British Society for Clinical Neurophysiology

*2018 Medical Student Essay Prize*

"How Clinical Neurophysiology helped in the diagnosis/management of a patient"

# Epilepsia partialis continuous as a consequence of POLG gene mutation: a new frontier in treatment using cathodal transcranial direct current stimulation

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## Introduction

Around 1 in 200 children born in the UK carry pathological mutations in their mitochondrial DNA, with approximately 1 in 6500 going on to develop serious mitochondrial disorders as a result[1]. This case report describes the spontaneous onset of multiple neurological symptoms in a previously fit and well 15-year-old girl, later found to possess a c.1399G>A, p.Ala467Thr mutation in her mitochondrial DNA. Clinical neurophysiology played a leading role in this case, assisting with both the diagnosis and the management of the patient.

## Case report

In June 2015 a previously healthy right-handed 15-year-old female presented to her local hospital with a prolonged generalised tonic clonic seizure (GTCS). The patient was apyrexial and required intubation and ventilation for a period of 48 hours. After extubation, the patient went on to develop focal jerking of her left upper limb proceeding to involve the rest of her body, which was initially refractory to multiple anti-epileptic drugs (AEDs). This pattern would continue periodically and EEG monitoring confirmed non-convulsive status epilepticus (see Figure 1). Investigations were performed in order to exclude infective, metabolic or structural causes. These included routine blood biochemistry and haematology, anti-NMDAR and anti-VGKC antibodies, CSF analysis and MRI of head and pelvis, all of which were normal. The patient eventually improved spontaneously and, after an admission lasting a total of 3 days, was discharged home with a regimen of oral phenytoin and levetiracetam.

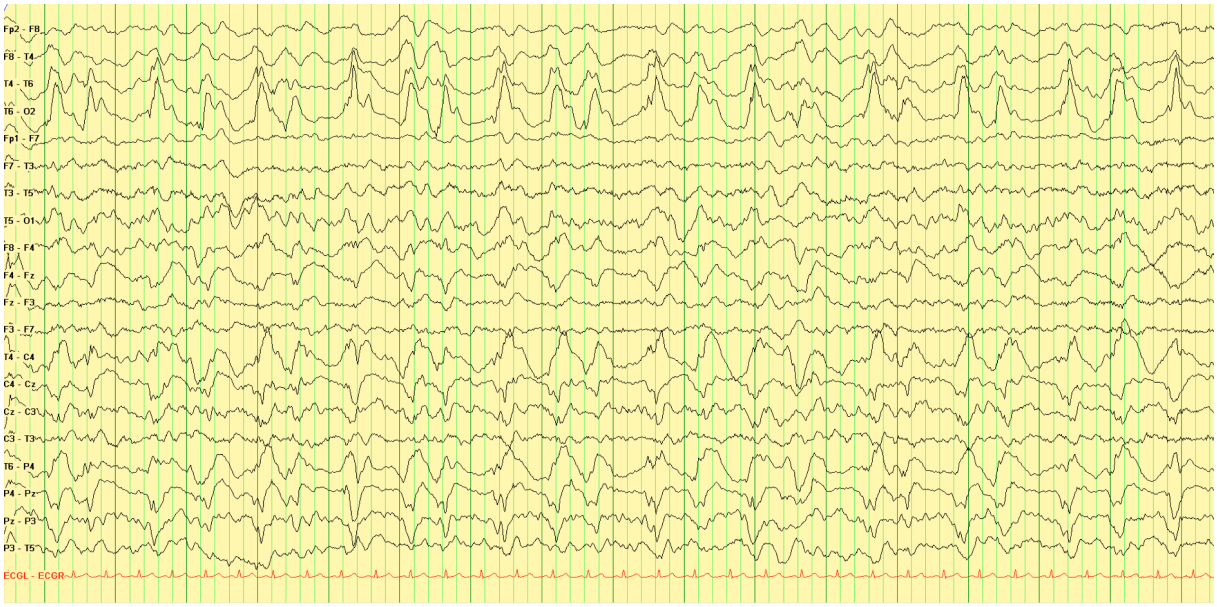


**Figure 1 EEG recorded in July 2015 confirming on-going subconvulsive status epilepticus arising from the right posterior hemisphere**

