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Reversible valproate hepatotoxicity due to mutations in mitochondrial DNA polymerase γ (POLG1)

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ABSTRACT

We report the case of a 2-year-old boy with seizures who developed hepatic failure shortly after commencing sodium valproate. Unexpectedly, liver function returned to normal on stopping the drug. Sequencing of the mitochondrial polymerase γ gene (POLG1) revealed four heterozygous substitutions, two of which have been identified in cases of Alpers-Huttenlocher disease.

In 1931 Alpers first described post mortem findings of “progressive degeneration of gray matter” in an infant with a rapidly progressive neurodegenerative illness.1 However, it was Huttenlocher who later recognised the clinical syndrome of psychomotor retardation, intractable epilepsy and liver failure.2 Explosive onset of seizures (generalised, focal and myoclonic) usually occurs between the ages of 1 and 3 years and patients frequently present in status epilepticus or with epilepsy partialis continua. In many cases the onset of this intractable epilepsy heralds an inexorable and rapid decline resulting in death within months. In addition to the pre-terminal hepatic failure, there are a number of other associated clinical features including developmental delay and regression, hypotonia, cortical blindness, ataxia and in older patients an axonal sensory neuropathy. Although the molecular aetiology of this disease was initially unclear, it has now become apparent that almost all infants and young children with Alpers-Huttenlocher disease have a disorder of oxidative phosphorylation secondary to depletion of mitochondrial DNA (mtDNA). Mutations in three genes (POLG1, DGUK and MPV17) are responsible for most cases of hepatocerebral mtDNA depletion, but interestingly, only mutations in POLG1 have been associated with Alpers-Huttenlocher disease, epilepsy not being a feature of mutations in either DGUK or MPV17.3–4 Administration of the anti-convulsant drug sodium valproate has been associated with a fatal hepato-pathy,2 and it has been suggested that young children with Alpers-Huttenlocher disease may be at increased risk of this complication.6 In these patients discontinuation of sodium valproate has not been associated with an improved clinical course in this fatal condition. Although the mutations identified in our patient have previously been reported as part of a study of the phenotypic presentation of POLG mutations,7 this is the first description of the case and discussion of the important clinical points it raises regarding the investigation and treatment of children with liver failure precipitated by sodium valproate treatment.

CASE HISTORY

A previously well, developmentally normal 2-year-old boy presented with new onset epilepsy following minor head trauma. A CT scan of his brain performed following his head injury was normal, although EEG showed sharp and slow wave focus in the right posterior quadrant. Following an unsuccessful trial of carbamazepine, he was placed on a gradually increasing regimen of sodium valproate, reaching a maximum dose of 25 mg/kg/day. Almost 2 months after commencing this drug he became unwell with persistent vomiting and encephalopathy and was admitted to hospital. His GCS on admission was 5 and his blood sugar unrecordable. He had deranged liver function tests, prolonged clotting, elevated ammonia, and a high plasma lactate (14.8 mmol/l). Sodium valproate was stopped and supportive therapy instituted. He regained normal consciousness after several hours, although plasma lactate remained elevated at 7.9 mmol/l. Brain MRI scan showed abnormal white matter signal in the occipital and medial temporal lobes bilaterally (fig 1A), findings which persisted on a follow-up scan 15 months later (fig 1B). Hepatic dysfunction progressed (table 1), but the child was considered unsuitable for liver transplantation at this time because of a presumptive diagnosis of Alpers-Huttenlocher disease. With conservative management and vitamin K supplementation, his liver function returned to normal over a 6-month period. His epilepsy is currently treated with levetiracetam and seizures are infrequent. In view of the high lactate, seizures and hepatic dysfunction, mitochondrial disease was considered and a muscle biopsy was performed. Blood DNA was investigated for mutations in POLG1.

METHODS

Standard histological and histochemical (including sequential cytochrome c oxidase (COX) and succinate dehydrogenase (SDH)) analyses were performed on frozen sections (10 μm) of skeletal muscle biopsy obtained from the patient’s left quadriceps. The activities of individual respiratory chain complexes and the matrix marker citrate synthase were determined as previously described.8 In these patients discontinuation of sodium valproate has not been associated with an improved clinical course in this fatal condition. Although the mutations identified in our patient have previously been reported as part of a study of the phenotypic presentation of POLG mutations,7 this is the first description of the case and discussion of the important clinical points it raises regarding the investigation and treatment of children with liver failure precipitated by sodium valproate treatment.

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Parental/guardian informed consent was obtained for publication of the person’s details in this report.

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City, CA) and a fluorescent DNA analyser (primers and conditions available online, Applied Biosciences 3100). The sequence obtained was compared with the GenBank reference (accession number: BC050559) and substitutions were confirmed by reverse sequencing.

RESULTS
Muscle biopsy revealed no histochemical or biochemical abnormalities and both Southern blot and long-range PCR were normal. Sequencing of POLG1 demonstrated four heterozygous substitutions, A467T, E1143G, Q879H and T885S (fig 2). Sequencing of parental DNA confirmed that the patient had inherited the A467T substitution in cis with T885S and in trans with Q879H and E1143G (fig 2).

DISCUSSION
Sodium valproate is a successful and frequently used first line therapy for a variety of different epileptic seizures and syndromes. Its use in very young patients with neurodevelopmental delay and epilepsy partialis continua has been questioned on the grounds that it may precipitate a neurometabolic decompensation in those with Alpers-Huttenlocher disease, leading to irreversible liver failure.6

Orthotopic liver transplantation has been attempted in patients with valproate-induced liver failure, some of whom have later been shown to have Alpers-Huttenlocher disease.9 10 Although successful engraftment was achieved in most patients, they invariably died a short time later following progressive neurological deterioration. Consequently, valproate-induced liver failure has been considered a contraindication to orthotopic liver transplantation, and this was the case for our patient. Fortunately, his liver failure slowly reversed and 2 years on his epilepsy has been successfully managed without neurological decline. He has an unusual genotype with four different substitutions and this may have influenced the clinical course of his disease. The A467T mutation is known to lower DNA binding affinity and catalytic efficiency of POLG1,11 but the role of the other substitutions is less clear. However, the E1143G mutation has been shown to partially rescue the deleterious effects of the W748S mutation (also associated with Alpers-Huttenlocher disease as well as ataxia and peripheral neuropathy), suggesting it may have a disease-modifying role.12 The Q879H and T885S substitutions have not been reported in controls, but in the presence of two confirmed mutations it is difficult to be certain of their precise role in the disease pathogenesis. Both occur within the polymerase domain of POLG1, a region of the gene specifically affected in Alpers-Huttenlocher disease (http://tools.niehs.nih.gov/polg/index.cfm). Although neither amino acid substitution appears to be severe (amino acid remains hydrophilic), the Q879H substitution does affect a phylogenetically conserved site (amino acid position 885 appears to be less well conserved) and is therefore likely to be contributing to disease.

This case illustrates a clinically important variation in the phenotype of Alpers-Huttenlocher disease, where liver failure has previously been considered a pre-terminal event and invariably associated with an inexorable neurological decline.13 Sodium valproate played a key role in precipitating the liver failure in this case, but the mechanism for this drug effect remains elusive. Based on our observations, we recommend sequencing of POLG1 in children with valproate-induced hepatic failure, particularly as identification of the E1143G

<table>
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mutation may indicate a more favourable outcome. Furthermore, we advise that, particularly in young children (<3 years old) with aggressive focal epilepsy, the POLG1 gene should be sequenced prior to commencing sodium valproate therapy. In situations where this is not possible, then serum lactate, ammonia and liver function should be closely monitored.

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REFERENCES