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Case Report

Response to immunotherapy in a patient with adult onset Leigh syndrome and T9176C mtDNA mutation

Miguel Chuquilin [a,*], Raghav Govindarajan [b], Dawn Peck [c], Esperanza Font-Montgomery [c]

[a] Department of Neurology, University of Missouri in Columbia, Five Hospital Drive CE 537 DC 047.00, Columbia, MO 65212, USA
[b] Department of Neurology, University of Missouri in Columbia, Five Hospital Drive CE 537, Columbia, MO 65212, USA
[c] Department of Genetics, University of Missouri in Columbia, 404 N Keene St, Suite 101, Columbia, MO 65201, USA

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ABSTRACT

Leigh syndrome is a mitochondrial disease caused by mutations in different genes, including ATP6A for which no known therapy is available. We report a case of adult-onset Leigh syndrome with response to immunotherapy. A twenty year-old woman with baseline learning difficulties was admitted with progressive behavioral changes, diplopia, headaches, bladder incontinence, and incoordination. Brain MRI and PET scan showed T2 hyperintensity and increased uptake in bilateral basal ganglia, respectively. Autoimmune encephalitis was suspected and she received plasmapheresis with clinical improvement. She was readmitted 4 weeks later with dysphagia and aspiration pneumonia. Plasmapheresis was repeated with resolution of her symptoms. Given the multisystem involvement and suggestive MRI changes, genetic testing was done, revealing a homoplasmic T9176C ATPase 6 gene mtDNA mutation. Monthly IVIG provided clinical improvement with worsening when infusions were delayed. Leigh syndrome secondary to mtDNA T9176C mutations could have an autoimmune mechanism that responds to immunotherapy.

1. Introduction

Subacute necrotizing encephalomyelopathy was first described by Leigh in 1951 and has since been referred to as Leigh disease or Leigh syndrome. Leigh syndrome is a devastating, neurodegenerative disorder with almost identical radiological and pathological changes but marked clinical and genetic heterogeneity. Patients usually present with progressive decline of central nervous system function due to focal, necrotizing lesions of the basal ganglia, diencephalon, cerebellum or brainstem. Clinical features include regression or psychomotor delay, weakness, hypotonia, truncal ataxia, intention tremor, lactic acidosis in blood, cerebrospinal fluid or urine [1]. Leigh syndrome is usually a disorder of infancy and early childhood although rare adolescent and adult cases have been reported. The prognosis is usually poor and most patients usually die before age 5 [1]. There is no known treatment. We report a patient with juvenile-adult onset of Leigh syndrome and apparent response to immunotherapy.

2. Material and methods

Case report.

3. Results

A 20 year old woman with learning disability and problems during school, non-athletic and described by family members as “clumsy” suffered a car accident in February 2015. This was followed by development of hypersomnia, frequent falls, increased headaches with migraine features, intermittent diplopia, bladder incontinence, behavioral changes with apathy, poor hygiene, irritability and disinhibition. She could not perform her activities of daily living (ADL) independently.

Her past medical history was significant for asthma, migraines and attention deficit hyperactivity disorder (ADHD) for which she used dextroamphetamine when she was 11 years old (discontinued due to development of paranoid behavior). She had normal motor milestones and was toilet trained at 18 months. She had speech problems since early age, with stuttering that needed speech therapy. Her school performance was below her peer levels and she had an individualized education program (IEP) until high school. Her family history was significant for migraines in her mother. The patient had 2 half-brothers on her father side, one had learning disability, delayed speech milestones and exercise-induced asthma. The other half brother had

* Corresponding author.
E-mail addresses: chuquilinaristam@health.missouri.edu (M. Chuquilin), govindarajanr@health.missouri.edu (R. Govindarajan), peckda@health.missouri.edu (D. Peck), fontmontgomerye@health.missouri.edu (E. Font-Montgomery).

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diagnosis of glycogen-storage disease type 3A (Cori disease). Home medications included amitryptiline 10 mg at bedtime, sumatriptan 25 mg PRN and medroxyprogesterone acetate 400 mg IM q3 months.

