

Mitochondrial Encephalopathy and Optic Neuropathy Due to m.10158 *MT-ND3* Complex I Mutation Presenting in an Adult Patient

Case Report and Review of the Literature

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Introduction: Establishing a diagnosis of mitochondrial disease in adults remains a clinician's challenge. We report a case of syndrome reminiscent of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) in an adult patient who carries m.10158T>C mutation in complex I respiratory chain gene *MT-ND3* (mitochondrially encoded NADH dehydrogenase 3).

Case Report: This 26-year-old man from Thailand presented with new-onset headaches, seizures, stroke-like episodes, and poor vision due to optic neuropathy and cortical blindness. Instead of expected mutations in the mitochondrial tRNA gene that are frequently associated with MELAS, the mutation in *MT-ND3* with variable tissue heteroplasmy (blood 5.3%, muscle 89.5%) was demonstrated. The patient's clinical features, blood biomarkers, neuroimaging findings, muscle biopsy with histochemical and functional in vitro analysis, and genetic studies were analyzed and compared with all previously reported ND3 disease cases.

Conclusions: ND3 disease due to m.10158T>C mutation was previously described only in patients with Leigh or Leigh-like syndrome. Our findings thus indicate that ND3 disease can manifest with atypical phenotype in adults. The diagnosis of mitochondrial disease caused by other than typical MELAS-associated mutations in adults with stroke-like episodes, headaches, and seizures should be considered. An analysis of tissue other than blood, which is more likely to harbor a tissue-specific mitochondrial DNA mutation at a measurable level, may be necessary for diagnosis.

Key Words: mitochondrial disease, *MT-ND3*, optic neuropathy, headache, stroke-like episodes, epilepsy

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Mitochondrial diseases are a diverse group of inherited disorders due to defects in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that encode for components of respiratory chain complexes, their assembly factors,

and those associated with mitochondrial structure or function. Up to 30% of childhood-onset mitochondrial disease is attributed to complex I deficiencies.¹ Complex I is comprised of 7 core subunits encoded by mtDNA (*MT-ND1-6*, *MT-ND4L*) and 38 core subunits encoded by nDNA. Complex I defects have heterogeneous clinical presentations which range from fatal multisystem infantile-onset syndromes to equally common adult-onset Leber hereditary optic neuropathy.¹ Unlike childhood-onset mitochondrial disease, in which about 80% cases are caused by nDNA mutations, approximately 75% of adult-onset disease results from mtDNA mutations.² The diagnosis of mitochondrial diseases in adult population is typically delayed because of their relatively low prevalence, nonspecific phenotypic expression, and limited resources which restrict access to functional, pathologic, and/or genetic testing and to multidisciplinary evaluation in routine clinical practice.³ We describe an adult patient carrying m.10158T>C *MT-ND3* mutation with disease onset at the age of 26. We emphasize clinical, biochemical, and radiographic clues to the etiology of his condition and stepwise approach to his diagnosis. Finally, we provide literature review of all cases with mutations in the same gene.

CASE REPORT

This 26-year-old man of Thai Chinese origin reported new-onset throbbing headaches. The headaches were accompanied by photophobia, phonophobia, and occasional nausea. They were of moderate to severe intensity, were aggravated by routine activities, lasted from several hours to a few days, and responded well to resting and sumatriptan. Several months later, he reported blurred vision associated with "blind spots." Approximately a year after the headache onset, he experienced a generalized tonic-clonic seizure after >24 hours of intense migraine-like headache. A brain magnetic resonance imaging (MRI) at the time was reportedly unremarkable. Phenytoin 400 mg daily was introduced. Two months later, at the age of 27, the first focal seizure occurred and was followed by residual left arm weakness and paresthesias, which resolved after several days. A repeat brain MRI revealed changes that were concerning for an acute ischemic stroke. Valproate was added to his antiepileptic regimen and, after a few months, was replaced with levetiracetam at 1000 mg twice a day. He experienced a 2-week episode of right peripheral vision loss with intermittent slurring of speech a month later and had at least 4 additional stroke-like episodes over the ensuing 12 months. The frequency of migrainous headaches and focal seizures fluctuated and correlated with the occurrence of the stroke-like episodes. Exercise intolerance and muscle cramps occurred with the disease progression.