One month later the patient returned to hospital, this time presenting with a history of five GTCS in rapid succession. A two day antecedent period was marked by symptoms including headache, unsteadiness, positive visual phenomena (described by the patient as coloured circles), and hypersomnolence. Once more the seizures were refractory to AEDs, in this case a combination of phenytoin, valproate, levetiracetam, and the patient again required intubation and ventilation. Following extubation she was encephaolpathic and exhibited regular focal motor seizures limited to her left upper limb. An EEG was performed, this time showing epilepsia partialis continua (EPC) via the right occipital leads. The patient was subsequently transferred to the regional neuroscience centre. Her electro-clinical course was characterised by focal status epilepticus with periodical generalisation, along with a new epileptic focus involving her right upper limb. Hyperintense regions involving the right occipital and posterior parietal lobes were visualised on the patient's MRI (see Figure 2). The seizures remained refractory to AEDs throughout, with a number of agents trialled. The patient was transferred to the paediatric intensive care unit (PICU) for thiopentone infusion titrated to achieve burst suppression pattern on EEG monitoring (see Figure 3). Head cooling was also performed as an adjuvant therapy.

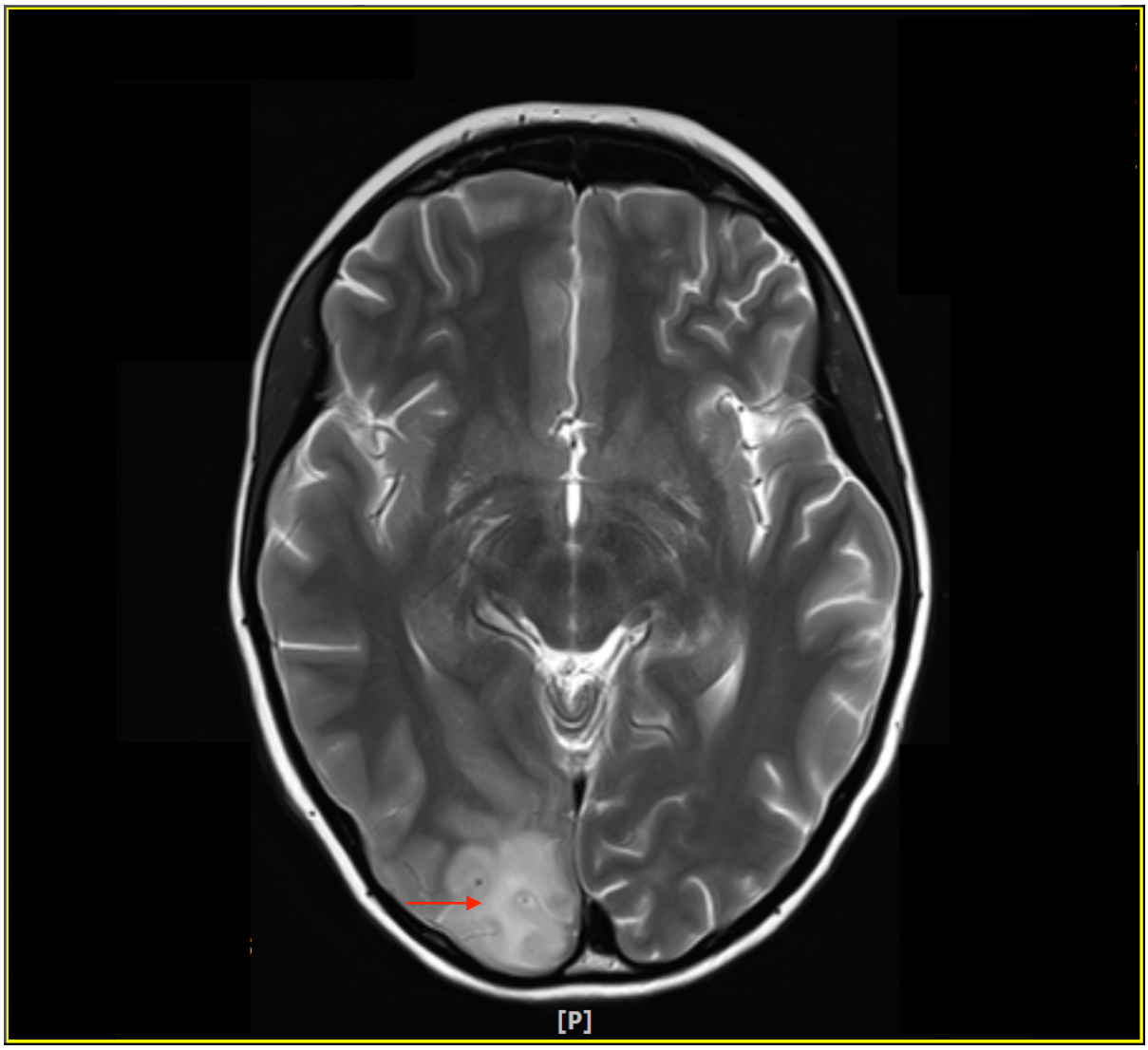


Figure 2 Axial T2WI FLAIR MRI showing hyperintensity in the right occipital lobe (red arrow)

