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Case Report

Progressive cavitating leukoencephalopathy associated with a homozygous *POLG* mutation of 264C>G (p.F88L)

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ABSTRACT

Progressive cavitating leukoencephalopathy is a childhood neurodegenerative syndrome characterized by brain MR imaging findings of patchy leukoencephalopathy with cavities and vascular permeability, initially affecting the corpus callosum and centrum semiovale, and eventually coalescing into large cystic regions of white matter. We report a case of progressive cavitating leukoencephalopathy in a 2-year-old female patient presenting as intermittent motor deficits which partially resolved over several months. Whole exome sequencing revealed a homozygous c.264C>G (p.F88L) *POLG* variant of uncertain pathogenicity which was potentially related to this presentation. Further testing and information are needed to prove the pathogenicity of this variant, but considering other studies which report similar genotypes in association with differing phenotypes, the current case report supports a possible pathogenicity. This case could therefore represent the first reported instance of progressive cavitating leukoencephalopathy in the presence of a *POLG* mutation.

Introduction

Leukoencephalopathy with cystic degeneration is a distinct brain magnetic resonance (MR) imaging pattern that is indicative of specific disorders including Alexander disease, vanishing white matter disease, neonatal cerebral energy depletion, infection, and mitochondrial dysfunction [1]. Isolated and well-delineated cysts, particularly suggestive of mitochondrial defects [1], are a characteristic finding in the recently described childhood neurodegenerative syndrome referred to as progressive cavitating leukoencephalopathy (PCL) [2]. PCL is characterized by brain MR imaging demonstrating patchy leukoencephalopathy with cavities and vascular permeability, indicated by varying degrees of contrast enhancement, initially involving the corpus callosum and centrum semiovale, and eventually coalescing into large cystic regions of white matter [2]. The genetic basis of PCL is presently uncharacterized; however, current data suggests an autosomal

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recessive inheritance pattern resulting in mitochondrial defects [2–4].

Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are rare autosomal recessive disorders characterized by a reduced number of mtDNA copies within affected tissues. This depletion of mtDNA results in insufficient synthesis of mitochondrial respiratory chain components, leading to impaired energy production and organ dysfunction [5]. The maintenance of mtDNA is sustained through the interaction of both mtDNA and nuclear DNA genomes; nuclear genes implicated in the pathogenesis of MDS are involved in mitochondrial nucleotide synthesis or mtDNA replication [6,7]. One nuclear gene required for mtDNA replication is *POLG*, which encodes the catalytic subunit of DNA polymerase gamma. *POLG*-related disorders comprise a continuum of diverse syndromes, which onset from infancy to adulthood, presenting with varying degrees of encephalopathy, epilepsy, hepatic impairment, developmental delay, lactic acidosis, myopathy, ataxia, sensorineural hearing loss, and ophthalmoplegia [8,9].

Case report

We report a case of cavitating leukoencephalopathy in a 2-year-old girl carrying a homozygous c.264C>G (p.F88L) mutation in *POLG*. She was born at 38 gestational weeks via normal spontaneous vaginal delivery to a 37-year-old Hispanic G4P2012 with no prenatal, intrapartum, or postnatal complications. She is the third of 3 children and her 2 older brothers are healthy with no medical conditions. The rest of her family history is unremarkable as well. Her parents deny consanguinity, although considering both of them hail from the same small town, this is still a possibility. This patient, prior to presentation, had a history of delay in multiple developmental domains, for which she was receiving physical, occupational, and speech therapy in preschool.

The patient presented at 2 years and 4 months of age with a 4-week history of progressive right upper extremity weakness, associated with decrements in usage, and significant left-handed preference. She then progressed to develop right lower extremity weakness as well over the following weeks. Neurologic examination at this time demonstrated moderate dysarthria, right-sided hemiparesis, left hemifacial droop, hyper-reflexia of the bilateral lower extremities, and Babinski sign on the left. She was prescribed mitochondrial supplements and referred to genetic counseling, gastroenterology, otolaryngology, ophthalmology, cardiology, and audiology, along with physical, speech, and occupational therapy. Throughout her extensive work-up following this admission, the patient's motor function fluctuated. She regained use of her right hand about 2 weeks postdischarge, but then developed progressive deficits in left-sided function, losing use of her left hand and becoming unable to walk without assistance. About 7 months after initial presentation, her symptoms started to improve. Over the course of a month, she regained the ability to walk and use both her hands, although with less coordination than before. Her dysarthria also resolved, and her speech and language skills far exceeded those prior to presentation. She did not experience pain, seizures, or deficits in vision or hearing during this period. Her parents did not recall an illness prior to presentation, and although she experienced some febrile illnesses since, these were not associated with further regression. No neurologic deficits were recorded during her last healthcare encounter at 3 years and 7 months of age. Although the lack of detail provided raises concerns about the thoroughness of this record, the absence of easily visualized major neurological deficits at this time is likely a valid assumption.