The antiepileptic regimen that eventually controlled the focal seizures included levetiracetam at a total daily dose of 3000 mg, lamotrigine at a total daily dose of 425 mg, and clonazepam 0.5 mg twice a day. Prolonged breakthrough seizures occurred in the setting of infrequent medication nonadherence. Topiramate 25 mg twice per day,

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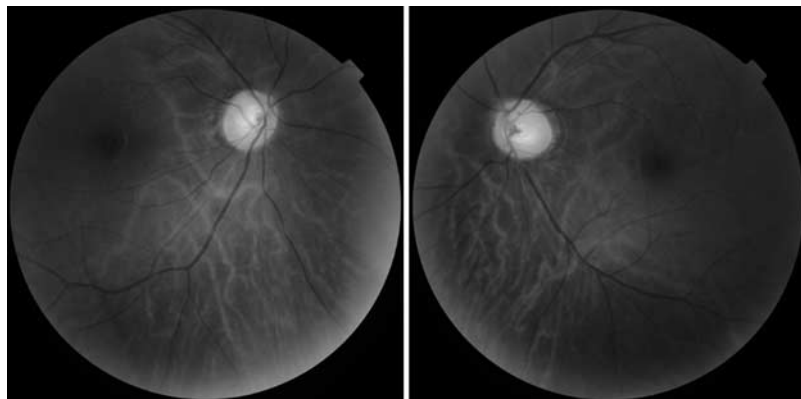


FIGURE 1. Fundus examination 24 months following the onset of visual symptoms revealed bilateral optic disc pallor. No retinal pigmentary changes were identified.

amitriptyline 75 mg per day, and riboflavin 400 mg per day resulted in excellent headache control.

His medical care was fragmented between our institution and a hospital in Thailand where he resided for >6 months per year. He was the only child and had no children. There was no history of neurological symptoms, including headaches and seizures, or systemic disorders in his family. Both of his parents had normal neurological examination. The patient smoked several cigarettes per week and reported moderate alcohol consumption for several years before the symptom onset. The headaches and the declining vision triggered binge drinking, which he aborted approximately 2 years later. He denied use of any illicit substances.

In between stroke-like episodes, his neurological examination, including oculomotor functions and muscle power, was normal, except for bilateral optic disc pallor (Fig. 1) with central and peripheral visual

field deficits. Metabolic testing documented plasma lactate in 1.1 to 3.3 mmol/L range (normal, <2.2) without pyruvate elevation. Repeated evaluations of glucose level, renal, and hepatic functions were all normal. Creatine kinase levels were normal. Transthoracic echocardiography showed normal cardiac structure and function with ejection fraction of 78%. Hearing acuity was intact. A single electroencephalogram with awake, drowsy, and asleep record obtained at our institution during an asymptomatic period revealed no epileptiform activity. The repeat brain MRI first obtained at the onset of stroke-like episodes demonstrated migrating pattern of cortical involvement with high signal on diffusion-weighted imaging (Fig. 2A) and a corresponding slightly decreased apparent diffusion coefficient in the acute phase that gradually increased to pseudonormal and high values over a course of weeks (Fig. 2B). Regional vasogenic edema (Fig. 2C) and cortical laminar necrosis (Fig. 2D) in the same areas became apparent

