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Recurrent super-refractory status epilepticus and stroke like episode in a patient with Behr syndrome secondary to biallelic variants in OPA1 gene

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ABSTRACT

Behr syndrome is associated with compound heterozygous dysfunction in *OPA1* gene and typically presents with a constellation of visual impairment due to early onset optic atrophy, cerebellar ataxia, peripheral neuropathy, deafness, and gastrointestinal motility problems. Our patient with biallelic variants in *OPA1* gene had delayed motor milestones, cerebellar ataxia, and optic atrophy in infancy. At the age of 7 years, he presented with recurrent episodes of super-refractory status epilepticus and metabolic stroke due to underlying mitochondrial dysfunction associated with *OPA1* gene dysfunction. Besides the two rare prior case reports of focal and myoclonic seizures in patients with Behr syndrome, epilepsy in general is not well described in the typical phenotypic spectrum and to the best of our knowledge. Dramatic clinical presentation with recurrent super-refractory status epilepticus and metabolic stroke has not been reported previously. There is only one prior report of metabolic stroke in a patient with Behr syndrome due to *OPA1* gene dysfunction.

Introduction

Behr syndrome was first described by Carl Behr in 1909. The typical phenotype includes early onset-optic atrophy, spasticity, spinocerebellar ataxia, peripheral neuropathy, gastrointestinal dysmotility and cognitive impairments. About a century later, authors reported cases of the Behr syndrome phenotype in patients with biallelic pathogenic variants in *OPA1* [1,2,3,4]. The *OPA1* gene encodes the mitochondrial protein OPA1, which belongs to the GTPase dynamin family. It localizes to the inner mitochondrial membrane and is felt to be essential to multiple mitochondrial processes, including inner mitochondrial membrane fusion, cristae structuration, maintaining integrity of the respiratory chain, apoptosis, and mitochondrial DNA maintenance [5]. The pathophysiology of this disorder is felt to be due to the lack of these key mitochondrial functions, but the specific pathophysiology remains poorly understood. In contrast to Behr syndrome, which is associated with biallelic pathogenic *OPA1* variants, and is therefore autosomal recessive in inheritance, monoallelic pathogenic variants in *OPA1* are associated with autosomal dominant optic atrophy (DOA), also known as optic atrophy, type 1. Individuals with this condition develop optic neuropathy and gradual vision impairment in first decade of life [5]. The "DOA plus" phenotype, seen in the most severely affected individuals with monoallelic pathogenic variants in *OPA1,* includes extra-ocular signs like deafness, ataxia, peripheral sensory- motor axonal polyneuropathy and chronic progressive external ophthalmoplegia [3].

There are scarce reports of seizures in patients with Behr syndrome [6,7]. Besides motor delay, ataxia and early onset bilateral optic atrophy, our patient with biallelic pathogenic *OPA1* gene variants had a unique presentation with recurrent episodes of super-refractory status epilepticus and metabolic stroke. Status epilepticus has not previously been reported to occur in this condition and there has been a single prior report of metabolic stroke [7].

Clinical presentation, diagnosis, and treatment

Our patient was born preterm at 35 + 6/7 weeks gestation via vacuum assisted vaginal delivery with a birth weight of 2483 g. Pregnancy was complicated by maternal tobacco use. There was no report of significant postnatal complications. Per parent's report, he was noted to have bilateral nystagmus since birth which gradually worsened through infancy. Optometry evaluation was obtained at 9 months of age and was reportedly reassuring. At the patient's 15 month well child check, his

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pediatrician saw the nystagmus and placed a pediatric ophthalmology referral. He was noted to have delayed gross motor milestones (sat independently at 12 months).

He presented to our institution at the age of 17 months. Detailed ophthalmology evaluation revealed bilateral congenital optic atrophy, a large area of retinal pigment epithelium atrophy and decreased visual acuity bilaterally (~20/260), coupled with a reduced scotopic electroretinogram response. Magnetic resonance imaging (MRI) of his brain with and without contrast obtained at 17 months was normal. During his initial consultation with pediatric neurology at 2 years of age, besides the ocular findings, he was noted to have generalized hyporeflexia with preserved muscle tone and strength, occasional high amplitude intention tremors, possible dysmetria and wide-based ataxic gait. He was delayed mainly in gross motor and fine motor domains with age-appropriate language milestones.