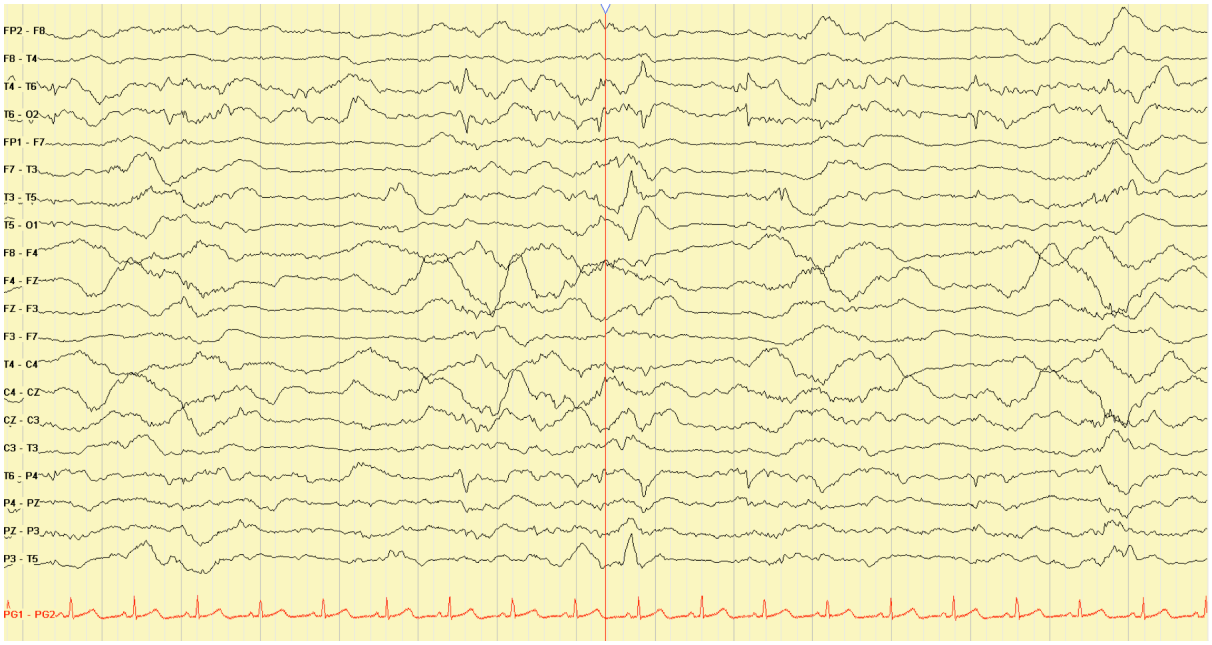


Figure 3 EEG recorded during PICU admission demonstrating burst suppression pattern. Patient intubated and ventilated, and on maximum dose of thiopentone.

After an 11 day recovery period following the withdrawal of thiopentone, the patient regained consciousness and went to have several days without a seizure. She then, however, continued to have on-going focal electrical status epilepticus according to EEG monitoring. Once more she was found to be encephalopathic. The patient remained on PICU for a period of 3 weeks before being discharged back to the ward, where she continued to suffer intermittent focal motor status epilepticus, particularly involving her right arm, right leg, and right paraspinal muscles (see Figure 4). This proved refractory to medical approaches involving IV phenobarbitone and benzodiazepines, and caused considerable pain and distress. Following in-depth discussion with Clinical Neurophysiology, approval was sought from the hospitals' Institutional New Interventional Procedure Committee for treatment in the form of cathodal transcranial direct current stimulation (tDCS; see below for further information). The tDCS therapy was delivered over the presumed seizure focus location according to EEG data. During each 20 minutes period of tDCS administration the regularity of seizures decreased significantly, although went on to increase in frequency immediately following the treatment period. After 3 days post-tDCS, however, the seizures abated completely (see Figure 5). 4 weeks later the seizures returned once more so a second course of tDCS was administered lasting for a total of 14 days.