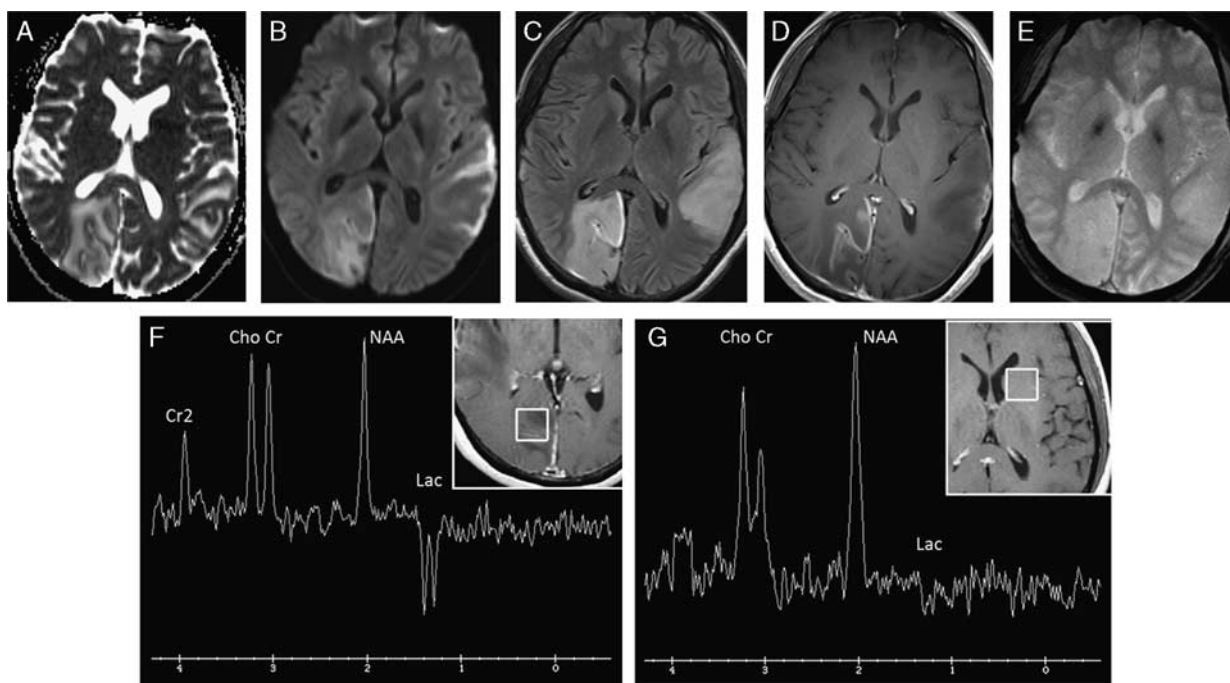


FIGURE 2. Apparent diffusion coefficient (A), diffusion-weighted imaging (B), fluid-attenuated inversion recovery (C), and contrast-enhanced T1 sequence (D) 4 weeks following an episode of left hemiparesis and left hemisensory loss, with concurrent auditory processing deficits, and persistent left homonymous hemianopsia, at age 29. Gradient echo sequence (E) showed bilateral calcifications in globus pallidus. Proton magnetic resonance spectroscopy (echo time 144 ms) demonstrated an inverted lactate doublet peak at 1.3 ppm in the affected right occipital lobe (F) and a lower-amplitude inverted lactate doublet peak in the normal-appearing left basal ganglia (G). Cho indicates choline; Cr, creatine; NAA, N-acetylaspartate; Lac, lactate.

