Pediatr Neonatol 2008;49(4):145–149

CASE REPORT

Mutation of Mitochondrial DNA G13513A Presenting with Leigh Syndrome, Wolff-Parkinson-White Syndrome and Cardiomyopathy

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Received: Mar 3, 2008
Revised: Apr 18, 2008
Accepted: Aug 28, 2008

KEY WORDS:
cardiomyopathy;
electron transfer complex I;
Leigh syndrome;
Wolff-Parkinson-White syndrome

Mutation of mitochondrial DNA (mtDNA) G13513A, encoding the ND5 subunit of respiratory chain complex I, can cause mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and Leigh syndrome. Wolff-Parkinson-White (WPW) syndrome and optic atrophy were reported in a high proportion of patients with this mutation. We report an 18-month-old girl, with an 11-month history of psychomotor regression who was diagnosed with WPW syndrome and hypertrophic cardiomyopathy, in association with Leigh syndrome. Supplementation with coenzyme Q10, thiamine and carnitine prevented further regression in gross motor function but the patient's heart function deteriorated and dilated cardiomyopathy developed 11 months later. She was found to have a mutation of mtDNA G13513A. We suggest that mtDNA G13513A mutation is an important factor in patients with Leigh syndrome associated with WPW syndrome and/or optic atrophy, and serial heart function monitoring by echocardiography is recommended in this group of patients.

1. Introduction

Leigh syndrome is a progressive neurodegenerative disease, which usually affects infants, but has also been described in adults. It is characterized by bilaterally symmetrical lesions in the brainstem and/or basal ganglia.[1] It is associated with defects in mitochondrial energy production. Many associated biochemical and molecular defects have previously been reported in the literature, including defects in pyruvate dehydrogenase complex, complex I (NADH ubiquinone reductase), complex II (succinate ubiquinone reductase), complex IV (cytochrome oxidase) and complex V (ATPase) of the mitochondrial respiratory chain.[2] The G13513A mutation in the mitochondrial ND5 gene was first reported in patients with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) in 1997.[3] In further reports, this mutation was reported to be related to Leigh syndrome accompanied by Wolff-Parkinson-White (WPW) syndrome and/or optic atrophy.[2,4–7] Here, we present a female infant with

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classical Leigh syndrome with onset at the age of 11 months, accompanied by WPW syndrome and dilated cardiomyopathy (DCM).

2. Case Report

An 18-month-old girl was brought to our outpatient clinic because of developmental regression. She was the first child of non-consanguineous parents. She was born at term via vaginal delivery after an uneventful pregnancy. She had poor body weight gain and delayed gross motor development. She could sit up alone without support at 10 months old and walk holding on to furniture at 11 months old. After a period of fever, she developed bilateral exotropia and became unable to sit well. Over the following 6 months, there was no further deterioration or improvement in motor achievement. She produced meaningful words at 11 months old and had gradual improvement in her language. At the age of 18 months, she was admitted to our hospital for evaluation.

On admission, her body weight was 8.1 kg (< 3rd percentile), and body length was 75.5 cm (3rd–10th percentile). She could say simple words such as "papa" and "mama", but could not sit steadily by herself. Bilateral exotropia, ptosis and mild spasticity of the lower limbs were found. Pale optic discs were detected by an ophthalmologist, but there was no obvious optic atrophy. Bilateral knee jerk was also exaggerated. Initial laboratory studies revealed normal complete blood counts, liver aspartase, blood urea nitrogen, creatinine and electrolytes. Serum lactate was elevated to 2.72 mmol/L (normal, <2.2 mmol/L). Brain magnetic resonance imaging revealed multiple lesions over the brainstem, periaqueductal area and bilateral thalami, compatible with a diagnosis of Leigh syndrome. Magnetic resonance spectroscopy of the basal ganglion also revealed a small lactate duplex. Cerebrospinal fluid lactate was also elevated to 2.8 mmol/L. Muscle biopsy from the left quadriceps showed no ragged red fibers, and electron microscopy found no evidence of mitochondrial cytopathy.

WPW syndrome with left bundle branch block was revealed by delta waves on an electrocardiogram. Echocardiography revealed hypertrophic cardiomyopathy (HCM) with borderline left ventricle contractility. The left ventricular ejection fraction (LVEF) was 61%. Attenuated wave V was noted on brainstem auditory evoked potentials, indicating significant brainstem involvement. Goggled visual evoked potential was absent. mtDNA G13513A mutation was detected in blood and muscle specimens using restriction fragment length polymorphism (RFLP) analysis, while direct sequencing of mtDNA in blood and muscle specimens also revealed G13513A heteroplasmic change (Figure). Coenzyme Q10, thiamine, and carnitine were prescribed for the patient following diagnosis of Leigh syndrome. Propranolol was also given for WPW syndrome. She was discharged in a stable condition.