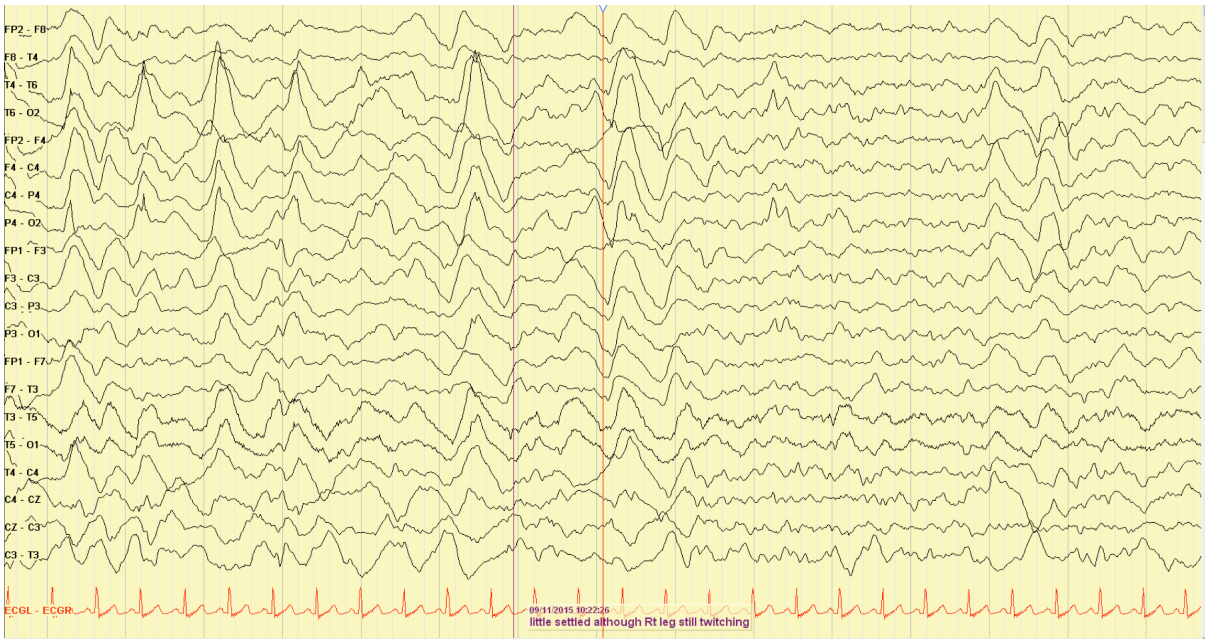


**Figure 4 Patient experiencing right leg twitching. EEG shows diffuse encephalopathy with focal abnormality in right posterior quadrant.**

The patient remained as an inpatient for the subsequent 4 months before she was discharged home. On-going intensive physical rehabilitation was provided in the community. Six months after discharge the patient had returned to school with some additional educational support. At a review during this time, she reported some unsteadiness but was able to walk unaided. She continues to suffer periodic, brief sensory seizures involving the right side of her body. She currently receives a course of levetiracetam 1750mg twice daily, phenobarbitone 90mg twice daily, and perampanel 8mg once daily. Clinical examination at this time revealed slight myoclonic jerks, decreased visual acuity affecting both eyes, restricted upgaze, astereognosis limited to her right side, areflexia, and an ataxic gait.

Gene sequencing was performed, including direct sequencing of the POLG gene, due to the high suspicion of a POLG-related mitochondrial disorder on the basis of the series of refractory EPC episodes suffered by the patient, with an occipital focus. A homozygous mutation c.1399G>A, p.Ala467Thr was identified. See Figure 6 for an overall timeline of events.

