Juvenile Alpers Disease

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**Background:** Alpers disease is commonly associated with polymerase γ deficiency and usually affects infants or young children.

**Objective:** To report a juvenile case of Alpers disease due to mutations in the polymerase γ gene (POLG1).

**Design:** Clinical, pathologic, biochemical, and molecular analysis.

**Setting:** Tertiary care university hospital and academic institutions.

**Patient:** A 17-year-old adolescent girl with intractable epilepsy and liver disease.

**Main Outcome Measures:** Clinical course and pathologic, biochemical, and molecular features.

**Results:** Biochemical and pathologic evidence suggested a respiratory chain defect, which was confirmed by enzyme analysis of the liver. Mutational analysis of POLG1 showed 2 novel mutations: T851A and R1047W.

**Conclusion:** The POLG1 mutations can cause juvenile and childhood Alpers disease.

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**REPORT OF A CASE**

A 17-year-old adolescent girl of New Zealand, European, and Pacific Island ethnicity was initially seen with clusters of occipital seizures characterized by a brief visual disturbance followed by head extension, clonic jerking of the right arm, and secondary generalization. An initial electroencephalogram demonstrated diffuse slowing. Handwriting had always been difficult, to the extent that she needed a stenographer to write some final examinations. Mild clumsiness and pes cavus had worsened during the previous 2 years. Nerve conduction studies showed peripheral neuropathy. Developmental milestones were otherwise normal, and she had normal intelligence. Her vision and hearing were also normal. Pregnancy and delivery had been unremarkable, and her height and weight were consistently between the third and tenth percentiles. At age 5 years, she had viral meningitis (coxackievirus B2 cultured from cerebrospinal fluid). The cerebrospinal fluid at this stage had a low glucose level (25 mg/dL [to convert to millimoles per liter, multiply by 0.0555]) and a significantly elevated protein level (0.57 g/dL [to con-
increased cortical signal, particularly in the occipital lobes.

Liver function test results became abnormal while the patient was taking carbamazepine and before valproate therapy: peak alanine aminotransferase, 396 U/L (reference range, 7-28 U/L) (to convert to microkatals per liter, multiply by 0.0167). Liver dysfunction persisted when valproate therapy was commenced but deteriorated when the patient received multiple drugs, including antituberculous therapy. Subsequent electroencephalograms showed frequent epileptiform discharges in the left posterior quadrant and continued diffuse slowing. Magnetic resonance imaging findings were initially normal but showed progressive abnormality with increased signal on T2-weighted images in the cortical and subcortical white matter and basal ganglia (Figure 1). The cerebrospinal fluid showed persistently low glucose levels (11-65 mg/dL) and elevated protein levels (0.11-0.47 g/dL), with few lymphocytes. Lactic acidosis (lactate levels of 61-110 mg/dL) (to convert to millimoles per liter, multiply by 0.111) was noted during the 2 weeks before death. Urinalysis showed generalized aminoaciduria and normal organic acid levels. Biopsies of the skin, muscle, and liver were nondiagnostic. Brain biopsy showed slight perivascular lymphocytic cuffing, perhaps representing cerebral angiitis.

A variety of infectious, inflammatory, and neoplastic processes were considered. The patient received empirical therapy for these conditions (immunosuppression, antibiotics, and therapy for tuberculosis), without any improvement. Consultation with a pediatric neurologist suggested the possibility of a mitochondrial disorder. She commenced a high-fat, low-carbohydrate diet and multivitamin therapy, with no improvement. Her neurologic decline continued, and she died at age 17 years 9 months of respiratory failure secondary to her neurologic condition. At autopsy, the brain showed extensive neuronal loss and gliosis, most prominent in the occipital lobes (Figure 2B), as typically seen in Alpers disease, but also in the basal ganglia and brainstem. The liver showed extensive steatosis and fresh necrosis (Figure 2A).

Respiratory chain enzyme analysis and real-time quantitative polymerase chain reaction for estimation of mtDNA content, performed on a muscle biopsy sample as described previously, showed normal activities of complexes I, II, III, and IV and of mitochondrial marker enzyme citrate synthase. In the liver (post mortem), there was marked deficiency of the respiratory chain enzymes containing subunits encoded by mtDNA (residual activities of 8% for complex I, 33% for complex III, and 19% for complex IV), with normal activity of the nuclear-encoded complex II (101%) and elevated activity of citrate synthase (316%).