The patient experienced mild improvements in her language skills over the following months, but was still unable to sit well despite medication and rehabilitation. She was intubated twice for respiratory infections and later required bilevel positive airway pressure (BiPAP) support at night. Her heart function also deteriorated rapidly. DCM was diagnosed 11 months later and her LVEF dropped to 26%. Captopril, furosemide and carvedilol were given for heart failure. Her respiratory and cardiac functions became stable, but BiPAP support was still needed at night. She remained exotropic, with no obvious visual response. She remained unable to sit steadily, despite regular rehabilitation, but no further regression in motor function was observed.

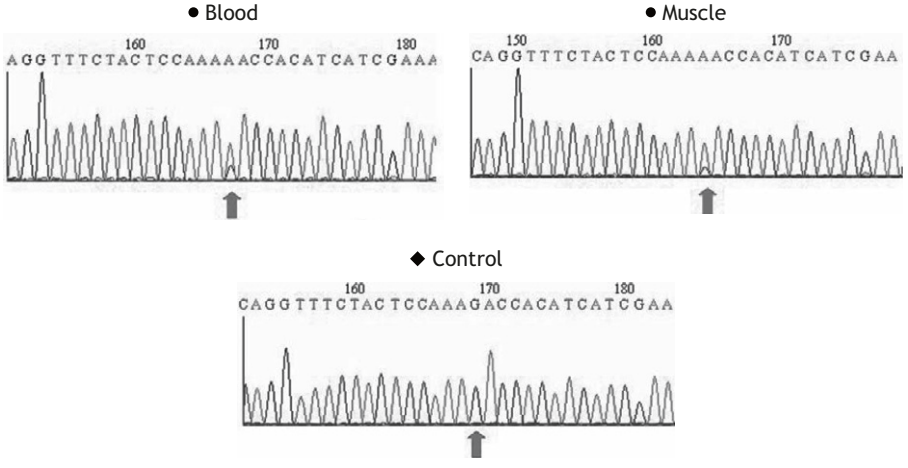

Figure Direct sequencing of mtDNA revealed G13513A heteroplasmic change.

3. Discussion

The G13513A mutation of mtDNA was first described by Santorelli et al in 1997 in patients with MELAS.[3] The mutation results in an amino acid substitution in the ND5 subunit of complex I and can significantly interfere with the function of complex I.[8] Mitochondrial complex I (NADH ubiquinone reductase) accepts electrons from NADH, transfers them to ubiquinone (coenzyme Q10) and uses the energy released to pump protons across the mitochondrial inner membrane. The ND5 subunit of complex I is a component of the hydrophobic protein fragment that contains around 15 transmembrane stretches, which are antiporter-like subunits probably involved in proton pumping activity.[9] However, the real function of ND5 in complex I is currently still unclear.

The most common reported result of G13513A mutation is Leigh or Leigh-like syndrome. There have been 14 reported cases of patients with Leigh or Leigh-like syndrome associated with mitochondrial G13513A mutation (Table).[2,5–7] These patients most often present with initial psychomotor retardation, followed by psychomotor regression, between 6 months and 5 years of age.

Our case also had severe heart involvement, including WPW syndrome and DCM. Cardiac conduction abnormalities are also frequently seen in some mitochondrial diseases, such as Kearns-Sayre syndrome, MELAS, and some specific defects of fatty acid oxidation.[10] It is significant that in the 15 reported cases of Leigh syndrome with mtDNA G13513A mutation, six patients (40%) also presented with WPW syndrome. In contrast, the G13513A mutation has never been reported in patients with other mitochondrial disease, such as MELAS or Leber's hereditary optic neuropathy in association with WPW syndrome.[11–13]

Table Clinical characteristics of all reported cases with mitochondrial G13513A mutation