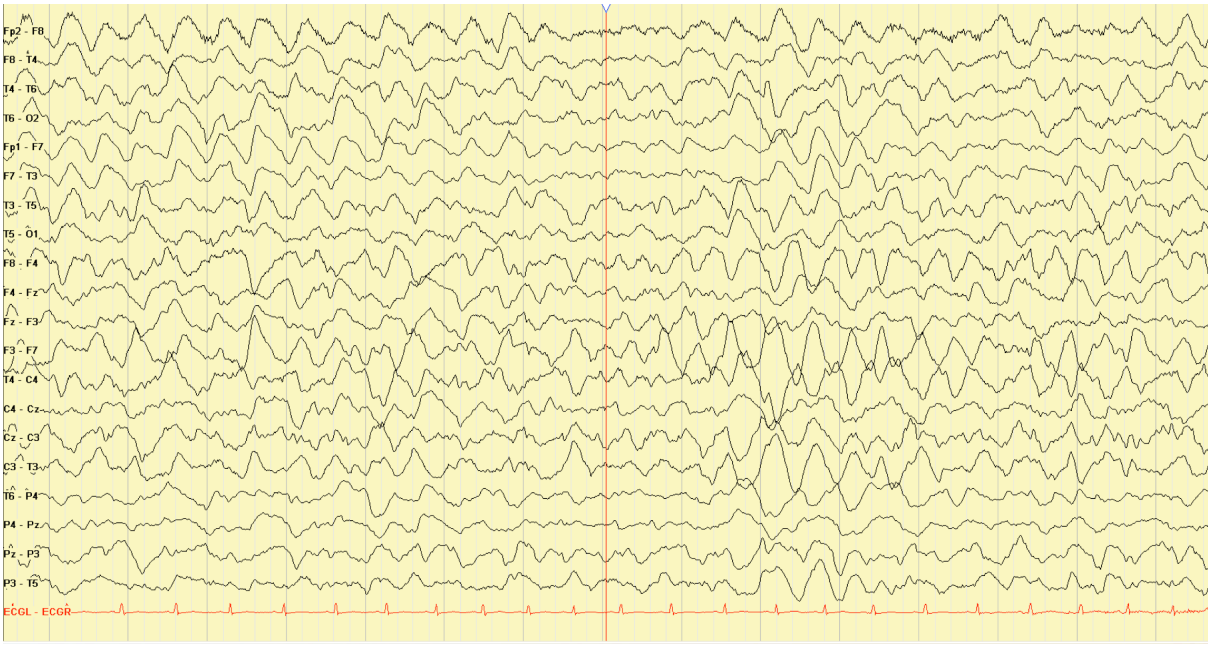


**Figure 5 EEG recorded post-tDCS demonstrating absence of seizure activity, with background encephalopathy.**

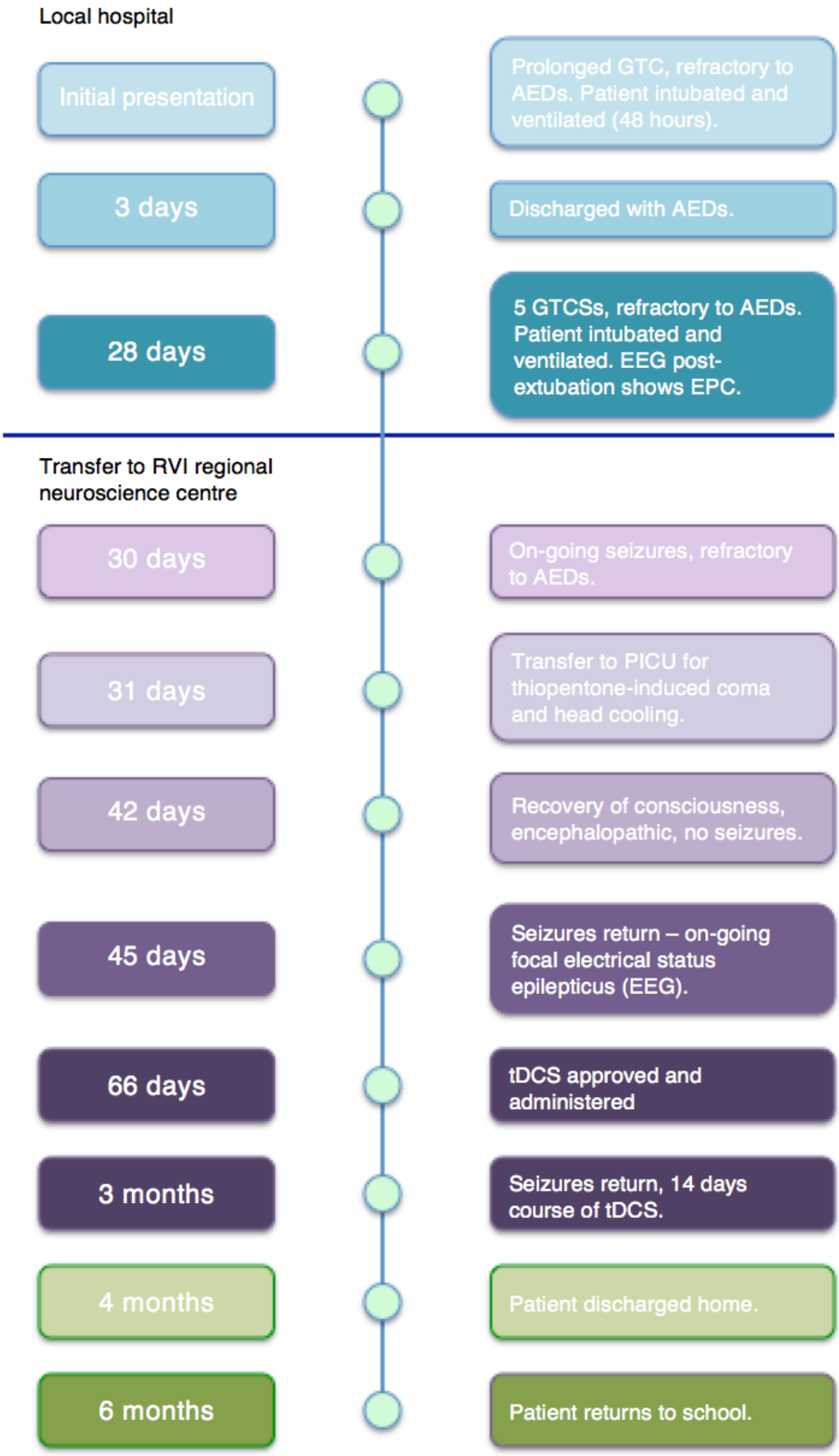


Figure 6 Timeline of events

# Discussion

## POLG gene

Polymerase gamma (pol γ) is a trimeric DNA polymerase protein complex that is active in mitochondrial DNA (mtDNA) where its functions include replication and proof-reading-based repair. Mitochondrial DNA is replicated continuously, independent of the cell cycle, as a result of the activity of a heterotrimeric protein known as pol γ (195 kDa). The POLG gene (chromosome 15q25) encodes the catalytic subunit of pol γ (140 kDa), and the POLG2 gene (chromosome 17q) encodes for its accessory dimeric subunit (55 kDa)[2]. The catalytic subunit has several functions; DNA polymerase, 3' → 5' exonuclease and 5'dRP lyase[3]. The dimeric subunit assists with processivity and DNA binding[4], increasing the affinity of pol γ for the DNA template. POLG mutations result in the depletion of mtDNA and are said to be a major cause of inherited mitochondrial syndromes[5].

## Mitochondrial disorders and epilepsy

The mutation (c.1399G>A, p.Ala467Thr) identified in the patient described in this case report is pathogenic and associated with a number of conditions including, but not limited to, mtDNA depletion syndrome, Alpers' syndrome[6], myoclonic epilepsy myopathy sensory ataxia, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO)[7], progressive external ophthalmoplegia[8], and POLG-related spectrum disorders[9]. It is the complexity relating to the heterogeneity of clinical signs and symptoms that poses a significant diagnostic challenge. A previous multi-centre study involving patients under the ago of 12 examined a total of 27 patients with confirmed POLG gene mutations. The study identified epilepsy in a number of patients (n=19/26, 73%), although