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POLG epilepsy presenting as new-onset refractory status epilepticus (NORSE) in pregnancy

Viva Levee ,[1] Karthikeyan Sivaganesh,[2] Andrew Schaeffer,[3,4] Kushan Karunaratne[1]

ABSTRACT

A 21-year-old woman developed explosive new-onset refractory status epilepticus when 18 weeks pregnant. She had been previously well with no history of seizures and a normal developmental history. She had initially presented with focal impaired awareness seizures but subsequently developed status epilepticus requiring intensive care unit admission and was successfully treated with multiple anti-seizure medications. Once stabilised she was stepped down to the inpatient neurology ward and then transferred to the tertiary centre for a planned late termination of pregnancy, which was the patient's choice. Following transfer, she again developed refractory status epilepticus, requiring intensive care readmission. Subsequent investigations identified a compound heterozygous POLG genetic mutation. We discuss the challenges in the acute clinical situation and important considerations in the diagnosis and management of POLG-related epilepsy.

CASE DESCRIPTION

A 21-year-old woman presented to a district general hospital with focal impaired awareness seizures when 18 weeks pregnant. She had no preceding febrile illness and was afebrile on admission. Seizure semiology comprised right upper limb extension followed by twitching and impaired awareness, progressing to bilateral tonic-clonic seizures. She had been previously well with no history of febrile seizures or meningitis in childhood, developmental delay, head injury or birth complications. Her paternal grandmother had a stroke at 16 years of age, and all close male relatives had short stature. There was no family history of deafness, epilepsy or other neurological disease.

Her focal seizures progressed to prolonged, refractory status epilepticus, requiring intensive care unit (ICU) admission. Seizure control was established with multiple anti-seizure medications. Intravenous corticosteroids were also given to cover for potential immune-mediated seizure pathology. Appropriate investigations found no underlying cause for the epilepsy. Her seizures stabilised and she was stepped down from ICU to the general neurology ward.

She was transferred to the tertiary centre hospital, under the obstetric team, for a late surgical termination of pregnancy at 23 weeks of gestation, in line with the patient's choice. On arrival, she was taking three anti-seizure medications (sodium valproate, phenobarbital and levetiracetam) and corticosteroids.

The day before the procedure, she again developed status epilepticus. There were two seizure semiologies: one involved right arm myoclonic jerks with preserved awareness; the second involved extensor posturing of the right arm, and flexor posturing of the left arm, progressing to generalised tonic-clonic activity.

An electroencephalogram (EEG) confirmed electroclinical status epilepticus. MR brain scan showed new abnormal cortical signal involving the left parietal, posterolateral temporal and occipital lobes (figure 1).

She was intubated, ventilated and loaded with phenobarbital. Once clinically stable for 48 hours, she underwent surgical termination of pregnancy. The differential diagnoses considered were mitochondrial disorders such as POLG (given the imaging changes and EEG showing a posterior propensity for seizure activity) or autoimmune encephalitis. Without a preceding febrile illness, we considered the febrile infection-related epilepsy syndrome subset of new-onset

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/pn-2024-004232).

[1]Imperial College Healthcare NHS Trust, London, UK
[2]Imperial College London, London, UK
[3]NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[4]Translational and Clinical Research Institute, Mitochondrial Research Group, Newcastle upon Tyne, UK

Correspondence to
Dr Kushan Karunaratne; kushan.karunaratne@nhs.net

Accepted 3 August 2024
Published Online First 28 August 2024

Check for updates

To cite: Levee V, Sivaganesh K, Schaeffer A, *et al*. *Pract Neurol* 2025;**25**:56–59.