On admission on 03/24/15 she was oriented ×3, had Medical Research Council (MRC) 3/5 strength in proximal upper and lower extremities and 4/5 in distal lower extremities and she could not do tandem gait. Cranial nerves II–XII, sensation and deep tendon reflexes were normal. Brain MRI showed bilateral T2/FLAIR hyperintensity in the basal ganglia (Fig. 1A, B). Cerebrospinal fluid (CSF) showed 21 mg/dl protein, 64 mg/dl glucose, 0 white blood cells (WBCs) and 3 red blood cells (RBCs). Oligoclonal bands were absent. Other tests such as VDRL, antinuclear (ANA) panel, Mayo Clinic paraneoplastic panel, serum protein electrophoresis, CSF Herpes simplex virus polymerase chain reaction (PCR) were normal or negative. Nerve conduction study in March 2015 showed small distal peroneal and tibial compound muscle action potentials (CMAP) amplitudes bilaterally. Electromyography was not tolerated by the patient. Computed tomography of chest, abdomen and pelvis was normal.

Due to acute/subacute onset and progressive symptoms in a young female patient, an autoimmune etiology was suspected and she underwent 5 sessions of plasmapheresis with improvement of her behavior, bladder incontinence, and muscle strength. She was able to walk with a walker and perform her ADLs on her own. She was discharged to a rehabilitation center on 04/03/15 and readmitted on 04/21/15 for dysphagia leading to aspiration and respiratory distress needing intubation. Examination showed primary gaze horizontal nystagmus, mild bifacial weakness, 3/5 muscle strength in deltoid, iliopsoas, quadriceps, tibialis anterior (with other muscles being 4/5), deep tendon reflexes were 1+ in biceps and triceps and absent in lower extremities. She was unable to walk or stand and failed her bedside swallow evaluation.

Brain MRI showed progression of T2/FLAIR hyperintensity in the bilateral basal ganglia, substantia nigra, midbrain, periaqueductal grey matter, and 2 foci of restricted diffusion within the left lentiform nucleus (Fig. 1C–E). CSF showed 11 mg/dl protein, 54 mg/dl glucose, with 0 RBC and WBCs. CSF lactic acid was elevated at 2.9 mmol/l. CSF myelin basic protein was elevated at 5.79 ng/ml. Serum lactate and pyruvate were normal. CSF NMDA-R, VGKC, GAD65, GABA-B, AMPA-R, ANNA-1 were negative. CSF and serum samples tested negative for mGluR1, mGluR5, LGI, Caspr2, MOG and AQP4 antibodies and there was no reactivity to suggest antibodies against unknown cell surface antigens. Urine organic acids, acylcarnitine profile, serum aminoacid profile were normal. Urine aminoacid testing showed generalized aminoaciduria. Fluorodexyglucose (FDG) PET scan in April 2015 showed increased uptake within the caudate and basal ganglia bilaterally (Fig. 1F). She received antibiotics for aspiration pneumonia, and 5 sessions of plasmapheresis with improvement of swallowing, and muscle strength to 4/5.

Patient was discharged to rehabilitation center and started receiving IVIG every 4 weeks with continued improvement of her behavior and strength, including going from walking with assistance of a walker to walking independently. She had episodes of paranoia that also improved. At 3 months follow up after discharge patient was oriented ×3, followed commands, cranial nerves were normal, strength was 4+/5 in hip flexion and otherwise 5/5, reflexes were 2+ all over and she could walk albeit a little unsteady but without support.

Given her baseline learning difficulties, coordination problems and brain MRI pattern suggestive of mitochondrial disease further genetic evaluation was performed. Karyotype was 46, XX. Whole exome array CGH + SNP analysis was normal. Mitochondrial genome testing showed a homoplasmic T9176C mutation in the MT-ATP6A gene which has been described in 1–5% of patients with Leigh Syndrome. Nuclear genome testing showed a new c.3483-7_3509del34 heterozygous mutation in polymerase gamma (POLG) that destroys the canonical splice acceptor site in exon 22. She also had mutations of unknown clinical significance in DARS2 (c.228-20dupT) and LRPPRC genes (c.1529 C > G).