note its absence in patients with the myocerebrohepatopathy syndrome[10]. Similarly to this case report, the same study also found that seizures typically began as focal seizures, evolving to bilateral GTCS (n=14/19, 74%). EEG was performed and found to show pathological changes in the majority of patients and epileptiform wave patterns were most commonly seen in the occipital region[10], again in keeping with the patient in this case report. MRI findings reported in this study further suggest a predominance of focal cortical lesions affecting the occipital lobes, appearing as hyperintensities involving cortical and subcortical areas on T2/FLAIR sequences[10].

In a separate study, the epileptic phenotypes of 56 children with a range of 'respiratory chain disorders' (1990 – 2006) were investigated. Six age-related epilepsy phenotypes were identified, including 4 cases (7%, median 71 months, range 14 – 120 months) of EPC. Tzoulis et al. similarly describe a typical pattern of seizures starting as simple motor seizures affecting an upper limb and then progressing to EPC[11]. In their study of 26 cases of patients with POLG gene mutations, Tzoulis et al. describe a progressive neurological disorder encompassing epilepsy, ataxia, neuropathy, myoclonus and late onset ophthalmoplegia, normally beginning in patients' teenage years[11]. This study describes occurrence of epilepsy in the majority of patients (22/26, 85%), with the presence of epileptiform focus in the occipital region during EEG monitoring[11], further supporting the predominance of POLG gene disorders affecting this region as seen in this case report patient. Furthermore, Tzoulis et al. propose that amino acid substitutions 1399G/A and 2243G/C with A467T and W748S respectively, lead to a recessive mitochondrial ataxic syndrome[11]. The former substitution is, of course, the one concerning the patient in this case report.