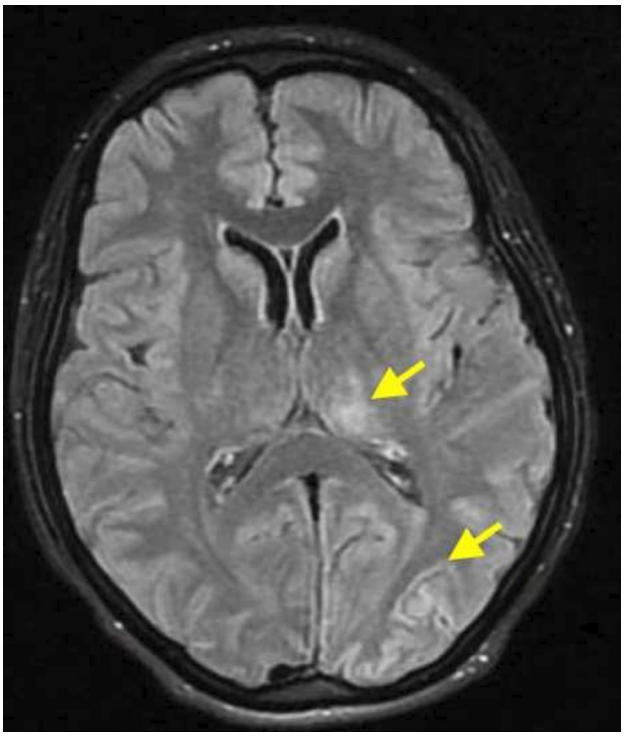

Figure 1 MR scan of brain T2 FLAIR 15/03: new abnormal cortical signal, involving the left parietal, posterolateral temporal and occipital lobes. FLAIR, fluid-attenuated inversion recovery.

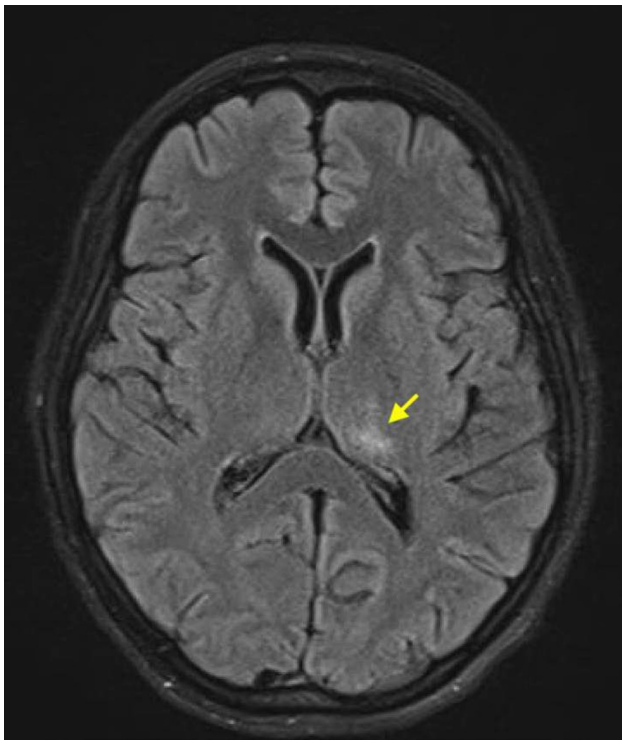

Figure 2 Repeat MR scan of brain T2 FLAIR 28/03: interval improvement of intracranial appearances would support a seizure-related cause of signal abnormalities. The persisting changes in the left posterior thalamus represent probable evolving gliotic scarring likely in the context of status epilepticus. FLAIR, fluid-attenuated inversion recovery.

refractory status epilepticus (NORSE) to be less likely. Cerebrospinal fluid (CSF) analysis showed a normal white cell count and protein concentration, with no oligoclonal bands. CSF was negative for viral PCR RNA and immune-mediated antibodies (anti-CASP2, NMDA, LGI1, GABA B, AMPA 1 and 2, GAD and glycine).

Once extubated, she remained in ICU with ongoing right arm jerking. Repeat EEG showed continuous repetitive discharges over the left posterior region, consistent with epilepsia partialis continua. Lacosamide was added as a fifth agent. Valproate was withdrawn given the possibility of POLG and thus concern about potential valproate hepatotoxicity.

Her seizure frequency improved over the next 4 weeks, and she was stepped down from the ICU. Abnormal jerking movements of the right arm persisted but were less frequent and self-terminating. Her mobility improved such that she could transfer with the assistance of two. Repeat MR scan of the brain with contrast showed persisting left thalamic changes, likely gliotic scarring (figure 2).

Her anti-seizure medications included phenobarbital 200 mg once daily, clobazam 10 mg twice daily, lacosamide 150 mg twice daily and levetiracetam 2 g twice daily. Weaning of prednisolone was recommended.

Subsequent POLG genetic testing on blood detected a biallelic compound heterozygous pathogenic variants in *POLG c.2243G>Cp.Trp748Ser* and *c.3720G>Cp*).