Sequencing of the entire mitochondrial genome in the liver DNA did not reveal any pathogenic mutations. Quantitative polymerase chain reaction showed that the ratio of mtDNA to nuclear DNA in the liver was deficient (0.17; mean [SD] of 6 control livers, 1.01 [0.15]; range, 0.78-1.19).

The POLG1 gene was screened by direct sequencing as described previously and was found to harbor 2 compound heterozygous missense mutations. The first mutation, A2551G in exon 16, predicts the substitution of a conserved threonine by an alanine at position 851 (T851A) (Figure 3A). The second mutation, C3139T in exon 20, changes a conserved arginine to a tryptophan at position 1047 (R1047W) (Figure 3B). These mutations are assumed to be pathogenic because they are...
not reported polymorphic changes, are absent from more than 200 control alleles, and change highly conserved amino acids. The threonine residue at codon 851 is in a region that is conserved in mice, frogs, flies, and yeast and that includes another pathogenic POLG1 mutation, G848S. The R1047W mutation changes the same arginine residue mutated by another previously reported pathogenic mutation, R1047Q. The patient’s maternal aunt does not carry either mutation.

Alpers disease is characterized by childhood encephalopathy and hepatopathy due to mitochondrial respiratory chain deficiency. Some adults with Alpers disease have been described but have not been studied at the molecular level. Mutations in POLG1 were first identified as a cause of Alpers disease by Naviaux and Nguyen, and recent studies have confirmed this association, showing that deficiency of polymerase γ is the most common autosomal recessive cause of Alpers disease in children. The present data suggest that mutations in POLG1 are also involved in juvenile Alpers disease.

The pattern of respiratory chain abnormality in the proband (complex I and IV deficiency) and the family history of a maternal aunt with neurologic regression and ataxia led to the initial consideration of mtDNA mutations. However, sequencing of the whole mitochondrial genome excluded this possibility. Finding mutations in POLG1 enabled us to also test the aunt, who carries neither mutation, indicating that her neurologic problems are unrelated. Confirmation of autosomal recessive (rather than maternal) inheritance has facilitated genetic counseling.

Mutations in POLG1 were originally associated with autosomal dominant or recessive familial progressive external ophthalmoplegia and multiple mtDNA rearrangements (particularly deletions) in postmitotic tissues. In addition, mutations in POLG1 can cause sensory ataxic neuropathy with dysarthria and ophthalmoplegia (of note, the present patient also had a peripheral neuropathy) and an ataxic syndrome without progressive external ophthalmoplegia. Alpers disease is associated with depletion of mtDNA in the liver. Thus, mutations in this gene can have various consequences for mtDNA and variously affect different tissues.

Metabolic diseases are less likely in adults than in children. The present patient, however, had several features that made a mitochondrial disorder more likely than acquired conditions, including symptoms and signs reflecting the involvement of multiple systems (brain, peripheral nervous system, liver, and kidney, as well as lactic acidosis). Mitochondrial disorders should be considered at any age, particularly when multiple organ systems are involved.

In conclusion, Alpers disease should be considered in adults with encephalopathy and intractable epilepsy, particularly when the liver or other organs are involved. Mutation screening of POLG1 should be considered in such patients and is vital for identifying the underlying cause and for genetic counseling.

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Author Contributions: Dr DiMauro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wiltshire, Sadleir, and Thorburn. Acquisition of data: Wiltshire, Akman, Sadleir, Haas, Zuccollo, McEwen, and Thorburn. Analysis and interpretation of data: Wiltshire, Akman, DiMauro, Akman, Zuccollo, and Thorburn. Drafting of the manuscript: Wiltshire, Akman, and Sadleir. Critical revision of the manuscript for important intellectual content: Wiltshire, DiMauro, DiMauro, Sadleir, Haas, Zuccollo, McEwen, and Thorburn. Obtained funding: DiMauro and Thorburn. Administrative, technical, and material support: Wiltshire, Akman, and Sadleir. Study supervision: DiMauro.

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REFERENCES


Announcement

Online Submission and Peer Review System Available. The Archives of Neurology editorial office has introduced an online manuscript submission and peer review system developed by ejournalPress that will serve the needs of authors, reviewers, and editors. The new system went live on November 14, 2005. See http://archneur.ama-assn.org for more detailed information.