Labs at presentation included an elevated lactic acid (2.4 mmol/L), normal ammonia, and increased pyruvic acid (0.17 mmol/L). Serum amino acids, urine organic acids, and carnitine profile were normal. The alkaline phosphatase (3.64 μkat/L) was also elevated, although the remainder of her liver function tests were within normal limits. Initial head computed tomography scan demonstrated bilaterally decreased density in the periventricular white matter of the frontal and parietal lobes. This prompted further neuroimaging with brain MR imaging (Fig. 1), which showed diffuse bilateral white matter signal changes with central cystic degeneration and peripheral diffusion restriction, but no abnormal contrast enhancement. MR imaging of the spine was also obtained and found to be unremarkable. EEG was not performed due to lack of seizure activity and high suspicion for mitochondrial disorder. MR spectroscopy (Fig. 2) at 5 months after initial presentation revealed mildly increased choline (Cho) peak, increased Cho/creatine(Cr) ratio, as well as reduced N-acetylaspartate (NAA)/Cr; however, no obvious large lactate peak was identified. This repeat brain MR imaging also showed an interval increase in the extent of white matter abnormality, but, notably, this was prior to clinical improvement.

Comprehensive mtDNA analysis did not reveal a large deletion, but did show a homoplasmic variant of unknown significance, m.1002C>T (12S rRNA). Whole exome sequencing (WES) disclosed a heterozygous c.1468+2T>C pathogenic variant in the *PCK2* gene, for which her mother was also heterozygous and her father negative. However, no clinically significant microdeletions or microduplications were identified on further investigation with a single nucleotide polymorphism microarray. WES also revealed a homozygous c.264C>G (p.F88L) variant in *POLG* gene of uncertain significance, with both her parents heterozygous for this variant as well.

Discussion

The patient's progressive and evolving symptoms, with a prior history of developmental delay, are suggestive of a metabolic condition rather than an acute process such as infection. The elevated lactic and pyruvic acid, with an otherwise unremarkable metabolic panel, are highly suggestive of either mitochondrial dysfunction or pyruvate dehydrogenase deficiency [10]. The more probable etiology of her presentation is further elucidated by the abnormalities detected on WES and finding of bilateral cavitating leukoencephalopathy on neuroimaging [3,11], which both strongly support mitochondrial dysfunction to be the cause of her disease.

We believe the *POLG* variant is the most probable pathogenic basis as opposed to the other abnormalities