TABLE 1. Genetic and Clinical Data of Published Cases With *MT-ND3* Mutations

Mutation	Source	No. Patients	Age at Onset	Outcome (Age at Imaging)	Phenotype	Neuroimaging
m.10158T>C p.Ser34Pro	Present case	1	27 y	Alive at 29 y	Migraine, epilepsy, stroke-like episodes, OA	Stroke-like cortical lesions with gyral vasogenic edema, BG calcifications
	6	1	5 mo	Death at 9 mo	LS	T2 high signal in BG, thalamus, brainstem, cerebellum
	4	3	1 y, 6 w, 17 d	Death at 3 y, 9 mo, 6 mo, 22 d	LS, LS-like disease	T2 high signal putamen, thalamus, brainstem, WM
	7,8	1	10 mo	NR	LS	NR
	9	2	6 w, 9 mo	Death at 6 mo, 3 y, 9 mo	LS, LS-like disease	NR
	10,11	2	4 mo, 4 w	Death at 5 mo, 7 mo*	LS-like disease	T2 high signal in putamen, GP, thalamus, brainstem, stroke-like cortico-subcortical changes
m.10134C>A p.Gln26Lys	5	1	4 y	NR	LS	T2 high signal in BG, cerebral peduncle
m.10191T>C p.Ser45Pro	12	1	<1 y	NR	LS	Thalamus, WM, stroke-like changes
	11	3	NR	7 mo, 4 y, 8 y	NR	T2 high signal in BG, brainstem, ± thalamus, cerebellum, stroke-like changes
	13	1	5 y	Alive at 12 y	Ataxia, epilepsy, strokes and stroke-like episodes, hearing loss	T2 high signal in BG, cortical areas
	14	1	4 w	Death at ~12 w	LS	CT: hypodensities in BG, midbrain, pons
	15	1	1 mo	Alive at 22 mo	LS-like disease	CT: symmetrical hypodensities in thalamus, cerebral peduncles
	7,8	1	15 mo	NR	LS	NR
	4	1	18 d	Death at 23 d	LS-like disease	NR (pathology: neuronal degeneration in medulla, dentate nucleus, hippocampus, ependymitis)
	10,11	2	At birth, 26 mo	Alive at 13 y, 19 y	LS-like disease	T2 high signal in BG, brainstem, ± thalamus, cerebellum, stroke-like changes; cortical atrophy
	16	1	24 y	Alive at 42 y	Epilepsy, stroke-like episodes, OA, cognitive decline	T2 high signal in R lentiform nucleus, midbrain
	17,18	1	21 y	Death at 27 y	Epilepsy (epilepsia partialis continua), OA	Cortico-subcortical lesions
m.10197G>A p.Ala47Thr	19	1	3 y	NR	Dystonia, dysarthria, mitochondrial encephalopathy	Bilateral gliosis in caudate and putamen
	11	1	NR	30 y	NR	T2 high signal in BG, thalamus, cerebellar atrophy
	8	1	7 mo	NR	LS	NR
	20	5-generation family: 18	5 y (proband), 8 y; 14-30 y	Proband alive at 39 y	OA with dystonia; OA	T2 high signal in BG
	11,21	3 families: 8 infants; 2 mothers	1-5 mo; 6 y, 14 y	Death 2 mo-11 mo, 2 alive at 5 y; alive at 37, 41 y	LS; dystonia	T2 high signal or CT hypodensity in BG, thalamus, brainstem, ± stroke-like changes, cortical atrophy; T2 high signal in BG, thalamus, cortical atrophy
	22	3	7 y, 4 y; 3 mo	NR, NR; alive after 1 y	Dystonia, ataxia; stroke-like episode	T2 high signal in BG, midbrain
9	1	2 y	Alive at 13 y	LS-like disease	NR	

*Patient 2 outcomes were inconsistent in the 2 articles; according to Lebon et al¹⁰ the patient died at 7 months, whereas Lebre et al¹¹ reported that the same patient underwent brain magnetic resonance imaging at 7.5 years BG indicates basal ganglia; CT, computed tomography; GP, globus pallidus; LS, Leigh syndrome; NR, not reported; OA, optic atrophy; WM, white matter.

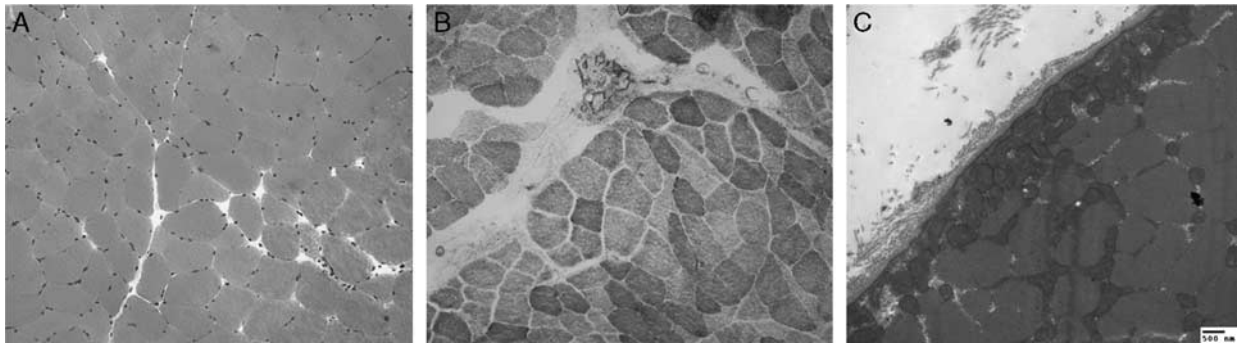


FIGURE 3. Skeletal muscle histopathology and histochemistry. Increased fiber size variation in a type 2 fiber-predominant muscle were noted on hematoxylin and eosin staining (A; original magnification $\times 20$). Combined succinate dehydrogenase/cytochrome oxidase staining revealed appropriate staining for both pathways (B; original magnification $\times 20$). Electron microscopy showed mild sub-sarcolemmal accumulation of mitochondria (C).