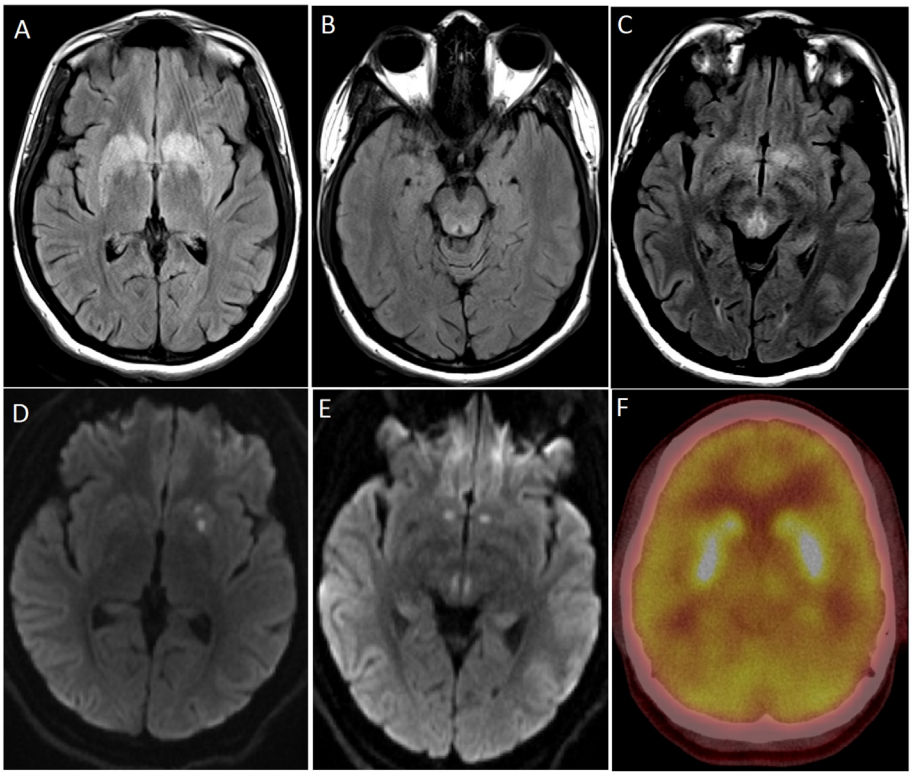

Fig. 1. (A and B) Brain MRI FLAIR sequence on 1st admission shows bilateral basal ganglia and periaqueductal area hyperintensity. (C) Brain MRI FLAIR sequence on 2nd admission shows worsening hyperintensity in bilateral basal ganglia and periaqueductal area. (D and E) Brain MRI DWI sequence shows diffusion restriction in left lenticular nucleus and periaqueductal area. (F) FDG PET shows increased uptake in bilateral basal ganglia.

Table 1
Cases of T9176C MT- ATP6A mutations reported in the literature.

Ref #	Sex Age of onset	Clinical features	Mutation load	MRI /NCS/EMG	Treatment	Prognosis
5	Girl 3 yo	Girl: Ataxia, nystagmus, slurred speech after febrile illness	100% homoplasmic	CT: bilateral basal ganglia hypodensities	None described	Girl: Recovered over 12 months. No more episodes up to 8 yo
	Mother 29 yo	Mother: sudden ataxia, headache, blurry vision, nystagmus	Mother 96%	Mother: normal MRI, serum lactate		Mother: improved over 9 months
	Boy 5 yo from different family	Boy: ataxia, slurred speech, lethargy after flu like illness, hypotonia, hyperreflexia		MRI:hyperintensities cauda, globus pallidus, pons		Boy: improved but has residual coordination and lethargy problems, "absence–like" events at 10 yo
6	3 females (30–48 yo)	Maternally–inherited, late–onset hereditary spastic paraparesis Spastic paraparesis, lower extremity hyperreflexia and distal weakness, pain, reduced vibration sense	100% homoplasmic	MRI: Normal EMG: normal or axonal neuropathy Normal serum lactate and pyruvate	None	All alive, men more disabled than women
	2 males (30–50 yo)					
7	Girl: 21 m	Cerebellar ataxia, speech delay, dystonia, respiratory distress, exacerbated by viral infections with attacks of paraparesis, dystonia, sighing, dyspnea	Siblings: 90–95% Mother: 25%	CT: Bilateral hypodensities cerebellum, pons, midbrain	Boy and girl that survived received vitamin B complex, vitamin E, carnitine	1 girl died
	Boy: 24 m					Boy: 8 yo cerebellar ataxia, dystonia, pyramidal syndrome, only speaks a few words, mental retardation
	Girl: 24 m					Girl 6yo: mild speech delay, ataxia
8	Boy 3 yo	Ataxia, lethargy, apnea after febrile illness	Boy 100% homoplasmic	MRI hyperintensities basal ganglia, thalamus, periaqueductal, periventricular, medulla	None described	Boy died after 1 month
	Mother 22 yo	Mother: developmental delay, progressive mental retardation, ataxia, nystagmus, pyramidal signs	Mother 93% Asymptomatic maternal uncle: 88% Asymptomatic maternal grandmother: 76%	Mother MRI: mild cerebellar atrophy		Mother: ataxia, nystagmus, mental retardation
9	2 brothers; 4 and 5 m	Poor sucking, hypotonia, brisk reflexes, hearing loss, no visual contact	>95% Asymptomatic mother: 80%	Brothers: leukodystrophy, diffuse cerebral and cerebellar white matter hyperintensity, posterior limb internal capsule	None	Died at 7 and 10 months of age
10	Woman 22 yo	Acute diplopia, blurry vision, eyelid ptosis, tachycardia, respiratory distress, seizures, ataxia	>99% homoplasmic	MRI bilateral hyperintensity pons, midbrain, diencephalon PET: reduction glucose metabolism in cerebral and cerebellar cortex	None described	Woman: not described
	Brother 4 yo	Brother: Leigh syndrome				Brother died 7 yo
	Mother	Mother: mild mental retardation	Mother: 30.5%			

