Paper

J R Coll Physicians Edinb 2015; 45: 281–3
http://dx.doi.org/10.4997/JRCPE.2015.407

A mitochondrial malady: stubborn seizures and atypical migraine

[1]M Vinjam, [2]R Newby, [3]R Davey
[1]Specialist trainee, Department of Neurology, Leeds Teaching Hospitals, Leeds, UK; [2]Specialist trainee, [3]Consultant neurologist,Department of Neurology, Pinderfields Hospital, Wakefield, UK

ABSTRACT A 22-year-old female migraineur presented with recurrent convulsive status epilepticus and ataxia. Her epilepsy proved refractory to treatment, necessitating the use of five anti-epileptic drugs and a course of steroids. Genetic testing revealed compound heterozygosity for two mutations of the polymerase-γ gene. The case highlights the clinical features and therapeutic challenges associated with this relatively common, but probably under-recognised, mitochondrial disease.

***Correspondence to** R Davey*
Pinderfields Hospital
Aberford Road
Wakefield WF14 DG
UK

***e-mail** richard.davey@midyorks.nhs.uk*

KEYWORDS epilepsy, ganglionopathy, migraine, mitochondrial, polymerase-γ

DECLARATION OF INTERESTS No conflict of interests declared

EDUCATION

CASE REPORT

A 22-year-old, right-handed woman presented following two episodes of convulsive status epilepticus. She had experienced recurrent myoclonic jerks, followed by a series of generalised tonic-clonic seizures, preceded by tonic head deviation. Her past medical history included three febrile convulsions at the age of 18 months. She had normal physical and cognitive development. In her mid-teens she developed migraine with visual aura, and suffered a single nocturnal epileptic seizure at the age of 16 followed by migraine aura-like visual disturbance lasting six months. Cranial magnetic resonance imaging (MRI) and an interictal standard electroencephalogram (EEG) performed at this time were normal. She had one son, was a non-smoker and did not drink alcohol or use illicit drugs.

Examination following her first episode of convulsive status epilepticus revealed down-beating nystagmus, areflexia and reduced joint position sensation in both feet. She responded well to an intravenous phenytoin infusion treatment for status epilepticus and was discharged on levetiracetam monotherapy.

Four months later she presented to Accident and Emergency with further generalised tonic-clonic seizures, which were treated with intravenous phenytoin after failure to respond to intravenous benzodiazepines. She regained consciousness but experienced persistent focal motor seizures of the left arm. Examination revealed no new neurological signs.

Blood tests revealed a white cell count of 22 x 10^9/L, normal electrolytes and glucose, and C-reactive protein of 41 mg/L. Creatine kinase was 4242 u/L on admission, and rose to 382,100 u/L four days later without myoglobinuria or renal dysfunction. Serum lactate was initially raised (4.1 mmol/L) but normalised following resuscitation. Antinuclear antibodies and antineutrophil-cytoplasmic antibodies were negative, as were voltage-gated potassium channel and N-methyl-D-aspartate receptor antibodies. Cerebrospinal fluid was acellular with normal protein and glucose; culture, cytology and viral polymerase chain reaction were negative. An EEG revealed continuous repetitive epileptic discharges over the right centro-temporal region. Cranial MRI (Figures 1 and 2), performed eight days after presentation, revealed right frontal cortical oedema.

She continued to suffer epilepsia partialis continua with intermittent generalised tonic-clonic seizures which proved refractory to anti-epileptic drug treatment. Control of both epilepsia partialis continua and generalised tonic-clonic seizures was eventually achieved through daily doses of 1800 mg sodium valproate, 3 g levetiracetam, 300 mg phenytoin, 60 mg clobazam and 400 mg carbamazepine, alongside a 14-day course of 4 mg dexamethasone.

Following discharge she was noted to develop hearing difficulties, mild gait ataxia and mild left hemiparesis. The latter resolved gradually over two months. Her medications were rationalised (phenytoin and sodium valproate were withdrawn). Audiometry confirmed mild sensory neural hearing loss bilaterally. Nerve conduction studies revealed a diffuse sensory ganglionopathy with no myopathic features. Genetic testing for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibres (MERRF), neuropathy, ataxia and retinitis pigmentosa (NARP) and familial hemiplegic migraine type 3 (SCN1A) were negative.

