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Case study

Partial status epilepticus – Rapid genetic diagnosis of Alpers' disease

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ABSTRACT

We describe four children with a devastating encephalopathy characterised by refractory focal seizures and variable liver dysfunction. We describe their electroencephalographic, radiologic, genetic and pathologic findings. The correct diagnosis was established by rapid gene sequencing. POLG1 based Alpers' disease should be considered in any child presenting with partial status epilepticus.

1. Introduction

Acute onset of intractable focal seizures is a rare, potentially catastrophic occurrence in children. In some, a specific infective agent such as the herpes simplex virus in Herpes Encephalitis is identified. In the absence of acute infection the differential diagnosis includes Stroke, Rasmussen's encephalitis, a structural brain defect such as tumour or focal cortical dysplasia, and progressive neurometabolic diseases such as Alpers' Disease.

Alpers' Disease[1] also called Alpers-Huttenlocher syndrome or Progressive Neuronal Disease of Childhood is an inherited autosomal recessive disorder characterised by defective mitochondrial DNA synthesis which leads to a fatal brain and liver disorder with multi-systemic involvement more recently described.[2] Previously, the diagnosis was made by the association of a clinical picture of Epilepsia Partialis Continua (EPC) with liver dysfunction and elevation of cerebrospinal fluid (CSF) protein. More recently, mutations in Polymerase Gamma 1 (POLG1) have been described in association with Alpers' Disease.

In view of its devastating outcome and wider genetic implications this diagnosis is important to consider in cases of epileptic encephalopathy or EPC in childhood and adolescence.

We describe four children seen in an 18-month period with focal epileptic encephalopathy and POLG1 mutations. The clinical picture, supported by more recently described imaging

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and electroencephalogram (EEG) features and the availability of gene sequencing, allowed rapid confirmation of the diagnosis within days.[3]

2. Case history

2.1. *Case 1*

A 17-month-old Caucasian boy of Irish origin with no family history of consanguinity presented acutely with focal seizures involving the right upper limb, which progressed over 24 h to EPC and failed to respond to repeated doses of lorazepam, fosphenytoin, phenobarbitone and a midazolam infusion. Treatment with propofol and thiopentone was initiated and seizure activity resolved.

Investigations at presentation showed elevated blood lactate (8.0 mmol/L – all reference ranges are presented in Table 1) and elevated liver enzymes (AST 226 U/L and ALT 141 U/L). CSF lactate was elevated (4.48 mmol/L) and protein was mildly elevated (542 mg/L).

Initial EEG revealed rhythmic high-amplitude delta with polyspikes/polysharps (RHADS), slow background and frequent electrographic seizures and an MRI brain on day 2 showed increased T2 signal and restricted diffusion in both thalami, and in the left posterior parietal cortex (Fig. 1). Clinical deterioration occurred on the fourth hospital day and he required inotropic support. He developed severe lactic acidosis (ph 7.0; lactate 8.0).

Repeat MRI Brain on day 8 showed progression of abnormality involving both thalami. MR spectroscopy showed the presence of lactate (Fig. 2).

The EEG showed diffuse severe encephalopathy with burst suppression pattern.

Over the next 48 h signs of multi-organ failure developed with clinical evidence of brainstem and neocortical dysfunction. Death occurred ten days after admission.

Post mortem pathologic examination was performed. The liver histology showed regenerative nodule formation with fibrosis fatty change and cholestatis. Neuropathologic examination revealed proliferation of Alzheimer type 2 astrocytes involving neocortex and superficial cortical white matter.

Table 1 – A summary of the key findings in each case.

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Female	Female	Female
Development pre-seizures	Mild GM delay (retrospectively)	Normal	Normal	Congenital Ataxia
Family history	Nil	Yes[a]	Nil	Nil
Onset of seizures	17 months	10 months	21 months	43 months
Epilepsia Partialis Continua (EPC)	Yes	No	Yes	Yes
Age at death	17 months	12 months	42 months	Alive
Haematological evidence of liver impairment [A]	Yes (AST 226 U/L and ALT 141 U/L)	Yes (AST 112, ALT 100 – normalised)	Yes, AST > 200	Normal
Elevated lactate blood/CSF [B]	Yes (Blood 8.0 mmol/L, 10 mmol/L; CSF 4.48 mmol/L)	No	No	No
Elevated CSF protein [C]	Yes (542 mg/L)	Yes (742 mg/L)	Yes (924 mg/L)	No
MRI – Cortical findings	Day2 – left posterior parietal cortex. Day2 – inc T2	Normal	Bilateral occipital lobe changes	Day1 normal
Thalamic involvement on MRI	Day2 – T2 changes; Day8 – extensive	No	No	Day7 T2 right thalamic changes
MRS detection of lactate	Yes	Not done	No	No
EEG pattern of RHADS	Yes, right hemisphere	Yes, right central region	Yes, left posterior quadrant	Yes, right centro-parietal region
Postmortem/ biopsy pathological findings	Brain neuronal loss, inflammation liver fibrosis, regenerative change	Not done	Muscle biopsy normal	Not done
POLG1 mutation	p.A467T/p.L966R	p.A467T/p.G848S	p.A467T/p.R852C	p.A467T/p.C418R

A = AST (aspartate transaminase) reference range = 7–27 U/L; ALT (alanine transaminase) reference range = 1–21 U/L. B = Blood lactate reference range = 0.5–2.2 mmol/L; CSF lactate reference range = 0.8–2.2 mmol/L. C = CSF protein normal = <400 mg/L.
a Maternal cousin, a 24 year old female with Alpers A467T homozygous, no consanguinity.