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.

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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 de-
defects [2–4].

Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are rare autosomal recessive disorders characterized by a re-
duced number of mtDNA copies within affected tissues. This
depletion of mtDNA results in insufficient synthesis of mito-
chondrial respiratory chain components, leading to impaired
energy production and organ dysfunction [5]. The mainte-
nance of mtDNA is sustained through the interaction of
both mtDNA and nuclear DNA genomes; nuclear genes im-
plicated in the pathogenesis of MDS are involved in mito-
chondrial 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 syn-
dromes, which onset from infancy to adulthood, present-
ing 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 leukencephalopathy in a 2-
year-old girl carrying a homozygous c.264C>−G (p.F88L) muta-
tion in POLG. She was born at 38 gestational weeks via nor-
mal spontaneous vaginal delivery to a 37-year-old Hispanic
G4P2012 with no prenatal, intrapartum, or postnatal compi-
lations. She is the third of 3 children and her 2 older brothers
are healthy with no medical conditions. The rest of her fam-
ily history is unremarkable as well. Her parents deny consan-
guinity, although considering both of them hail from the same
small town, this is still a possibility. This patient, prior to pre-
sentation, 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 weak-
ness, 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 moder-
ate dysarthria, right-sided hemiparesis, left hemifacial droop,
hyper-reflexia of the bilateral lower extremities, and Babins-
iki sign on the left. She was prescribed mitochondrial sup-
plements and referred to genetic counseling, gastroenterol-
ogy, otolaryngology, ophthalmology, cardiology, and audiolo-
gy, 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 devel-
oped progressive deficits in left-sided function, losing use of
her left hand and becoming unable to walk without assis-
tance. About 7 months after initial presentation, her symp-
toms started to improve. Over the course of a month, she re-
gained the ability to walk and use both her hands, although
with less coordination than before. Her dysarthria also re-
solved, 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 as-
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 car-
nitine 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 com-
puted 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 en-
hancement. 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 disor-
der. MR spectroscopy (Fig. 2) at 5 months after initial presen-
tation 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 identi-
fied. This repeat brain MR imaging also showed an interval in-
crease in the extent of white matter abnormality, but, notably,
this was prior to clinical improvement.

Comprehensive mtDNA analysis did not reveal a large dele-
tion, but did show a homoplasmic variant of unknown signi-
ificance, m.1002C>T (12S rRNA). Whole exome sequencing
(WES) disclosed a heterozygous c.1468+2T>C pathogenic vari-
ant in the PCK2 gene, for which her mother was also heterozy-
gous and her father negative. However, no clinically significant
microdeletions or microduplications were identified on fur-
ther investigation with a single nucleotide polymorphism mi-
croarray. 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 unremark-
able metabolic panel, are highly suggestive of either mito-
chondrial 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 leukencephalopathy 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
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 ophthalmparesis 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.
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 lactic acid 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, electronomyogram, muscle biopsy, mitochondrial activity, and mutant protein enzyme activity. Brain MRI following the patient’s clinical improvement was also unavailable.

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