Following a consultation with genetics, he underwent further testing which included a normal chromosomal microarray and a 16 gene optic atrophy panel, which revealed compound heterozygous pathogenic variants in the *OPA1* gene: c.2287del (p.Ser763Valfs*15) and c.1311A > G (p.Ile437Met). Subsequent testing showed that the c.2287del (p.Ser763Valfs*15) variant was maternally inherited and the c.1311A > G (p.Ile437Met) variant was paternally inherited. He was diagnosed with Behr syndrome due to the combination of his clinical findings and genetic testing results.

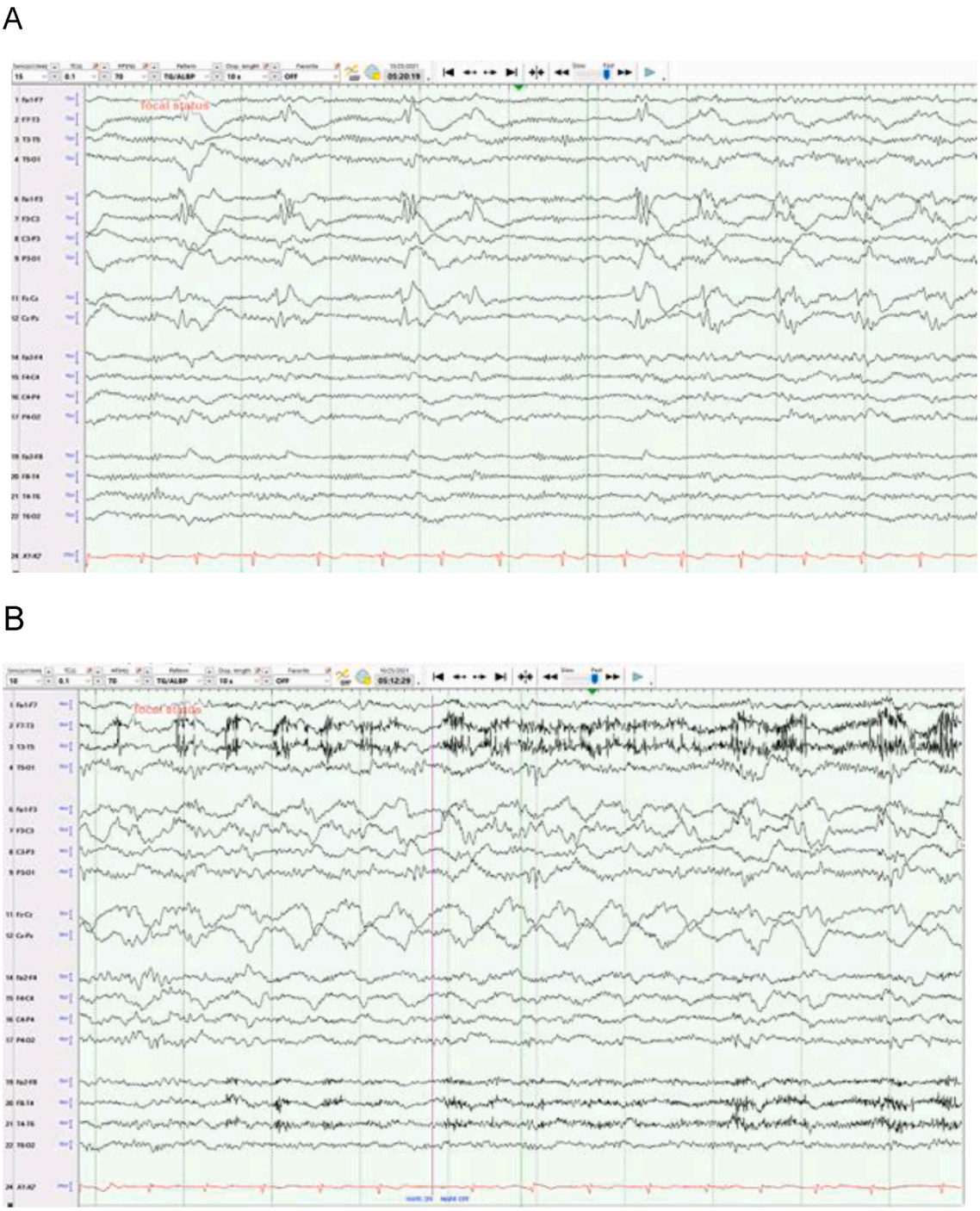

Fig. 1. EEG with longitudinal bipolar montage from first admission showing (A) lateralized periodic discharges and (B) focal status epilepticus in the left parasagittal region with rhythmic sharp waves with voltage maximum in F3, P3 and Cz electrodes.