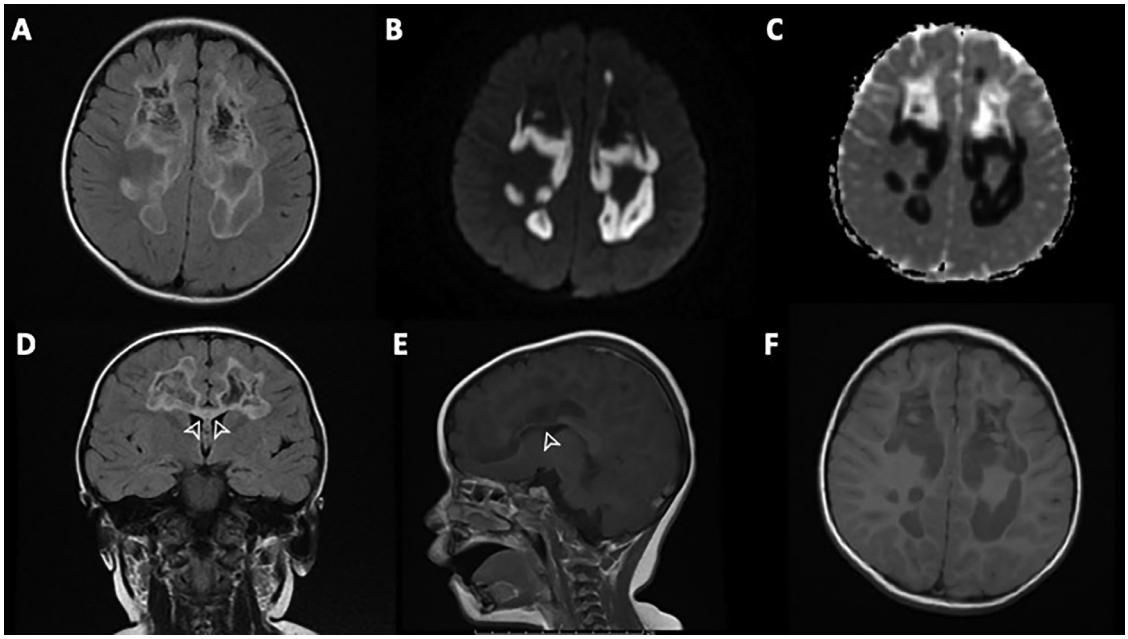

Fig. 1 – Brian MR images at 2 years and 4 months of age. A and D, Axial fluid-attenuated inversion recovery (FLAIR) image (A) and coronal FLAIR image (D) demonstrates a bilateral leukoencephalopathy with central cavitation and hyperintense rim involving the centrum semiovale and anterior corpus callosum (arrowheads). B and C, Axial diffusion-weight image (B) and apparent diffusion coefficient map (C) shows restricted diffusion in the peripheral portion of the affected white matter with increased diffusivity in the cavitations. E, Sagittal T1-weighted image shows involvement of the anterior corpus callosum (arrowhead). F, Axial T1-weighted image demonstrates sparing of the subcortical white matter (U-fibers). No abnormal enhancement was visualized on postcontrast images.

detected on WES. The heterozygous *PCK2* gene variant is associated with an autosomal recessive phosphoenolpyruvate carboxykinase (PEPCK) deficiency [12], but this is an improbable cause of the patient's symptomology due to several considerations. This patient's mother had the same heterozygous variant with no symptoms, there is no patient history of hypoglycemia or liver dysfunction consistent with PEPCK deficiency [13], and single nucleotide polymorphism microarray was negative for a microdeletion or microduplication which could have resulted in a uniparental disomy. The patient's homoplasmic mtDNA variant is reported as a polymorphism occurring at a rate of 2703:1 [14,15], and this in conjunction with her mother not exhibiting symptoms suggests that this variant is also unlikely to be pathogenic. Excluding these other 2 variants as the etiology of the patient's disorder alludes to her *POLG* variant as a possible cause. However, we caution that the pathogenicity of the c.264C>G (p.F88L) *POLG* gene variant is uncertain [16].

In-silico analyses predicting the effect of this variant on protein function are conflicting, with PROVEAN classifying it as "deleterious"[17], PolyPhen-2 hypothesizing it to be "benign" [18], and MutationAssessor projecting a "medium" functional impact [19]. Additionally, the amino acid substitution secondary to this missense mutation is conservative and therefore unlikely to affect secondary protein structure. There are also a limited number of reported cases of this variant in the literature, and for these reasons this *POLG* variant could be benign. However, the evidence that is present so far supports a possible autosomal recessive pathogenicity.

The frequency of this allele in the Latino population is estimated at 0.02% (8/35388), which is significantly higher than its frequency in the general population of 0.003%, coinciding with the Hispanic heritage of the patient in the current case report [20]. Thorough review of the literature revealed that the c.264C>G (p.F88L) *POLG* variant was previously recorded 4 times in association with mitochondrial dysfunction and once as an unclassified variant [21–23]. Tang et al. reported on a 42-year-old patient carrying both the c.264C>G (p.F88L) *POLG* gene variant and the known pathogenic mutation c.1399G>A (p.A467T) [21]. This patient was found to have a definitive molecular diagnosis of mtDNA depletion, but no clinical information was provided [21]. Interestingly, this patient might be the same one as in a case presented by Satayaprasert and Lou, who described a 41-year-old female patient carrying the exact same *POLG* gene variants [24]. The patient in this study presented with sensory ataxic neuropathy, dysarthria, and ophthalmoparesis syndrome, one of several disorders related to *POLG* gene mutations. Two more instances of the c.264C>G (p.F88L) *POLG* variant in association with *POLG*-related mitochondrial disease were reported by Masingue et al. [8] One of these patients, who also carried a pathogenic c.2243G>C (p.W748S) *POLG* variant [21], presented with myoclonic epilepsy myopathy sensory ataxia. The other patient, who was also affected by a c.856_856-4 deletion, presented with mitochondrial recessive ataxia syndrome.

