTH or vigabatrin [2,17,18]. However, children can also develop various seizure types including focal onset with impaired awareness, generalized tonic clonic seizures, tonic seizures, and myoclonic seizures; and often require polytherapy with lamotrigine and/or valproic acid [18,19]. However, most patients develop refractory epilepsy with daily seizures with risk for feeding problems, developmental delay, respiratory infections, and status epilepticus leading to high mortality rates [19]. The pathogenic variant of *PAFAH1B1* is often *de novo* in setting of intragenic variant with rare familial cases of autosomal dominant pattern of inheritance [20]. If suspected, this can be diagnosed by molecular genetic testing starting with chromosomal microarray analysis to additional testing with gene-targeting testing and comprehensive genomic testing [2].

4. Discussion

Our patient initially presented with IESS, onset at 3 months of age, confirmed on EEG at 4 months of age (Fig. 1), and was found to be CMV positive on urine qPCR. The mother had a flu-like illness around 24–25 weeks GA, raising a concern for cCMV infection. While the features of developmental delay, IESS, and type 1 lissencephaly could be the sequelae of cCMV, this child did not have other radiographical features of cCMV such as intracranial calcifications or periventricular cysts. There was also absence of extra-CNS anomalies often associated with cCMV infection, such as chorioretinitis or sensorineural hearing loss (SNHL). It was found previously that the median CMV load in postnatally infected infants was significantly lower than in congenitally infected infants (1.0×10^5 copies/ml versus 8.5×10^6 copies/ml, respectively) [21]. Our patient had a relatively low urine CMV titer of 1,200 IU/mL (or 636 copies/mL), suggesting that a postnatal, rather than cCMV infection was more likely. This uncertainty prompted further metabolic and genetic work-up. WES trio revealed a *de novo* heterozygous pathogenic variant in *PAFAH1B1* (c.405G $>$ A, p.W135*). Retrospectively, her neurological presentation was fitting for *PAFAH1B1*-related lissencephaly with her lack of facial dysmorphisms, the presence of developmental delay and poor visual tracking, early onset of refractory IESS, and later focal and tonic seizures (Fig. 3). Her MRI finding of lissencephaly also showed a posterior-anterior gradient due to scattered shallow gyri appreciable in the frontal region (Fig. 2), in line with *PAFAH1B1* mutation. The discrepancy between her initially presumed diagnosis of cCMV and the absence of other radiographical and systemic anomalies raised the question of alternative etiology. Overall, the identification of a genetic etiology allowed for better guidance for her multidisciplinary treatment plan and further parental counseling.

5. Summary

Taken together, the definitive diagnosis is genetic in our case, rather than cCMV infection, specifically due to a *de novo PAFAH1B1* variant. Our case has illustrated that WES has enabled a corrected diagnosis when clinical/imaging diagnosis is less certain.

Ethical statement

We have consulted Lifespan IRB (Institutional Review Boards) and were told ‘an anecdotal report on a series of patients seen in one’s own practice and a comparison of these patients to existing reports in the literature would not require IRB approval’.

Declaration of generative AI in scientific writing

The authors did not use generative artificial intelligence (AI) in preparation of this manuscript.

CRediT authorship contribution statement

Nga Ying Eng: Writing – original draft, Validation, Methodology, Investigation, Data curation. **Duyu A. Nie:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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