Is It ADEM, POLG, or Both?

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Objective: To describe a child with apparent brain biopsy–confirmed acute disseminated encephalomyelitis (ADEM) but genetic confirmation of compound heterozygosity for DNA mutations of the polymerase γ (POLG) gene.

Design: Case report.

Setting: Tertiary referral center.

Patient: A 4-year-old boy presented with ataxia and encephalopathy.

Results: Magnetic resonance imaging demonstrated multiple focal areas of T2 prolongation. The patient’s family refused steroid treatment. His symptoms improved then progressed. Magnetic resonance imaging findings also progressed. A cerebrospinal fluid specimen revealed myelin basic protein and oligoclonal bands. A brain biopsy specimen demonstrated demyelination, suggesting progression of ADEM. However, polymerase chain reaction amplification and sequencing revealed 2 heterozygous mutations of the POLG gene, suggesting mitochondrial disease. The patient died 9 months after his initial presentation.

Conclusions: This case raises interesting questions about whether ADEM triggered severe neurologic degeneration in a patient with mitochondrial disease, whether mitochondrial disease predisposed to a pathologic immune response, or whether mitochondrial disease can mimic an autoimmune disease. Mitochondrial disease–causing mutations may help explain the poor outcome in some cases of apparent autoimmune central nervous system disease.

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IMPROVED GENETIC AND RADIOgraphic testing techniques have blurred the borders between autoimmune and neurogenetic disease. Several patients who clinically appeared to have multiple sclerosis or variations of autoimmune demyelination but carried variants of the proteolipid protein 1 (PLP1) gene have been described in the literature. The PLP1 gene usually causes Pelizaeus-Merzbacher disease or hereditary spastic paraeparesis type 2. It was unclear whether the cases were unusual presentations of a neurogenetic disease or whether the mutation induced an abnormal autoimmune response.1,2 Mouse studies of juvenile Batten disease, another neurogenetic disease, have revealed an autoimmune attack against glutamic acid decarboxylase 65; the authors speculated that the causative gene might affect glutamic acid decarboxylase 65 in a way that induces the abnormal autoimmune response.3 In Duchenne muscular dystrophy, dystrophinopathy appears to induce a secondary autoimmune response;4 prednisone has become a standard part of therapy in these cases.5 We describe a patient with apparent brain biopsy–proved progressive acute disseminated encephalomyelitis (ADEM) in whom genetic testing supported mitochondrial disease due to compound heterozygous mutations in the polymerase γ (POLG) gene.

REPORT OF A CASE

A 4-year-old boy presented with 1 week of ataxia after an otitis media infection. His birth and developmental and medical histories were unremarkable. His family history revealed only 1 relative with cerebral palsy due to hypoxia (further details not available). Initial brain magnetic resonance imaging in this case revealed multiple focal areas of T2 prolongation with gadolinium enhancement. The affected regions included the left parietal lobe, the internal capsule and head of the caudate, and the right middle cerebellar peduncle (Figure 1A). The findings were thought to be most compatible with ADEM. The
family declined treatment with steroids, and the patient improved during hospitalization. After discharge, the family failed to appear for routine follow-up appointments but brought the child to the emergency department several times for worsening ataxia. Each time, they refused admission. With the help of social services, the patient was readmitted 3 months after his initial presentation.

At readmission, he was somnolent and responded only to tactile stimuli, with loss of extracocular movement on the right and right arm and leg spasticity and hypertonia. Magnetic resonance imaging revealed enlargement of previously identified lesions and new foci of T2 prolongation in the left frontoparietal subcortical white matter, genu of the corpus callosum, genu of the right internal capsule, anterior thalamus, and bilateral cerebellar hemispheres, with extension into the bilateral cerebellar peduncles. Subacute hemorrhage was present in the left thalamus and putamen (Figure 1B). Magnetic resonance spectroscopy showed an elevated lactate level, a markedly depressed N-acetylaspartate level, and a markedly elevated choline level in the left basal ganglia, findings most compatible with an aggressive tumor such as glioblastoma multiforme (Figure 1C). However, magnetic resonance perfusion studies showed no evidence of increased perfusion in the lesions, findings more consistent with a fulminant inflammatory process such as tumeform demyelination than with neoplasm. Biopsy of the deep left frontal lesion revealed multiple fragments of heavily gliotic white matter diffusely infiltrated by abundant foamy histiocytes, scattered lymphocytes, and occasional plasma cells (Figure 2A). A myelin stain showed remarkable loss of myelin with macrophages containing myelin particles (Figure 2B). As expected, the reactive astrocytes were intensely highlighted by glial fibrillary acidic protein (Figure 2C), and the macrophages stained for the macrophage marker CD68 (Figure 2D). No microorganisms were identified, and there was no evidence of a neoplasm. These findings were most consistent with an active demyelinating process.