## Transcranial direct current stimulation technical details

Transcranial direct current stimulation (tDCS) is a form of non-invasive neuromodulation involving the delivery of low levels of constant direct current (1 – 2mA) to specific locations within the brain, pertaining to the origin of clinical signs and symptoms. The traditional tDCS configuration involves attaching two electrodes are attached to the patient's scalp. Electrode placement may be made with reference to the International 10/20 EEG system[12]. This involves measurements between nasion and inion, as well as left pre-auricular and right pre-auricular regions to create a series of reference points (see Figure 7). There are myriad permutations of electrode placement and current flow that may be explored according to clinical requirement, although the discussion of this is beyond the scope of this essay. Anodal tDCS causes depolarisation of the resting membrane potential (RMP) leading to an increase in neuronal excitability. Cathodal tDCS causes a hyperpolarisation in the RMP, thus decreasing the excitability and firing of neurons[13,14]. The effects of tDCS can last beyond the completion of the therapeutic sessions themselves, extending over a period of time afterward[15]. The period of time is determined by tDCS duration and intensity[16].

### *Transcranial direct current stimulation methods used in this case*

The configuration used in the treatment of the patient in this case study involved locating the cathode over the site of lesions seen on serial MRI scans indicative of the cause of the patient's pathology (see Figure 2). Furthermore, EEG data demonstrating phase-reversal in adjacent leads indicating seizure activity corresponded with changes visualised on MR imaging, concordant with suitable electrode placement location. The location in this case was T6 and this led to the placement of the cathode over the right occipito-temporo-parietal region (see Figure 7).

