**OBSERVATION**

**Juvenile Alpers Disease**

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

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

**Design:** Clinical, pathologic, biochemical, and molecu- lar 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 patho- logic, biochemical, and molecular features.

**Results:** Biochemical and pathologic evidence sug- gested 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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LPERS DISEASE, OR PROGRES-

sive neuronal degenera- tion of childhood (Online Mendelian Inheritance in Man [OMIM] 203700), is

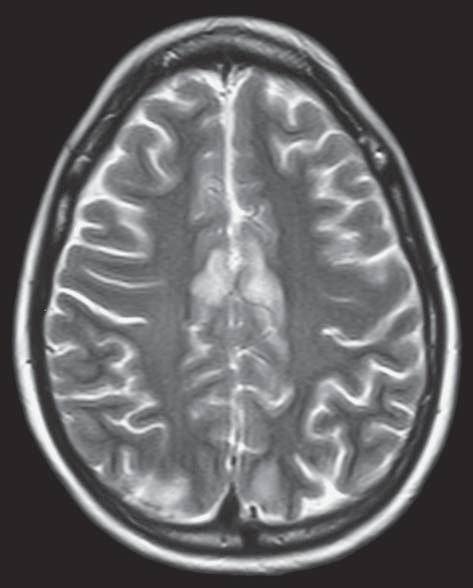
**A**

characterized by developmental regres- sion, intractable epilepsy, progressive neu- rologic deterioration, liver disease, and death usually before 10 years of age.1-3 Neu- ropathologic changes include patchy neu- ronal loss and gliosis, particularly in the striate cortex,4 whereas the liver shows ste- atosis, cellular necrosis, focal inflamma- tion, and fibrosis.5 In 2004, Alpers dis- ease was attributed to mutations in the catalytic subunit of the mitochondrial DNA (mtDNA) polymerase gene polymerase 'Y (*POLG1*),6 and this association has been confirmed in several series.7-10

Alpers disease is typically a disease of childhood, and it may not be given suffi- cient attention in juvenile cases. We de- scribe a 17-year-old adolescent girl with clinical, electroencephalographic, patho- logic, and biochemical features of Alpers disease caused by mutations in *POLG1* and suggest that this diagnosis be considered in adults with encephalopathy or intrac- table epilepsy, especially with liver dis- ease. In these patients, mutational analy- sis of *POLG1* is mandatory.

**REPORT OF A CASE**

A 17-year-old adolescent girl of New Zea- land, European, and Pacific Island ethnic- ity was initially seen with clusters of oc- cipital seizures characterized by a brief visual disturbance followed by head ex- tension, clonic jerking of the right arm, and secondary generalization. An initial elec- troencephalogram demonstrated diffuse slowing. Handwriting had always been dif- ficult, to the extent that she needed a ste- nographer to write some final examina- tions. Mild clumsiness and pes cavus had worsened during the previous 2 years. Nerve conduction studies showed periph- eral neuropathy. Developmental mile- stones were otherwise normal, and she had normal intelligence. Her vision and hear- ing were also normal. Pregnancy and de- livery had been unremarkable, and her height and weight were consistently be- tween the third and tenth percentiles. At age 5 years, she had viral meningitis (cox- sackievirus B2 cultured from cerebrospi- nal fluid). The cerebrospinal fluid at this stage had a low glucose level (25 mg/dL [to convert to millimoles per liter, multi- ply by 0.0555]) and a significantly el- evated protein level (0.57 g/dL [to con-



**Figure 1.** Axial T2-weighted magnetic resonance image showing an increased cortical signal, particularly in the occipital lobes.

vert to grams per liter, multiply by 10.0]), out of keeping with viral meningitis. She made a full recovery. She be- gan experiencing migraines at age 12 years, with visual aura and vomiting.

Family history showed that a maternal aunt, cur- rently aged 48 years, had an undiagnosed neurologic con- dition, with delayed early milestones and ataxia begin- ning at age 3 years. She regressed neurologically between ages 5 and 7 years, with subsequent severe intellectual disability. A maternal uncle died at age 3 months of “cot death.”