Further blood tests revealed she was heterozygous for p.Ala467Thr and p.Trp748Ser polymerase-γ (POLG) mutations. She was referred to the Rare Mitochondrial Disease Service in Newcastle. She now takes co-enzyme Q10 and has found rizatriptan and atenolol partially effective for migraine treatment and prevention. Recently, her 19-year-old brother (one of two siblings) presented with seizures. He has been confirmed to have identical POLG mutations.

DISCUSSION

Mitochondria are primarily responsible for energy production inside the cell; mitochondrial diseases manifest through a chronic failure to meet cellular energy demand, with highly active tissues such as those of the nervous system often prominently affected. The mitochondrial respiratory chain harnesses energy through oxidative phosphorylation to produce adenosine triphosphate. This unique chain of enzymes is maintained by two genomes, one nuclear (nDNA), and the other mitochondrial (mtDNA). POLG, a nuclear gene, encodes a subunit of the DNA polymerase which maintains healthy mtDNA inside the cell.

Recognition of the clinical and radiological 'signposts' for mitochondrial disease is important as this illuminates specific management considerations but is challenging as the phenotypic spectrum is broad and presentation often insidious. Mitochondrial diseases are common, with an estimated prevalence of 20 in 100,000 in the north of England.[1] The sum frequency in the general population of the 20 most common POLG mutations is approximately 2% (although it varies greatly between different populations) resulting in a calculated disease frequency of 1:10,000. This makes POLG-related disorders the most common of all the currently recognised mitochondrial diseases.[2] Nevertheless, POLG-related disorders may be under-diagnosed.

A wide spectrum of clinical manifestations has now been attributed to POLG mutations since they were first described in 2001.[3] Inheritance is autosomal recessive in the majority of cases. They can be categorised into one of several clinical phenotypes (Table 1) with the typical phenotype characterised by progressive external opthalmoplegia, ataxia, migraine and treatment resistant epilepsy. Knowledge of disease phenotypes is still evolving. Disease expression varies in timing from infancy to late adulthood and progression is unpredictable; fulminant epilepsy can develop suddenly late in the disease course.[4] Characteristic MRI findings include progressive posterior atrophy, while acute cortical swelling can occur due to epilepsia partialis continua, as demonstrated in this case.[5]

Obtaining diagnostic proof of mitochondrial disease can be challenging. While blood and cerebrospinal fluid lactate measurement, cardiac testing, EEG, neuroimaging and muscle biopsy may be useful (all of these tests can be normal in POLG-related disorders), a molecular genetic diagnosis is most definitive. This is most conveniently obtained from a blood sample as an initial test before proceeding to muscle biopsy.[6]

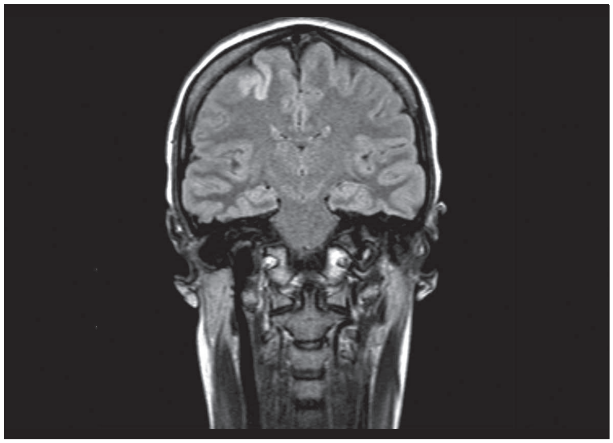

FIGURE 1 Cranial MRI (FLAIR sequence) showing high signal at the right frontal cortex. This appearance probably represents cerebral energy deficiency secondary to convulsive status epilepticus

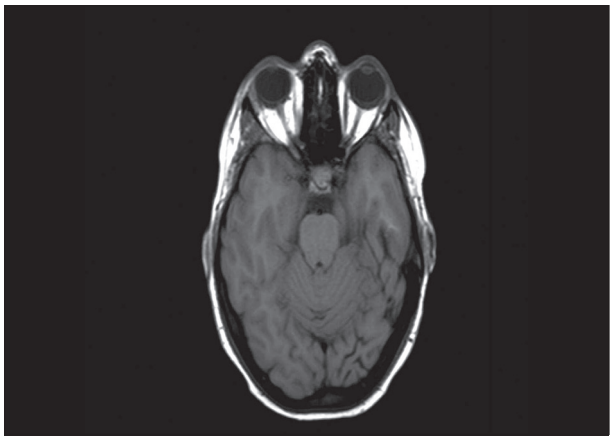

FIGURE 2 Cranial MRI (T1 sequence) showing atrophy of the left occipital lobe

When should testing for POLG gene mutations be considered? We recommend testing in young patients with drug-resistant epilepsy, patients with persistent stroke-like deficits and progressive neurological disability, especially sensory ataxia and hearing loss.