(continued on next page)

Table 1 *(continued)*

11	Boy 12 m	Hyperpnea, microcephaly, external ophthalmoplegia, dystonia, developmental delay	100%	Familial bilateral striatal necrosis MRI hyperintensity putamen, periaqueductal region	None described	6 yo: needs to hold onto furniture, severe language delay, static
	Boy 8 yo	Headache, altered mental status after viral illness, language regression, dystonia, chorea, myoclonus	98% Unaffected mother: 7% Unaffected brother 55% Unaffected sister 76%			11 yo: learning disabled, poor coordination, motor tics, static
12	Boy 9 m	Seizures, hypotonia, coma during febrile illness	>95% Unaffected mother 50% Unaffected maternal uncle: 70%	CT hypodensity basal ganglia, brainstem	None described	Died within hours
	Boy 9 m	Coma, periodic breathing, seizures, pyramidal signs, following febrile illness				Died within 3 weeks
13	Boy 6 m	Hypotonia, developmental delay, seizure, retinitis pigmentosa	>95%	MRI Hyperintensity basal ganglia, midbrain, pons	None described	Bedridden at age 10
	Boy 8 yo	Ataxia, chorea, neuropathy, abnormal eye movements	>97%			Mental retardation age 9
	Boy 3 yo	Ataxia, pyramidal signs, dysarthria, oculomotor palsy, mental retardation	97% Unaffected mother 52%			Slowly progressive
This patient	20 yo	Long history clumsiness, language and learning problems, worse after car accident	100% homoplasmic	MRI Hyperintensity bilateral basal ganglia, periaqueductal area	IVIG, plasmapheresis Carnitine 1500 mg BID Coenzyme Q10 200 mg TID Vitamin B50 complex Lipoic acid 400 mg TID Vitamin E 200 IU qday Vitamin C 100 mg TID Selenium 25 μg qday	Improvement after plasmapheresis and IVIG infusions Deterioration when IVIG is delayed

Ref: reference number; m: months; yo: years-old; BID: twice a day; IU: international units.

4. Discussion

Leigh syndrome is associated with defects in the pyruvate dehydrogenase complex, electron transport chain complexes I, III, IB, ATP synthase and mitochondrial electron transport assembly proteins. These abnormalities are due to mutations in mitochondrial and nuclear genes. The most commonly mutated mitochondrial gene is ATPase 6, with the most frequent mutation being 8993T > G. The nuclear gene most frequently mutated in Leigh syndrome is SURF1 [1].

Our patient met criteria for clinical diagnosis of Leigh syndrome due to her progressive neurologic disease with cognitive, behavioral and motor symptoms, signs of brainstem and basal ganglia disease, elevated CSF lactate, and compatible brain MRI pattern [2].

Leigh syndrome has characteristic neuroimaging findings with symmetrical T2 hyperintensities in deep grey matter including thalamus, lentiform and caudate nuclei, periaqueductal grey matter and midbrain tegmentum [1].

Our patient history and presentation is peculiar because although she had prolonged history of learning problems, clumsiness and poor athletic performance, she developed new symptoms of diplopia, behavioral changes, incontinence, generalized weakness and headache rather subacutely after a motor vehicle accident, all of which responded to immunomodulatory therapies such as plasmapheresis and IVIG. Although the subacute clinical presentation, increased uptake on PET scan and improvement with plasmapheresis or IVIG suggested a possible autoimmune mechanism; the MRI pattern was more in link with metabolic or mitochondrial disease, which led us to do genetic testing that showed the known T9176C mutation in ATP6A associated with Leigh syndrome.