At the age of 7 years, he presented to the local Emergency Department (ED) with status epilepticus, which was his first seizure in his lifetime. The seizure was prolonged (>30 min) and unprovoked, consistent with right sided focal motor seizures with retained awareness. Electro-encephalogram (EEG) showed left lateralized periodic discharges (Fig. 1A) and focal status epilepticus in the left parasagittal region with rhythmic sharp waves with voltage maximum in F3, P3 and Cz electrodes (Fig. 1B). He was treated with intravenous (IV) doses of lorazepam, levetiracetam, phenobarbital, fosphenytoin, lacosamide, propofol infusion (<24 h) and finally pentobarbital infusion coma for 4 days, with which status epilepticus resolved. MRI brain with and without contrast showed a small focus of diffusion restriction with FLAIR (Fluid- attenuated inversion recovery) hyperintensity in the left frontal cortex that had quickly resolved on repeat MRI brain that was obtained 3 days later and therefore was thought to represent a post-ictal change. He was discharged home on maintenance dosing of levetiracetam, lacosamide and modified ketogenic diet.

He was readmitted 5 days later for recurrence of status epilepticus with prolonged unprovoked right focal motor seizures, which resolved after administration of multiple doses of benzodiazepines and propofol infusion for 24 h. MRI brain did not show findings concerning for stroke. EEG after resolution of clinical seizures, showed focal non– convulsive status epilepticus originating in the right temporal region in T4, T6 electrodes (Fig. 2). Clobazam was started in addition to continuing levetiracetam, lacosamide and ketogenic diet. He was discharged after 9 days. At the time of discharge, he could no longer walk, had lost most of his ability to speak, and required nasogastric tube feeds due to aspiration. After therapy, he eventually regained a few useful words, but went on to require gastrostomy placement.

About a month later, the patient presented with a third recurrence of status epilepticus. He had focal motor seizures with impaired awareness characterized by right facial twitching and rhythmic shaking of right upper extremity lasting 45 min which resolved following administration of intranasal midazolam, IV diazepam and levetiracetam. Following clinical resolution of status epilepticus, he was awake, not following verbal commands, but was localizing to painful stimuli on the left. He was noted to have right hemiparesis which was attributed to Todd's paralysis. However, due to lack of clinical improvement after several hours of observation, MRI brain was obtained which demonstrated multiple new foci of acute diffusion restriction in the left thalamus, left median parietal lobe, left parieto-occipital cortex, and left frontal cortex. The distribution of these lesions did not follow a vascular territory, which raised suspicion for metabolic stroke (Fig. 3). As his mental status was not improving after completion of MRI brain, continuous EEG monitoring was started and showed waxing and waning continuous 100–400 mcV spike and polyspike- wave discharges mainly in left posterior electrodes (O1, T5, P3 with occasional spread to O2) concerning for focal non-convulsive status epilepticus (Fig. 4). He received boluses of IV lorazepam, lacosamide and fosphenytoin without significant improvement in EEG and therefore he was started on pentobarbital infusion which resulted in burst suppression. Pentobarbital was eventually weaned after 12 days with recurrence of intermittent subclinical seizures off pentobarbital.

He was febrile with a temperature of 103.1F upon admission. Due to fever, he underwent sepsis work-up which was nonrevealing including cerebrospinal fluid (CSF) analysis which was unremarkable with negative meningitis -encephalitis panel and a negative CSF culture. The pediatric genetics team was consulted due to metabolic stroke, and they recommended a trial of IV arginine infusion which he tolerated well with no side effects, but which did not lead to improvement of the suspected stroke radiologically or clinically. Repeat MRI brain obtained 19 days after admission showed evolution of previous diffusion restriction abnormalities in the left cerebral hemisphere and left thalamus and a new area of increased gray matter T2/FLAIR signal in the left frontal lobe, representing likely interval infarct. He was discharged home after a 30-day hospitalization on levetiracetam, clobazam, topiramate and epidiolex. Lacosamide and ketogenic diet were discontinued during this admission since they were felt to be ineffective in controlling the seizures.

On his follow up 6 months after discharge, he was clinically seizure free. He was receiving intensive physical, occupational and speech therapy. He had regained the ability to stand with support and has recovered function of his right upper and lower extremities. He could speak 2–3-word phrases.