Unfortunately no disease-modifying therapies exist for patients with POLG mutations, though gene therapies are currently in early development. We believe use of newer anti-epilepsy drugs is often preferable to older drugs since, although no more efficacious, some have no or minimal hepatic metabolism and tolerability can be better. Intravenous magnesium may be helpful in refractory cases of convulsive status epilepticus.

J R Coll Physicians Edinb 2015; 45: 281–3

TABLE 1 Phenotypes associated with POLG gene mutations

Disease	Alternative/previous nomenclature	Principal features
Alpers-Huttenlocher syndrome		Severe childhood-onset encephalopathy with intractable epilepsy and hepatic failure
Childhood myocerebrohepatopathy spectrum		Infantile-onset developmental delay, lactic acidosis, myopathy
Myoclonic epilepsy myopathy sensory ataxia	Mitochondrial spinocerebellar ataxia with epilepsy	Spectrum of disorders with epilepsy, myoclonus, myopathy, and sensory ataxia
The ataxia neuropathy spectrum	Mitochondrial recessive ataxia syndrome, sensory ataxia neuropathy dysarthria and ophthalmoplegia	Ataxia (cerebellar and sensory) and neuropathy (axonal sensorimotor and sensory ganglionopathy). Can develop seizures and ophthalmoplegia
Autosomal recessive progressive external ophthalmoplegia		Progressive weakness of the extraocular muscles resulting in ptosis and ophthalmoparesis
Autosomal dominant progressive external ophthalmoplegia	Chronic progressive external ophthalmoplegia 'plus'	Ophthalmoplegia, generalised myopathy, sensorineural hearing loss, axonal neuropathy, ataxia, depression, Parkinsonism, hypogonadism, cataracts
Other (rarely) reported features		Psychiatric illness, chorea, diabetes mellitus, cardiomyopathy, retinopathy

Importantly, certain drugs can result in serious harm, notably sodium valproate (which can precipitate liver failure).[7] Other potentially toxic drugs include tetracycline, gentamicin and statins. Monitoring liver function tests, especially in the first few months after introduction of a new therapy, is paramount.

Genetic counselling is essential, especially so in females of child bearing age. Carriers (heterozygotes) of POLG mutations are usually asymptomatic, although rarely mild neurological symptoms have been reported. In the UK we recommend referral to the Rare Mitochondrial Disease Service, a nationally commissioned group that offers diagnostic testing and management advice.

KEY POINTS

1. Consider testing for POLG mutations in patients with drug-resistant epilepsy, migraine, sensory ataxia and hearing loss.
2. Many mitochondrial disorders can be diagnosed with blood tests without the need for muscle biopsy. In the UK a nationally commissioned service exists to aid this process.
3. Sodium valproate can precipitate liver failure in patients with POLG gene mutations and should be avoided.

REFERENCES

1 Schaefer AM, McFarland R, Blakely EL et al. Prevalence of mitochondrial DNA disease in adults. *Ann Neurol* 2008; 63: 35–9.
2 Cohen H, Chinnery PF, Copeland WC. POLG-Related Disorders *GeneReviews*. http://www.ncbi.nlm.nih.gov/books/NBK26471 (accessed 22/10/15).
3 Van Goethem G, Dermaut B, Lofgren A et al. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. *Nat Genet* 2001; 28: 211–2.
4 Tzoulis C, Engelsen BA, Telstad W et al. The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. *Brain* 2006; 129: 1685–92.
5 Engelsen BA, Tzoulis C, Karlsen B et al. POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. *Brain* 2008; 131: 818–28. http://dx.doi.org/ 10.1093/brain/awn007
6 Chinnery PF. Could it be mitochondrial? When and how to investigate. *Prac Neurol* 2006; 6: 90–101. http://dx.doi.org/10.1136/jnnp.2006.090050
7 Bindoff LA, Engelsen BA. Mitochondrial diseases and epilepsy. *Epilepsia* 2012; 53(Suppl): 92–7. http://dx.doi.org/10.1111/j.1528-1167.2012.03618.x