One year later there have been no further generalised seizures, but she reported occasional myoclonus, predominantly right sided, which worsens after exercise. Her jerks increased after reducing levetiracetam, which was reinstated. She has developed bilateral ptosis without ophthalmoplegia, with a right hemiparesis and a high-stepping gait.

Family members were offered genetic counselling and testing. We suggested holding further pregnancy plans until optimising the epilepsy (and her general physical and mental health).

A timeline is available as online supplemental material on the website summarising the sequence of events.

DISCUSSION

Genetics and pathogenesis

The nuclear POLG gene encodes polymerase gamma (POLG), forming the catalytic subunit of mitochondrial DNA (mtDNA) polymerase, an enzyme involved in repairing and replicating mtDNA.[1] Anagnostou *et al* identified 128 POLG pathogenic mutations associated with POLG epilepsy.[2] 84% had at least one of the pathogenic variants p.Ala467Thr, p.Trp748Ser and p.Gly848Ser.[2] A recent multicentre retrospective study of status epilepticus in POLG identified that 54% of those who developed status epilepticus were compound heterozygous for the pathogenic POLG variant.[3] Those with autosomal dominant disease did not develop seizures or status epilepticus.[3] Those associated with

Levee V, *et al*. *Pract Neurol* 2025;**25**:56–59. doi:10.1136/pn-2024-004232

early-onset disease were predominantly compound heterozygous (80%), whereas juvenile to adult onset were mainly homozygous (78%).[3]

These pathogenic mutations damage mitochondria, affecting metabolic pathways leading to neuronal depletion and degeneration.[4] Mitochondrial dysfunction and seizures cause further cell damage leading to enhanced adenosine triphosphate consumption (ATP).[5] The occipital cortex is extremely metabolically active and therefore vulnerable.[6] Unsurprisingly, this area is significantly involved in POLG epilepsy.

POLG disease has an 'acute-on-chronic' course. The onset of epilepsy probably reflects the development of focal necrotic lesions of the brain, visible on MR scans; such structural damage may further trigger seizures.[4]

POLG-related disease results in a clinical neurological spectrum including seizures, ataxia, peripheral neuropathy, encephalopathy and progressive external ophthalmoplegia,[3] each either in isolation or as part of a clinical syndrome. POLG mutations are the most common cause of mitochondrial epilepsy at all ages.[7]

POLG epilepsy

POLG-related epilepsy is a common presentation of POLG-related disease. About 50–80% of patients develop epilepsy at some point.[4] The most common seizure type is focal to bilateral tonic-clonic seizures with predominantly occipital epileptiform discharges.[3] Myoclonic seizures, epilepsia partialis continua, generalised status epilepticus and NORSE also commonly occur. A multicentre retrospective study found that status epilepticus occurred in over three-quarters of people with POLG epilepsy.[3] Over 70% of those with status epilepticus have refractory or super refractory status epilepticus, and especially those with early-onset disease.[3] POLG should clearly be considered as a cause of NORSE.

The onset of POLG epilepsy peaks in early childhood and adolescence, but rarely may present later in life.[8] It is more common in females, with risk of deterioration in pregnancy.[9]

Direct sequencing of the POLG gene is the gold standard method for diagnosing POLG-related epilepsy.[2] Prompt diagnosis is imperative as it impacts treatment, notably avoiding certain antiseizure medications, such as sodium valproate. EEGs provide diagnostic information. Most cases have occipital lobe predilection with focal changes, and this can be an early finding.[1 8] Serum lactate and muscle biopsy also support the diagnosis.[8]

Typical MR brain scan abnormalities include high T2/fluid-attenuated inversion recovery-weighted signal intensity lesions in the thalamus, occipital cortex, cerebellar white matter as well as cerebellar atrophy.[5 10] The occipital lobes seem especially involved in POLG disease yet epileptic activity in this region usually occurs before MRI lesions appear.[5]

NORSE in the context of POLG mitochondrial disease

NORSE is rare but more common in young, previously fit and healthy people, and especially adult females. The NORSE institute website recommends genetic testing as per section 6 in the diagnostic workup, which includes mitochondrial disorders such as POLG (https://www.norseinstitute.org/definitions).