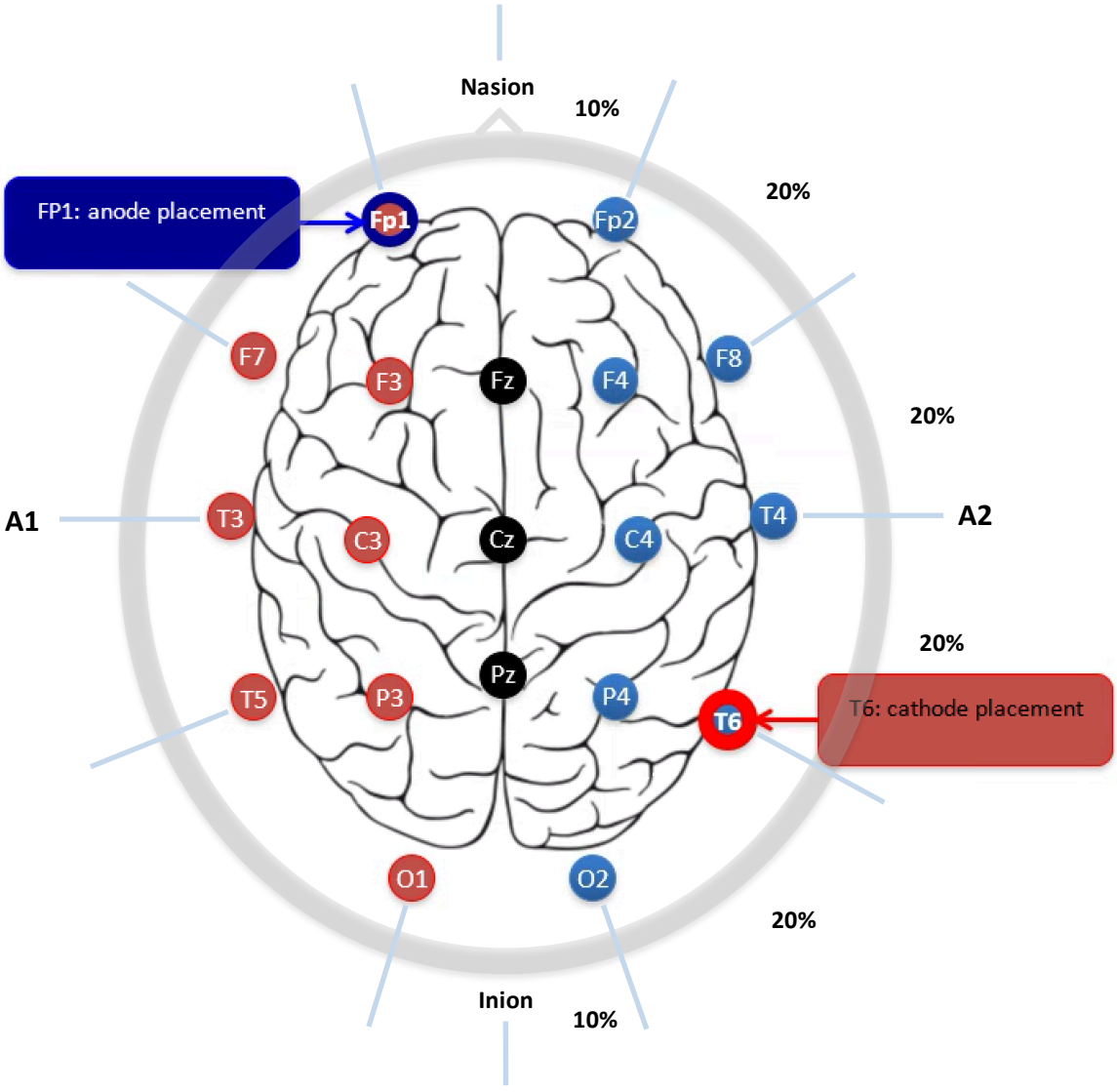


Figure 7 Electrodes placement in this case. F = frontal, T = temporal, P = parietal, O = occipital, A1 = left pre-auricular, A2 = right pre-auricular

FP1 was selected as the site for anode placement, due to its contralateral location with respect to T6, as well as its position far away from any lesions seen on either MRI or EEG. This decreased the risk of causing further seizure activity through the excitatory effects of anodal stimulation. The parameters used in the tDCS therapy for the patient included a stimulus intensity of 2 mA for duration of 20 minutes. The safety of these parameters is supported by evidence within a number of studies carried out wherein a total of 176 children received tDCS (0.7 mA – 2.0 mA, 9 – 20 minute sessions) with no occurrence of serious adverse events[17,18,19,20].

## Transcranial direct current stimulation

There is a building interest in the application of tDCS for treatment of many neurological conditions, including focal epilepsy. Investigations into the use of tDCS in the treatment of a wide variety of epileptic conditions encompass patients of all ages. One particular case report details the case of 30-month-old child with a diagnosis of early onset epileptic encephalopathy[21]. While the results of this study did not demonstrate a reduction in the frequency of seizures, they did show a reduction in inter-ictal sharp wave amplitudes after treatment with high-definition tDCS. Bikson et al. carried out a review of evidence concerning the safety of tDCS wherein they examined the under 18-year-old population. No serious adverse effects were reported during 2800 sessions involving 500 child patients[22]. A randomised controlled trial (RCT) encompassing 36 child patients, aged between 6 – 15 years old, examined the safety and efficacy of the use of cathodal tDCS in cases of focal epilepsy[20]. Children were divided into active and sham groups, with the active group receiving 1 mA cathodal tDCS for a period of 20 minutes. EEG recordings carried out over a 4 week period showed decreased epileptiform discharge per 30 minute period in the active group. After the 4 week period, however, levels of epileptiform discharged had recovered to baseline level. An earlier comparable study (also 1 mA current delivered for a period of 20 minutes) although examining an adult rather than a child population showed similar decrease in the frequency of EEG epileptiform activity as well as seizure frequency[23].

Weaknesses in examining cases of tDCS use in intractable epilepsy within the literature include small sample size, model of epilepsy variation, variation in the current and duration of therapy (per session and per course), and electrode placement location

variation. Another important consideration is the nature of the developing child's brain. Between the ages of 12 – 18 humans undergo brain development processes such as reduced synapse density[24], cognitive circuitry refinement[25], continuing myelination and increasing volume of white matter, as well as fractional anisotrophy[26] (a measure of the degree to which water diffusion is constrained according to microstructural white matter organisation). This indicates the requirement for future studies to plan for longitudinal follow-up and comparison of brain development in tDCS patients with that of non-tDCS children and adolescents.

## Conclusion

The mitochondrial disorders described above carry a very poor prognosis, with a relentless course and no current available cure[28]. Disease morbidity and mortality can, in fact, be closely linked to epilepsy severity and it is not uncommon for these patients to suffer fatal outcomes during episodes of refractory status epilepticus[11].

In this case of a teenager suffering potentially fatal refractory seizures related to POLG gene-related mitochondrial disorder, tDCS was an effective therapy. Refractory seizures similarly affect a large number of patients suffering from mitochondrial disorders so this finding could potentially be beneficial to a wide number of them. Further research is warranted to elucidate the efficacy, as well as the long-term effects on the developing brain, of this treatment that may lead to significant improvement in quality of life for this patient group.

***Word count***

| Section | Words |
|---|---|
| **Main text** | 2305 |
| **Captions** | 117 |
| **Figures** | 140 |
| **Total** | **2562** |

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