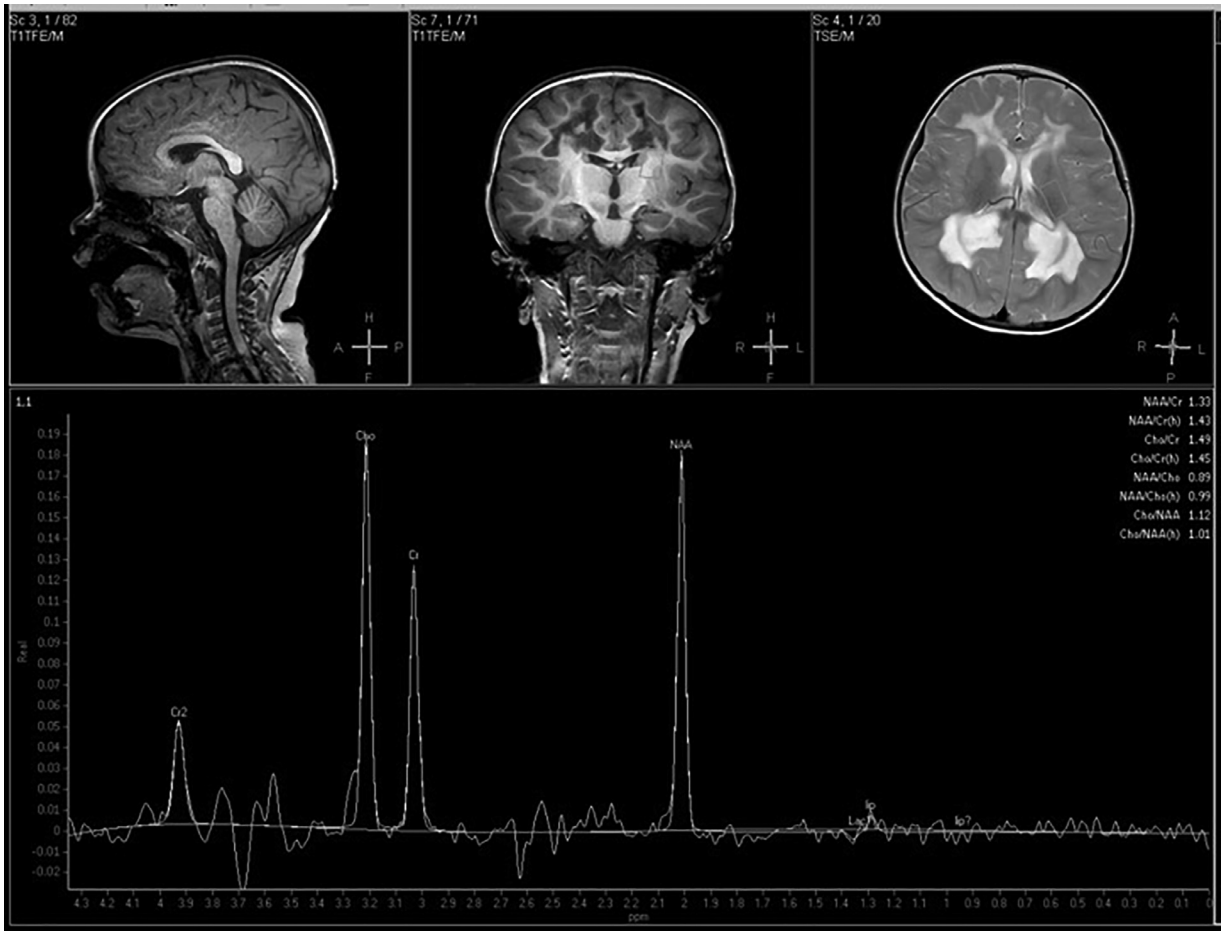

Fig. 2 – Proton MR spectroscopy. Single- and multivoxel examination over supratentorial signal abnormality demonstrates mildly increased Cho peak, increased Cho/Cr ratio, and reduced NAA/Cr ratio. There is no obvious large lactate peak.

These multiple findings of the c.264C>G (p.F88L) variant acting as an autosomal recessive pathogenic mutation lend credence to attributing this patient's disease to her *POLG* variant, the precedent for which is established in the literature [23]. And although each instance of the variant was associated with a distinct presentation, there are no apparent direct correlations linking genotype to phenotype for *POLG* mutations; one *POLG* mutation can lead to a marked array of differing diseases [9]. This variability in presentation is speculated to be related to genetic modifiers in nuclear DNA and mtDNA, immune dysfunction, viral infection, mitochondrial toxins, or accumulation of mtDNA mutations secondary to polymerase dysfunction [8]. This current case could therefore represent yet another unique phenotypic presentation of 1 particular *POLG* variant, but it should be re-emphasized that there is still ongoing uncertainty about the pathogenicity of the c.264C>G (p.F88L) *POLG* variant.