several days and several weeks after the stroke-like episodes, respectively. Bilateral calcifications in globus pallidus were noted on the first and all subsequent brain MRIs (Fig. 2E). Other brain structures, including deep white matter, thalamus, cerebellum, and brainstem were normal. Proton magnetic resonance spectroscopy showed an inverted doublet lactate peak both in the affected right occipital cortex (Fig. 2F) and in the normal-appearing left basal ganglia (Fig. 2G). The described clinical features, suggestive of MELAS, prompted screening for MELAS-associated mutations m.3243A>G and m.3271T>C, which were absent. Given strong likelihood of a mitochondrial disorder, next generation mtDNA sequencing was pursued (Medical Genetics Laboratories, Baylor College of Medicine, Houston, TX). The testing revealed m.10158T>C mutation in complex I gene *MT-ND3* measured at a low level of heteroplasmy of 5.3% in blood. Subsequently, a skeletal muscle biopsy was performed. In this tissue, m.10158T>C mutation was documented at high level of heteroplasmy (89.5%). Mild increase in peripheral NADH staining was noted. There were no ragged red fibers, succinate dehydrogenase-rich or cytochrome oxidase-negative fibers (Fig. 3B). Electron microscopy revealed mild clustering of subsarcolemmal mitochondria (Fig. 3C). Electron transport chain analysis in frozen muscle, performed at Center for Inherited Disorders of Energy Metabolism (CIDEM), Cleveland, OH, showed complexes I, III (rotenone-sensitive NADH-cytochrome *c* reductase) activity of 0.4 $\mu\text{mol}/\text{min}/\text{g}$ or 31% of mean control value. Complexes II, III, and IV activity was within normal limits. Quality control marker enzymes (citrate synthase, lactate dehydrogenase) were robust. CIDEM laboratory final report noted inconclusive complex I activity. Mutation analysis in alternative tissues, such as urinary epithelial cells, and mitochondrial functional studies using transmitochondrial cybrids were not available.

DISCUSSION

The *MT-ND3*-encoded protein is a core subunit of the mitochondrial membrane respiratory chain NADH dehydrogenase (NADH-ubiquinone oxidoreductase 3; electron transport chain complex I) that is believed to mediate enzyme catalytic activity, rather than complex I assembly or stability.^{4,5} To date, about 60 patients with 4 different *MT-ND3* mutations have been described (Table 1).^{4–22} The m.10158T>C mutation has been identified, as pathogenic, primarily in infants with Leigh syndrome (subacute necrotizing encephalopathy) or Leigh-like disease. Our patient's phenotype, initially suggestive of MELAS, resembles an adult-onset phenotype of m.10191T>C ND3 disease, which includes epilepsy, stroke-like episodes, and optic atrophy.^{16,17} Mild subsarcolemmal mitochondrial accumulation, as well as the high proportion of mutant mtDNA in muscle, is consistent with previous studies of patients harboring *MT-ND3* mutations.^{4–6,13,16,17,22} The inconclusive complex I activity analysis was not surprising as it was previously

demonstrated that respiratory chain enzyme analysis is most likely to yield diagnosis if there is a clinically apparent myopathy,²³ which was absent in this patient's case. Neuroimaging revealed a pattern distinct from all previously reported cases with complex I mtDNA mutations (Table 1), and reminiscent of the findings described in MELAS.²⁴ The apparent absence of the characteristic imaging findings characteristic of complex I deficiency (brainstem lesions, cerebellar atrophy, basal ganglia involvement),¹¹ further challenges attempt at genotype-phenotype correlation in mitochondrial diseases.

The somatic mosaicism seen in this patient, reflecting tissue heteroplasmy, presumably underlies the atypical and CNS-predominant phenotype. The less severe clinical expression than that previously reported with the m.10158T>C mutation in Leigh disease is consistent with the phenotypic heterogeneity as described among adult patients.²⁵ Our case echoes the established recommendation to assess mtDNA in tissues which are more likely to harbor a tissue-specific mutation.²⁶ Next generation sequencing of the mitochondrial genome, combined with deletion/duplication and depletion analysis, rather than targeted screening for most common pathogenic mtDNA mutations, should be the first-line testing in adult patients with suspected mitochondrial disease.

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