Epilepsy: when family history holds the key to diagnosis

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There may be many causes of epileptic seizures, so thorough clinical history taking and examination to determine the seizure semiology is paramount. In this article, the authors describe a patient with new-onset seizures whose family history proved pivotal to targeted genetic testing and appropriate antiepileptic drug therapy.

**Presentation**

A 22-year-old man, born to consanguineous (first cousin) parents, was admitted in status epilepticus following a minor head injury. There was no prior history of seizures. He was stabilised in an intensive therapy unit with sodium valproate 1g twice a day. He then complained of visual symptoms with blurring in his left eye, as well as occasional flashing lights and colourful vision lasting a few seconds. These were thought to be seizures of occipital lobe origin. Examination showed a left homonymous hemianopia. Magnetic resonance imaging (MRI) of the brain showed an area of increased signal in the right occipital lobe without enhancement, which at the time was thought to represent brain contusion. Electroencephalography (EEG) showed diffuse slowing of background rhythms (in the theta/delta range, with no alpha rhythm) consistent with a diffuse encephalopathy. Brief cognitive testing with the Six-item Cognitive Impairment Test (6CIT) scored 8/28, suggesting some mild cognitive impairment.

Family history was significant. Two of the patient’s cousins, also children of consanguineous parents, had died in status epilepticus more than 10 years earlier. One had sensorineural hearing loss and developed blackouts from about the age of eight years, progressing to refractory myoclonus epilepsy leading to death at age 17 years. As a mitochondrial disorder was suspected clinically, muscle biopsy had been performed, which showed significant numbers of cytochrome c oxidase (COX) negative fibres; real-time polymerase chain reaction showed that these harboured high levels of mitochondrial DNA (mtDNA) deletions. This cousin’s eldest sister also developed jaundice with elevated liver-related blood tests. Ultrasound showed a diffusely

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**Epileptic seizures may take many different forms, and there may be many causes of epileptic seizures. Clinical history taking and examination aim to characterise seizure semiology in order to determine appropriate investigations and treatment. As epilepsy syndromes may now sometimes be defined by their underlying genetic mutations, a thorough family history may also be a crucial supplement to generic clinical skills. We present a patient in whom not only clinical phenotype but also family history were critical to appropriate investigation. Rather than a dry academic exercise, this genetic characterisation may have important implications for the avoidance of inappropriate investigation and antiepileptic drug treatment, as well as having ramifications for the wider family.**
Case notes ❚ Epilepsy diagnosis

Epilepsy diagnosis

Case notes

hyperechoic liver consistent with fatty infiltration.

Discussion

Using the terminology suggested in the revision of the classification of epilepsies developed by the International League Against Epilepsy,1 there are a number of epilepsy syndromes that may be termed genetic epilepsies. These continue to increase in number as new associations between genetic mutations and epilepsy syndromes are characterised.2 Diagnosis of genetic epilepsy syndromes may be facilitated by the additional clinical features observed along with the seizure disorder (eg dementia).3 In the present case, the clinical features and the family history were indicative of a mitochondrial disorder, hence prompting targeted genetic testing and thus avoiding the requirement to undertake invasive investigation with a muscle biopsy.

Mutations in the POLG gene, over 150 of which have been described to date, have been associated with a broad spectrum of clinical phenotypes characterised by progressive neurological disorder, often commencing in the teenage years. Inheritance is more often recessive than dominant. Presentations range from childhood onset Alpers–Huttenlocher syndrome to adult-onset sensory ataxic neuropathy dysarthria and ophthalmoplegia (SANDO).4–9

Epilepsy is a common presenta-tion of POLG mutations.6,7 In the majority of patients there is an occipital EEG focus, causing occipital seizures, which are characterised by flickering coloured lights, often persistent for long periods of time; in addition there may also be nystagmus, metamorphopsias and ictal visual loss. Brain MRI may show high signal lesions in the occipital cortex. In retrospect, the occipital high signal seen on our patient’s MRI scan was probably due to continuous epileptic activity, reflecting the underlying disease rather than a consequence of trauma.

Episodes of status epilepticus are common in POLG-related mitochondrial disease and often have a fatal outcome despite intensive treatment. Liver failure associated with the use of sodium valproate is also recorded.5,6 The factors underlying phenotypic heterogeneity associated with POLG mutations are unknown, although in patients with the p.Ala467Thr mutation the clinical presentation has been noted to be similar in siblings (as in our patient’s cousins), suggesting a genetic basis.8 The finding of significant variations in mtDNA in different p.Ala467Thr-associated POLG phenotypes suggests downstream molecular defects caused by the point mutation.9

In summary, in addition to careful characterisation of seizure semiology, obtaining a detailed family history may be critical to the diagnosis of epilepsy syndromes, with implications for targeted genetic testing and the avoidance of inappropriate investigations and certain antiepileptic drugs.

Acknowledgement

The authors would like to thank Dr T.P. Enevoldson for sharing information on the family history.

Declaration of interests

No conflicts of interest were declared.

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References