The patient was treated early with midazolam hydro- chloride followed by maintenance therapy with phe- nytoin sodium. She had a cluster of seizures after 1 month, remained seizure-free for 4 months, and then developed status epilepticus. During the next 2 months, she had re- peated admissions to the intensive care unit with status epilepticus or encephalopathy. Although she had lucid periods between episodes, overall she developed step- wise deterioration, with memory impairment, slurred speech, and left-sided hemiparesis. A variety of anticon- vulsant agents, including carbamazepine, valproate so- dium, lamotrigine, intravenous benzodiazepines, topi- ramate, gabapentin, and intermittent doses of phenobarbital sodium, were tried without sustained ben- efit. Liver function test results became abnormal while the patient was taking carbamazepine and before valpro- ate therapy: peak alanine aminotransferase, 396 U/L (ref- erence range, 7-28 U/L) (to convert to microkatals per liter, multiply by 0.0167); peak 'Y-glutamyltransferase, 1234 U/L (reference range, 7-36 U/L) (to convert to mi- crokatals per liter, multiply by 0.0167); and peak aspar- tate aminotransferase, 322 U/L (reference range, 12-27

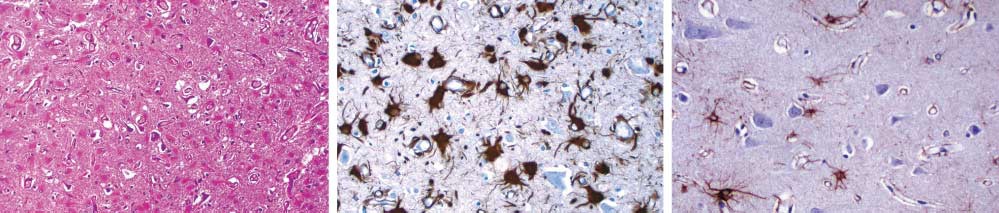
U/L) (to convert to microkatals per liter, multiply by 0.0167). Liver dysfunction persisted when valproate therapy was commenced but deteriorated when the pa- tient received multiple drugs, including antitubercu- lous therapy. Subsequent electroencephalograms showed frequent epileptiform discharges in the left posterior quad- rant and continued diffuse slowing. Magnetic reso- nance imaging findings were initially normal but showed progressive abnormality with increased signal on T2- weighted images in the cortical and subcortical white mat- ter 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 lym- phocytes. 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 empiri- cal therapy for these conditions (immunosuppression, an- tibiotics, and therapy for tuberculosis), without any im- provement. Consultation with a pediatric neurologist suggested the possibility of a mitochondrial disorder. She commenced a high-fat, low-carbohydrate diet and mul- tivitamin therapy, with no improvement. Her neuro- logic decline continued, and she died at age 17 years 9 months of respiratory failure secondary to her neuro- logic condition. At autopsy, the brain showed extensive neuronal loss and gliosis, most prominent in the occipi- tal lobes (**Figure 2**B), as typically seen in Alpers dis- ease, 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 quan- titative polymerase chain reaction for estimation of mtDNA content, performed on a muscle biopsy sample as described previously,8,11 showed normal activities of complexes I, II, II+III, III, and IV and of mitochondrial marker enzyme citrate synthase. In the liver (post mor- tem), there was marked deficiency of the respiratory chain enzymes containing subunits encoded by mtDNA (re- sidual 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 activ-

ity of citrate synthase (316%).

Sequencing of the entire mitochondrial genome in the liver DNA did not reveal any pathogenic mutations. Quan- titative 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 previously8 and was found to harbor 2 com- pound heterozygous missense mutations. The first mu- tation, A2551G in exon 16, predicts the substitution of a conserved threonine by an alanine at position 851 (T851A) (**Figure 3**A). The second mutation, C3139T in exon 20, changes a conserved arginine to a trypto- phan at position 1047 (R1047W) (Figure 3B). These mu- tations are assumed to be pathogenic because they are



A B C

**Figure 2.** Histopathologic features of the brain and liver. A, Liver histologic examination (hematoxylin-eosin, original magnification x40) showing microvesicular steatosis with central nuclei. B, Glial fibrillary acid protein stain (original magnification x40) of the patient’s cerebral cortex showing activated astrocytes, a sign of gliosis. C, Glial fibrillary acid protein stain (original magnification x40) of the normal cerebral cortex.