Our patient is also heterozygous for a POLG mutation affecting the splice acceptor site at exon 22. POLG mutations can cause conditions such as Alpers syndrome, progressive external ophthalmoplegia (PEO) or sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO). Our patient did not have clinical evidence of POLG-related disease, including liver failure, myoclonic seizures or PEO; although she had small peroneal and tibial CMAP amplitudes which can be secondary to myopathy or motor neuropathy (she refused repeated nerve studies and muscle biopsy). Although our patient's POLG deletion has not been described before, and it affects a splice site, it is not necessarily pathogenic on its own. Skipping exon 22 would either cause nonsense mediated decay of the transcript or, if translated, make a dysfunctional DNA polymerase [3]. An Alpers syndrome patient compound heterozygous for A467T and 3482 + 2T- > C splicing POLG mutations has been reported. His asymptomatic father had the 3482 + 2T- > C mutation, which affects the splicing of intron 21 and is very close to our patient's mutation [4]. Based on this report, we think that our patient's POLG mutation is likely recessive and non-clinically manifest on its own, as she had no mutation in the other allele.

The ATPase 6 gene encodes part of the mitochondrial F0-F1 ATP synthase (complex V of oxidative phosphorylation). Complex V is

composed of at least 16 subunits, of which 2 (ATP6 and 8) are mtDNA-encoded. Complex V synthesize ATP utilizing the proton gradient created by the respiratory chain complexes I–IV [5,6]. The T9176C mutation in ATPase 6 results in the replacement of a highly conserved leucine residue (aminoacid 270) by proline. In the literature there are reported cases of patients with the T9176C mutation and most of them presented with Leigh syndrome; although other presentations include bilateral striatal necrosis, hereditary spastic paraparesis, ataxia and mental retardation (Table 1) [5–13]. The prognosis is usually poor in cases of Leigh syndrome, although the 3 cases described by Wilson only had one episode of neurological deterioration, triggered by a viral or febrile illness, followed by spontaneous improvement over 9–12 months with a very good prognosis [5].

The reason for our patient's clinical improvement after plasmapheresis and IVIG treatment is unclear since Leigh syndrome is a mitochondrial disease. Although her CSF was normal (including negative oligoclonal bands) and serum and CSF testing for cell surface antibodies was also negative; her brain PET scan showed hypermetabolism in bilateral basal ganglia corresponding to her MRI hyperintensities. Mitochondrial disorders such as POLG mutations, mitochondrial neurogastrointestinal encephalopathy (MNGIE), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and Leigh syndrome have been reported to have hypometabolism in PET scan [14–18]; although acute MELAS lesions can also have hypermetabolism [19]. It is known that PET hypermetabolism can also be seen in autoimmune encephalitis [20] and we believe that our patient's PET findings are related to an underlying autoimmune process triggered by her mitochondrial disease which can explain her improvement after immunotherapy. There are published cases of mitochondrial diseases such as Leber's hereditary optic neuropathy (LHON), PEO and POLG mutations mimicking multiple sclerosis or acute demyelinating encephalomyelitis (ADEM) including the presence of oligoclonal bands [21,22]. There is also a case of inflammatory mitochondrial myopathy secondary to a tRNA Leu mtDNA mutation that responded to IVIG infusions [23]. Although we do not know the actual mechanism for our patient's response immunotherapy, we can postulate a hypothesis. The T9176C is a known pathogenic mtDNA mutation and affects ATP synthesis [6,24]. Reduced ATP production can increase the mitochondrial transmembrane potential (with resultant hyperpolarization) and increase reactive oxygen species (ROS) production [25]. ROS are known damage-associated molecular patterns (DAMPs) that can activate the necroptosis pathway [26]. Impaired ATP synthesis can also induce necroptosis [27]. Cell necrosis can lead to release of immunogenic material and activate immune and inflammation pathways (inflammasome) [26,28]. In ischemic stroke models, it has been shown that IVIG can suppress inflammasome-mediated neuronal death [29].

5. Conclusions

Leigh syndrome secondary to T9176C mutations may have an underlying autoimmune mechanism amenable to immunotherapy. Further research on the role of the inflammation/immune pathway activation in patients with Leigh syndrome and T9176C mtDNA mutations, other ATP synthase mutations and other mitochondrial diseases is needed in order to explore the role of immunotherapy in these conditions.

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