The patient was treated with 30 mg/kg of methylprednisolone sodium succinate (Solu-Medrol) for 5 daily doses followed by an oral prednisolone taper, with only minimal clinical improvement. His hospitalization was complicated by steroid-induced hyperglycemia and witnessed physical abuse by his mother. He was subsequently placed in state custody. He eventually required percutaneous gastrostomy tube placement for feeding and was discharged to a long-term care facility. He died 9 months after his initial presentation.

After his discharge but before his death, several of his laboratory test results returned and were reviewed. Urinary organic acids demonstrated a mild increase in vanillate levels, presumably from diet. Levels of serum amino acids, very long-chain fatty acids, and plasma carnitine were normal, as were the results of an acyl carnitine profile. The cerebrospinal fluid specimen demonstrated normal levels of protein, but the myelin basic protein level was higher than 1000 ng/mL and oligoclonal bands were present. No atypical cells were present on cytologic examination. Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6 were not detected by polymerase chain reaction. The serum lactate level was slightly high at 23.4 mg/dL (reference range, 4.5-19.8 mg/dL) (to convert to millimoles per liter, multiply by 0.111); however, the cerebrospinal fluid lactate level was normal. DNA POLG sequencing revealed compound heterozygous mutations C752T (T251I) and C1760T (P587L).

DNA POLG is the nuclear-encoded polymerase that is responsible for replication of the mitochondrial genome. It consists of 2 subunits, a catalytic subunit encoded by POLG1 (now known as POLG) and an accessory subunit encoded by POLG2. POLG is located on
Homozygosity for the A467T mutation and compound heterozygosity for A467T in POLG are most commonly associated with autosomal recessive progressive external ophthalmoplegia, sensory ataxic neuropathy, and Alpers syndrome, which is characterized by a clinical triad of psychomotor retardation, intractable epilepsy, and liver failure in infants and young children. Our patient’s POLG sequencing revealed compound heterozygosity at T251I and P587L. Horvath et al8 described 8 patients with this combination of mutations; all were adults, and 7 of the 8 had progressive external ophthalmoplegia. Six patients also had myopathy; 1 had ataxia; and 1 had neuropathy. One patient had only isolated myopathy. This combination of mutations was also described in 2 sisters with mitochondrial neuromuscular syndrome but no leukoencephalopathy.9,10 Also, 3 families with autosomal recessive progressive external ophthalmoplegia were compound heterozygous for the T251I and the P587L gene mutations.11 Our patient had progressive ataxia, asymmetrical right ophthalmoplegia, seizures, and brain biopsy findings that were consistent with rapidly progressive demyelination, suggesting a wider phenotypic spectrum associated with POLG mutations.

Demyelinating disease—or what appears to be demyelinating disease—has been reported previously in patients carrying other mutations associated with mitochondrial disease. There is a “Leber plus” phenotype that has a radiographic appearance suggestive of multiple sclerosis12; however, most patients with multiple sclerosis do not carry Leber mitochondrial DNA mutations.13 An adult man with a multiple sclerosis–like clinical presentation, compatible radiographic imaging results, and oligoclonal bands in a cerebrospinal fluid specimen had a heterozygous S646L mutation in the optic atrophy 1 (OPA1) gene, which codes for a mitochondrial protein and is associated with autosomal dominant optic atrophy.14 Carelli and Bellan15 suggested that mitochondrial dysfunction in Leber and OPA1 mutations may induce an autoimmune response. Conversely, mitochondrial dysfunction has been proposed as a contributor to axonal degeneration in multiple sclerosis, although the initial trigger of this dysfunction remains unclear.16 Our patient’s presentation, antecedent infectious prodrome, and radio-
graphic, laboratory, and pathologic evidence were all consistent with acute autoimmune demyelinating disease, but the subsequent degenerative course was unusual for ADEM and triggered the search for mitochondrial causes. We wonder whether the underlying POLG mutation triggered an autoimmune reaction, as suggested by Carelli and Bellan for other mitochondrial mutations, or whether the stress of ADEM triggered severe mitochondrial dysfunction, leading to our patient's decline and death.

Which came first? Mitochondrial dysfunction or the autoimmune response? Did both occur, or can mitochondrial disease mimic autoimmune disease? Could the POLG mutation have been an incidental finding in a child with severe ADEM? Further work is needed to clarify the time line and pathogenesis in cases like these and to clarify how mitochondrial dysfunction contributes to poor outcomes in other patients who appear to have autoimmune disease.

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REFERENCES