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.12 The R1047W mutation changes the same argi- nine residue mutated by another previously reported pathogenic mutation, R1047Q.13 The patient’s maternal aunt does not carry either mutation.

**COMMENT**

Alpers disease is characterized by childhood encepha- lopathy and hepatopathy due to mitochondrial respira- tory chain deficiency. Some adults with Alpers disease have been described but have not been studied at the mo- lecular level.14,15 Mutations in *POLG1* were first identi- fied as a cause of Alpers disease by Naviaux and Nguyen,6 and recent studies7,8,16 have confirmed this association, showing that deficiency of polymerase 'Y is the most com- mon autosomal recessive cause of Alpers disease in chil- dren. The present data suggest that mutations in *POLG1* are also involved in juvenile Alpers disease.

The pattern of respiratory chain abnormality in the pro- band (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. How- ever, sequencing of the whole mitochondrial genome ex- cluded this possibility. Finding mutations in *POLG1* en- abled us to also test the aunt, who carries neither mutation, indicating that her neurologic problems are unrelated. Con- firmation of autosomal recessive (rather than maternal) in- heritance has facilitated genetic counseling.

Mutations in *POLG1* were originally associated with autosomal dominant or recessive familial progressive ex- ternal ophthalmoplegia12,17 and multiple mtDNA rear- rangements (particularly deletions) in postmitotic tis- sues. In addition, mutations in *POLG1* can cause sensory ataxic neuropathy with dysarthria and ophthalmople- gia18 (of note, the present patient also had a peripheral neuropathy) and an ataxic syndrome without progres- sive external ophthalmoplegia.19 Alpers disease is asso- ciated with depletion of mtDNA in the liver.8,20 Thus, mu- tations in this gene can have various consequences for mtDNA and variously affect different tissues.21

Metabolic diseases are less likely in adults than in chil- dren. The present patient, however, had several features that made a mitochondrial disorder more likely than ac-



T851A

R1047W

**A**  **C**  **C**  **A** **T**  **C**  **C** **T**  **C G**  **C C**  **G** **C**  **T**  **G**  **A A**  **G**  **G**  **G**  **C** **A** **T**

**A**

**C**

**G T**

A

B

**Figure 3.** Electropherogram of the polymerase 'Y gene sequence showing the 2 novel mutations found in this compound heterozygous patient: A2551G in exon 16, resulting in a T851A amino acid change (A), and C3139T in exon 20, resulting in an R1047W amino acid change (B).

quired conditions, including symptoms and signs re- flecting the involvement of multiple systems (brain, pe- ripheral nervous system, liver, and kidney, as well as lactic acidosis). Mitochondrial disorders should be consid- ered at any age, particularly when multiple organ sys- tems are involved.

In conclusion, Alpers disease should be considered in adults with encephalopathy and intractable epilepsy, par- ticularly when the liver or other organs are involved. Mu- tation 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 analy- sis. *Study concept and design:* Wiltshire, Sadleir, and Thor- burn. *Acquisition of data:* Wiltshire, Davidzon, Akman, Sadleir, Haas, Zuccollo, McEwen, and Thorburn. *Analy- sis and interpretation of data:* Wiltshire, Davidzon, DiMauro, Akman, Zuccollo, and Thorburn. *Drafting of the manuscript:* Wiltshire, Akman, and Sadleir. *Critical revision of the manuscript for important intellectual content:* Wiltshire, Davidzon, DiMauro, Sadleir, Haas, Zuccollo, McEwen, and Thorburn. *Obtained funding:* DiMauro and Thorburn. *Administrative, technical, and ma- terial support:* Wiltshire, Davidzon, Akman, Sadleir, and Thorburn. *Study supervision:* DiMauro.

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***Announcement***

**Online Submission and Peer Review System Avail- able.** The *Archives of Neurology* editorial office has in- troduced an online manuscript submission and peer re- view 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:

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