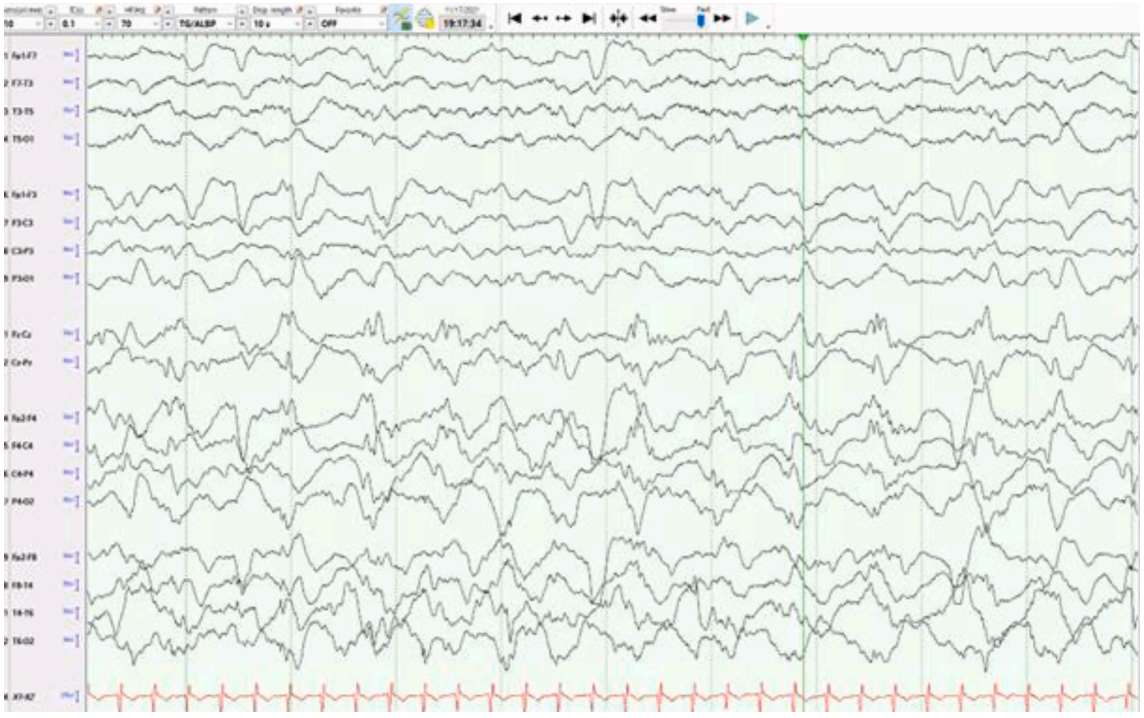

Fig. 2. EEG from second admission showing focal status epilepticus originating in the right temporal region in T4, T6 electrodes.