Case no./ sex	Age at onset*	Brain MRI	Cardiac involvement	Ocular symptoms	Reference
1/F	19 mo	BG, brainstem	WPW	Optic atrophy, ptosis, strabismus	7
2/M	9 mo	Brainstem, thalamus	WPW	Ptosis	7
3/M	28 mo	Brainstem, thalamus	PSVT	(−)	7
4/M	9 mo	Brainstem	ICRBBB	Ptosis, strabismus	7
5/F	5 yr	BG, brainstem, cerebral lesion	WPW, PSVT, AV block	Ptosis	7
6/F	4 yr	BG, brainstem	(−)	Optic atrophy, ptosis, strabismus	7
7/M	6 mo	SN	Transient HCM	Opthalmoplegia	2
8/M	1 yr 9 mo	SN, dorsal medulla	Severe HCM	ND	2
9/M	1 yr 9 mo	SN, dorsal medulla	ND	Ptosis, opthalmoplegia	2
10/M	ND	Superior colliculi, red nuclei	ND	Opthalmoplegia	5
11/F	3 yr	BG	ND	Optic atrophy, nystagmus	5
12/M	Adult	Midbrain, pons	HCM	Optic atrophy, exotropia	5
13/M	1 yr 6 mo	ND	WPW	Strabismus, optic atrophy	6
14/F	9 yr	ND	WPW	Optic atrophy, ptosis, nystagmus, opthalmoplegia	6
15/F (our case)	11 mo	BG, brainstem, thalamus	WPW, LBBB, DCM	Ptosis, strabismus, opthalmoplegia	

*The onset age of symptoms other than developmental delay. BG = basal ganglion; WPW = Wolff-Parkinson-White syndrome; PSVT = paroxysmal supraventricular tachycardia; ICRBBB = incomplete right bundle branch block; AV = atrioventricular; SN = substantia nigra; HCM = hypertrophic cardiomyopathy; ND = no data; LBBB = left bundle branch block; DCM = dilated cardiomyopathy.

There have been few studies on the pathogenic mechanisms of mitochondrial dysfunction in WPW syndrome. Abnormal mitochondria have been found in surgically resected pathways in WPW syndrome.[14] Mutation in the PRKAG2 gene, which encodes the γ2 regulatory subunit of AMP-activated protein kinase, leads to familial WPW syndrome with autosomal dominant trait.[15] The AMP-activated protein kinase has been described as a "cellular fuel gauge",[16] and the mutation may result in defects during cardiac morphogenesis, resulting in development of an accessory pathway. Mitochondria also play an important role in cellular energy regulation, and mutations in their DNA might have similar effects to PRKAG2 mutations.

Cardiomyopathy is a common finding in complex I deficiency.[4] Both DCM and HCM are frequently accompanied by altered levels of specific OXPHOS/respiratory enzyme activities.[10] Although HCM has also been reported in patients with G13513A mutation in other series (Table, Patients 8 and 12),[5,6] it may transform into DCM, as in the case presented here. There has been another record of a patient with the mitochondrial C3303T mutation who was reported to have progressed from HCM to DCM within 1 year.[17] Mitochondrial C3303T encodes the mitochondria tRNA for leucine, and its mutation may have resulted in the development of cardiomyopathy.[18] DCM is thought to occur during the later stages of severe oxidative stress,[19] and because cardiomyopathy related to mitochondrial cytopathies may change in pattern, serial follow-up by echocardiography is needed.

Patients with mitochondrial encephalomyelopathy usually have a high frequency of ophthalmic manifestations, including pigmentary retinal degeneration, external ophthalmoplegia, ptosis, and optic neuropathy.[20] These can be the first signs of the disease, and develop long before central nervous system involvement becomes apparent.[6] In the 15 reported cases (Table), six patients (40%) also presented with optic atrophy. Complex I deficiency is the usual cause of Leber's hereditary optic neuropathy and dominant optic atrophy. The genes involved in these disorders regulate the bioenergetic efficiency of the mitochondrial respiratory chain, the buffering of reactive oxygen species overproduction, the machinery of fission/fusion and the control of apoptosis.[21] mtDNA G13513A mutation leads to complex I disorders, which may partially explain the high incidence of optic atrophy.

In summary, we have reported a patient who presented with the classical symptoms of Leigh syndrome, and WPW syndrome. mtDNA G13513A mutation was detected by RFLP and direct sequencing. In the literature review, WPW syndrome and optic atrophy were common findings associated with this mutation. The patient suffered from rapid deterioration in heart function over a 1-year period. We suggest that screening for mtDNA G13513A mutation and complex I activity should be performed in patients with Leigh syndrome in association with WPW syndrome and/or optic atrophy. Serial heart function monitoring by echocardiography is also suggested for this group of patients.

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