Nonetheless, this patient's findings on neuroimaging are not consistent with other *POLG*-related disorders in the literature [8]. There are no published articles with cavitating leukoencephalopathy involving *POLG* mutations, although this imaging pattern has been reported in association with other nuclear gene and mtDNA mutations [3,11,25]. With this context, we believe that this patient's *POLG* mutations rather precipitated another condition of mitochondrial dysfunction, PCL. The patient's rapid onset of motor symptoms and eventual partial resolution could herald the episodic course of neurologic deterioration characteristic to PCL [2]. Furthermore, although no abnormal contrast enhancement was demonstrated, the brain MR imaging findings of irregular diffuse white matter abnormalities with cystic degeneration, affecting the centrum semiovale and corpus callosum, are strongly consistent with those described in PCL [2]. MR spectroscopy demonstrated decreased levels of NAA, but an obvious lactate peak was not seen (this was present in 9 out of 10 cases previously reported) [2]; however, this patient did have an elevated serum lactic acid. The molecular basis of PCL has so far not been characterized, but considering that the current literature strongly suggests a contribution of mitochondrial dysfunction [2,3,11], it is certainly possible that this patient's mutation in *POLG* could have precipitated her disorder. And although we cannot definitively confirm mitochondrial dysfunction with her *POLG* variant, this specific mutation was previously reported as most likely to be deleterious leading to MDS [21]. We believe this is the first published case of PCL in the presence of a *POLG* mutation, specifically the c.264C>G (p.F88L) variant.

The differential diagnosis of episodic neurologic deterioration with cystic changes on MR imaging should also include the neurodegenerative diseases Leigh syndrome, also referred to as subacute necrotizing encephalopathy [26]. However, Leigh syndrome findings on neuroimaging typically involve the basal ganglia and brainstem, and so this patient's case might be classified as a "Leigh-like syndrome" due to atypical imaging [27]. Ultimately, the neuroimaging findings are much more consistent with PCL, although there could be some overlap between these conditions.

Another important consideration in the differential diagnosis of mitochondrial dysfunction associated with *POLG* mutation is Alpers-Huttenlocher syndrome [6]. This early-onset encephalopathy can present with hypotonia as well, but the episodic nature of this patient's symptoms and lack of seizures or evidence of significant liver dysfunction are otherwise inconsistent with this diagnosis [6]. Additionally, the neuroimaging in Alpers-Huttenlocher syndrome typically demonstrates cerebral atrophy and hypomyelination [1,28], rather than a cavitating leukoencephalopathy.

The clinical stability and partial resolution present in the current case is consistent with some previous reports of PCL [2], although the mechanism attributable to this evolving disease severity is yet undetermined. We speculate that exacerbations of PCL, similar to those of Leigh syndrome [29], could be secondary to increased stress and demand for which dysfunctional mitochondria are unable to compensate. Previously reported cases of PCL were treated with morphine for pain control, steroids, intravenous immunoglobulin, dichloroacetate, mitochondrial cocktail, or acyclovir [2]; however, there are no current studies on efficacy of treatment options. The patient in the current case received a mitochondrial cocktail containing pediatric doses of Coenzyme Q10, alpha lipoic acid, vitamin B complex, and folinic acid. Although her symptoms did improve following treatment, one should not necessarily assume a correlation. Unfortunately, the clinical progression described in prior reports of PCL is typified by periods of stability or remission followed by progressive deterioration [2], and thus this patient's long-term prognosis is poor.

Limitations of this report, which restrict the certainty of pathogenicity of the p.F88L *POLG* variant, include the following unavailable patient information: mtDNA copy number, electromyogram, muscle biopsy, mitochondrial activity, and mutant protein enzyme activity. Brain MRI following the patient's clinical improvement was also unavailable.

Conclusion

To conclude, intermittent neurodegenerative changes with brain MR imaging evidence of white matter abnormalities with cystic changes indicates a short list of potential diagnoses including PCL and other mitochondrial disorders. This clinical presentation should prompt further work-up with MR spectroscopy and genetic analysis. Further research is needed in order to investigate the role of nuclear gene and mtDNA mutations in relation to the underlying cause of this disorder.

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