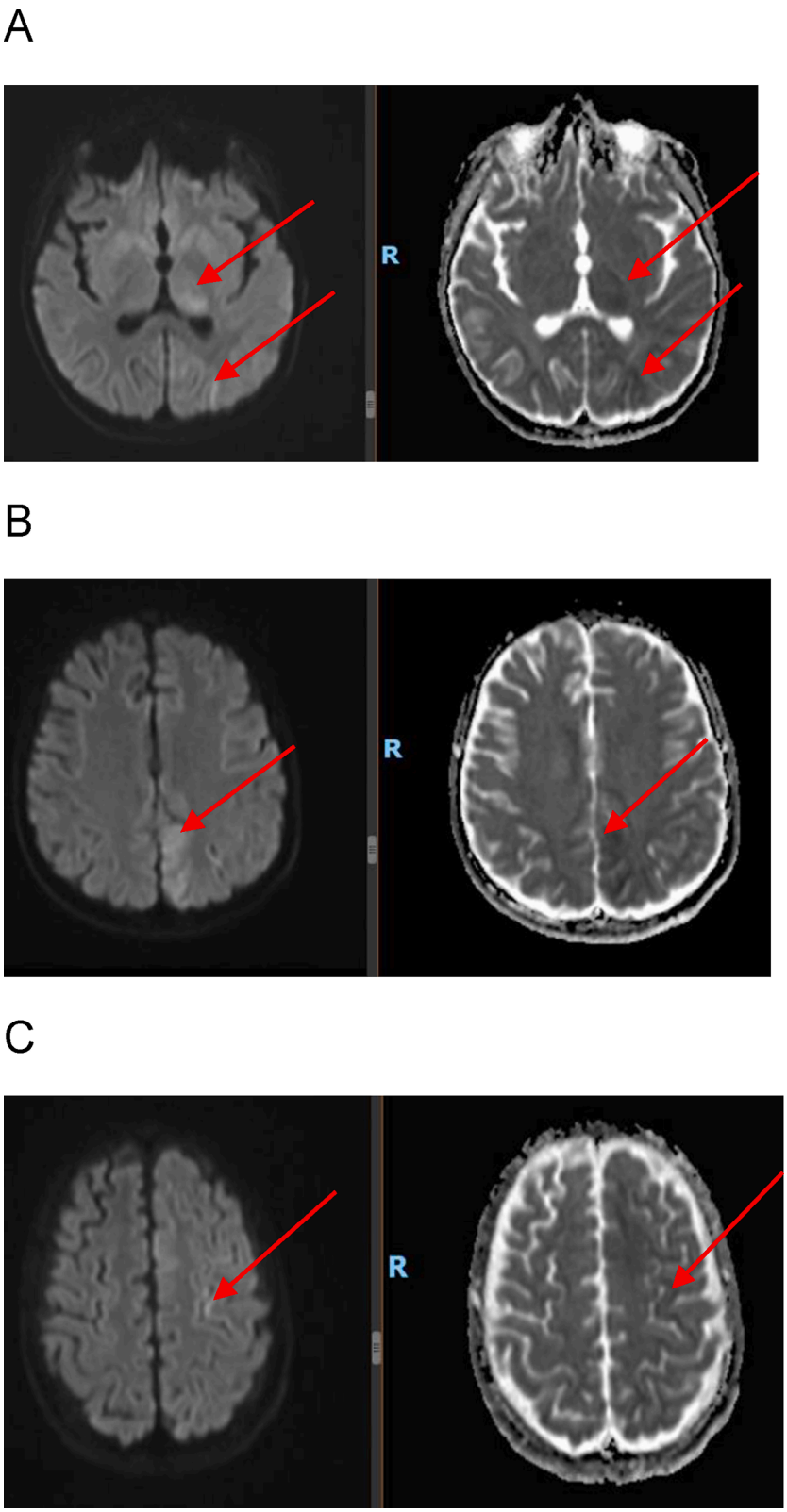

Fig. 3. MRI brain with DWI (diffusion- weighted imaging) and ADC (apparent diffusion coefficient) showing diffusion restriction in (A) left thalamus and cortical gray matter near the left parieto-occipital junction, (B) median left parietal lobe, and (C) left frontal cortical gray matter.

Discussion

The *OPA1* gene encodes an intra- mitochondrial dynamin which plays a crucial role in mitochondrial fusion, cristae structure, maintaining integrity of the respiratory chain, apoptosis, and mitochondrial DNA maintenance [5]. Biallelic pathogenic variants in *OPA1* gene are known to cause Behr syndrome and our patient had typical phenotypic features of Behr syndrome including early-onset bilateral optic atrophy, motor delay, and cerebellar ataxia, but had a novel clinical presentation with recurrent super-refractory focal status epilepticus.

Fig. 4. EEG during third admission showing focal status epilepticus with continuous rhythmic spike and polyspike- wave discharges in left posterior quadrant.

Seizures are rarely reported in patients with Behr syndrome. Nasca et al reported a young boy who at the age of 4 years, developed myoclonic seizures in addition to developmental delay, cerebellar atrophy, and optic atrophy. EEG showed poor organization of cerebral activity and sharp waves in occipital regions. Seizures were reportedly well controlled, but he developed psychomotor regression at the age of 8 years after an episode of accidental head trauma [6]. Another report of seizures in Behr syndrome is in a 12-year-old girl with prolonged focal seizures, myoclonic jerks, and metabolic stroke. Seizures responded well to anti-seizure medications (ASMs) per report [7].

In contrast to the two previously reported cases, our patient had a dramatic presentation with recurrent super-refractory focal status epilepticus which required escalation of treatment with multiple ASMs finally needing pentobarbital coma and emergent initiation of ketogenic diet, which was ultimately found to be ineffective. This unique clinical presentation has not been previously reported in patients with Behr syndrome. All 3 clinical presentations in our patient were consistent with focal convulsive status epilepticus, which after the initiation of treatment with anti-seizure medications, demonstrated resolution of motor manifestations but continued as non-convulsive electrographic status epilepticus needing escalation of treatment.