Results for POLG genetic tests take time. Difficult clinical scenarios can arise where autoantibody-negative autoimmune encephalitis is a possible diagnosis, needing decisions regarding immunotherapy treatment. In these situations, the absence of markers of central nervous system (CNS) inflammation, relevant neuroimaging, EEG findings and seizure semiology typical for POLG (eg, explosive onset, myoclonic seizures, epilepsia partialis continua) help distinguish the two.

POLG epilepsy in pregnancy

Hikmat *et al* found almost all women with POLG who developed epilepsy during pregnancy were homozygous or compound heterozygous for the variants *p.Ala467Thr* and *p.Trp748Ser*.[9] The hyperoestrogenic state of pregnancy can worsen seizures and status epilepticus in pregnant women with pathogenic POLG mutations. High oestrogen is 'proconvulsant' as it contributes to increased concentrations of brain-derived neurotrophic factor, leading to the release of excitatory neurotransmitters, thus lowering the seizure threshold.[9] The heightened metabolic state during pregnancy increases lactate production, potentially further increasing mitochondrial stress.[9] Pregnancy in the context of POLG epilepsy is high risk and may be associated with preterm labour, pre-eclampsia and premature delivery.[9]

The termination of pregnancy in this case perhaps helped with seizure control.

Management

Valproate is absolutely contraindicated in anyone with POLG mutations as this can precipitate fulminant liver failure. Valproate causes hepatotoxicity through its action as a histone deacetylase inhibitor and also by inhibiting fatty acid beta-oxidation in the liver.[8] It further compromises mitochondrial function specifically in POLG disease without inhibiting *pol γ* or acting on the DNA replication pathway.

Medications that inhibit mitochondrial function should be used only cautiously.[1] Valproate should probably be avoided if there is any clinical suspicion of mitochondrial disease as well as if there are further indications of possible POLG disease such as neuroimaging and EEG findings of occipital lobe predominance. Any child or adolescent presenting with intractable seizures should probably be

screened for POLG before starting valproate.[11] This is something we should consider integrating into future clinical practice.

POLG epilepsy is severe and poses a therapeutic challenge as most patients are refractory to anti-seizure medications. There is currently no randomised trial evidence for the most effective combination of anti-seizure medication.[1] Patients with refractory status epilepticus require a mean of six anti-seizure medications as well as anaesthetic agents.[3] Terminating status epilepticus rapidly is a major priority. Epilepsy and optimisation of seizure frequency are the most important prognostic factors associated with increased morbidity and mortality in those with POLG disease.[4]

POLG-related epilepsy in pregnancy requires close input from the neurology and obstetric team. The main focus is to achieve rapid seizure control with anti-seizure medications such as carbamazepine, lacosamide and perampanel often used in combination with benzodiazepines such as midazolam in intensive care or clobazam on the wards.[4] Women of childbearing age should be counselled about the associated risks before and during pregnancy. Risk stratification for these patients is difficult, it has been suggested using EEG to look for posterior dominant changes,[9] but this has not been robustly studied.

Key points

- POLG may occur in isolation or as part of a syndrome with a combination of features including ptosis, chronic progressive external ophthalmoplegia and sensory ataxic neuropathy; relevant family history and neuroimaging consistent with POLG disease should also prompt relevant genetic testing.
- POLG may present with new-onset refractory status epilepticus, including in pregnancy.
- Early discussion with a mitochondrial specialist centre and reference to clinical guidelines is imperative to achieve the best patient-centred care.

Further reading

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There are patient-centred *Clinical Care Guidelines* available from the *Wellcome Centre for Mitochondrial Research* based within the Medical Centre of Newcastle University, including the management of epilepsy and specifically for pregnancy in mitochondrial disorders.

We advise using these guidelines and other resources on the website for the clinical management of these patients. There are also European consensus statements for ‘Stroke-like episodes’ (including POLG and drug use) and ‘Safety of drugs’ (referring to valproate) at the website mitochondrialdisease.nhs.uk.

Contributors VL, KS and KK conceived the idea for the paper. VL and KS wrote the first draft. KK and AS reviewed and edited the manuscript. VL revised the drafts, consented the patient and created the timeline. KK provided the imaging and is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement statement Patient consent has been obtained with use of BMJ consent form.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed by Lina Nashef, London, UK.

Data availability statement Data are available in a public, open access repository.

ORCID iD

Viva Levee http://orcid.org/0000-0003-4850-6791

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