Seizures are common in children with mitochondrial disorders with a prevalence of 20 to 60 % [8,9]. The pathophysiology of seizures in mitochondrial disorders is felt to be due to impaired oxidative phosphorylation leading to ATP deficit. This results in an imbalance between excitatory and inhibitory neurons that leads to excessive neuronal excitation and seizures [10]. Unique features seen more commonly in seizures due to mitochondrial disorders include onset in the posterior quadrant and occipital lobe, non-convulsive status epilepticus and epilepsia partialis continua lasting months, which can be medically intractable from the onset and may at times have a minimal EEG correlate. These intractable seizures often lead to progressive neurodegenerative changes and epileptic encephalopathy [8]. All seizure types have been described in patients with mitochondrial disorders and EEG findings can be variable including background slowing, focal/multifocal or generalized epileptiform discharges or hypsarrhythmia in infants [11]. Our patient's EEG demonstrated continuous ictal activity in the left posterior electrodes (O1/P3/T5) with no clinical correlate, consistent with focal non-convulsive status epilepticus during his most recent admission.

Benzodiazepines, fosphenytoin, levetiracetam and lacosamide are the first line agents for treatment of status epilepticus in patients with mitochondrial disorders [12]. Phenobarbital and propofol are also used, although it must be noted that patients with mitochondrial disorders are at higher risk to develop propofol infusion syndrome [12,13]. Valproic acid is contraindicated in patients with mitochondrial disorders, especially in patients with POLG1 dysfunction as it may cause fulminant hepatic failure and carnitine deficiency [14]. Ketogenic diet has been reported to be efficacious in treatment of seizures in mitochondrial disorders [15]. We avoided valproic acid in our patient and used propofol for a short duration (<24 h) without any complications. There have also been reports of fatal propofol infusion syndrome when propofol is used along with ketogenic diet as the former impairs fatty acid oxidation [16]. Our patient was not on ketogenic diet and propofol simultaneously. He did not have any adverse effects from any of the medications administered or the ketogenic diet.

While the super-refractory recurrent status epilepticus was the dominant and exceptional feature of our patient's clinical presentation, the occurrence of a stroke like episode (SLE) is also noteworthy. Although SLEs are known to occur in mitochondrial disorders like Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) and Myoclonic Epilepsy with Ragged Red Fibers (MERRF), Leigh syndrome, and Kearns Sayre syndrome (KSS), they have been reported only once in association with Behr syndrome [7].

The exact pathogenesis of SLEs in mitochondrial disorders is unclear. The proposed theories include regional breakdown of mitochondrial energy metabolism in the brain with failure of oxidative phosphorylation and production of reactive oxygen species, mitochondrial angiopathy in the setting of mitochondrial dysfunction in the smooth muscle cells of small cerebral vessels which results in vascular occlusion with neuronal loss [17,18,19]. It is also thought that recurrent and prolonged seizures increase the neuronal energy demand thereby exacerbating the energy deficit which in turn provokes further seizures in a vicious cycle and may also lead to stroke like episodes [12].

Although there have been studies of IV arginine for treatment of metabolic stroke in adults, there is limited literature on its use in

children [21,22]. Despite this, it is commonly recommended by mitochondrial specialists. Reduced synthesis of nitric oxide and its precursors (arginine and citrulline) is thought to play a part in causing SLEs in mitochondrial disorders [20,22]. Ganetzky et al reported use of IV Arginine in 9 pediatric patients with a total of 17 SLEs. About 47 % of acute stroke-like episodes showed a positive clinical response to IV arginine and 6 % of episodes showed clinical improvement that could not be directly attributed to IV arginine response as other concurrent therapies (e.g., antiepileptic treatment) were also used. Arginine was found to prevent not only the progression of SLE but was also beneficial in treating recurrent SLEs. No adverse events were reported in this study [21]. Our patient had no adverse effects with Arginine although it did not clearly seem to help as repeat MRI showed new lesions concerning for stroke.

Conclusions

We report a patient with biallelic pathogenic variants in *OPA1* gene who, in addition to the typical features of Behr syndrome, had a unique presentation with recurrent super-refractory status epilepticus and metabolic stroke. Status epilepticus has not been previously reported in Behr syndrome. Occurrence of metabolic stroke is extremely rare in this condition.

Ethical statement

All authors mentioned in the manuscript have read and approved the manuscript prior to submission.

Our research has not been submitted or published elsewhere.

No patient identifiers have been used in the case report.

CRediT authorship contribution statement

Spoorthi Jagadish: Writing – review & editing, Writing – original draft, Conceptualization. **Amy R.U.L. Calhoun:** Writing – review & editing. **Sreenath Thati Ganganna:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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