Atypical presentation of Leigh syndrome associated with a Leber hereditary optic neuropathy primary mitochondrial DNA mutation

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A R T I C L E   I N F O

Article history:
Received 21 February 2011
Accepted 21 February 2011
Available online 26 February 2011

Keywords:
Atypical Leigh syndrome
Leber hereditary optic neuropathy
Mitochondrial DNA mutation
Phenotypic variation

A B S T R A C T

Leber hereditary optic neuropathy (LHON) is caused by point mutations in mitochondrial DNA (mtDNA), and is characterized by bilateral, painless sub-acute visual loss that develops during the second decade of life. Here we report the case of a five year old girl who presented with clinical and neuroradiological findings reminiscent of Leigh syndrome but carried a mtDNA mutation m.11778G>A (p.R340H) in the MTND4 gene usually observed in patients with LHON. This case is unusual for age of onset, gender, associated neurological findings and evolution, further expanding the clinical spectrum associated with primary LHON mtDNA mutations.

1. Introduction

Mutations in mitochondrial DNA (mtDNA) are associated with a spectrum of clinical syndromes including among others, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) and Leber hereditary optic neuropathy (LHON) [1]. The m.11778G>A transition changes a conserved arginine to a histidine residue within the most evolutionarily conserved region in the MTND4 gene encoding a component of complex I of the mitochondrial respiratory chain [2]. This mutation is typically associated with the LHON phenotype, and is is far the most common LHON mutation, accounting for approximately 70% of cases observed among Caucasian populations [3]. It generally causes the most severe visual failure with only about 4% of patients experiencing visual recovery. The penetrance for developing optic atrophy differs depending on the gender of the individual carrying this mutation; the risk is 43% for males and 11% for females [4]. However, the risk of visual failure in both genders increases when this mutation arises in haplogroup J, and decreases when the mutation arises in haplogroup H [5]. The m.3460G>A is the second most common mtDNA mutation causing LHON, and also causes severe visual failure, although more than 20% of patients experience visual recovery. The m.14459G>A is the most pathogenic mtDNA mutation causing LHON, and is associated with visual loss, dystonia, a generalized movement disorder, pseudobulbar syndrome, and myopathic features among other clinical manifestations [6].

Leigh syndrome is usually a devastating neurodegenerative disease (also called subacute necrotizing encephalopathy) that presents mostly in infancy. From a neuroradiological perspective, it consists of almost identical lesions in the central nervous system, e.g., focal, bilaterally symmetrical lesions, particularly in the basal ganglia, thalamus, and brainstem [7,8]. The clinical presentation of Leigh syndrome is highly variable with considerable heterogeneity and is characterized by a wide variety of clinical features. Most frequently, the central nervous system is affected, with psychomotor retardation, epilepsy, nystagmus, opthalmoparesis, optic atrophy, ataxia, dystonia, or respiratory failure associated with brainstem dysfunction. Some patients also present with involvement of the peripheral nervous system, including polyneuropathy, myopathy, or non-neurological abnormalities such as diabetes, short stature, hypertrichosis, cardiomyopathy, anemia, renal failure, vomiting, or diarrhea (atypical Leigh syndrome) [9]. The disease is usually fatal [10]. Leigh syndrome can be caused by mutations affecting either the mitochondrial or the nuclear genome leading to dysfunction of subunits of the respiratory chain (particularly complexes I, II, IV, or V), coenzyme Q10 deficiency, pyruvate dehydrogenase complex or pyruvate carboxylase deficiencies [9,11].
Although various neurological features have been reported to be associated with the m.11778G>A and other primary LHON mutations, atypical Leigh syndrome is not a common feature.

Here we report the case of a child with a clinical phenotype suggestive of atypical Leigh syndrome associated with a primary mtDNA mutation typically observed in cases of LHON.

2. Materials and methods

All of the investigations in this study were undertaken as part of clinical diagnosis and medical management. No research investigations were performed, although informed consent approved by the Baylor College of Medicine Internal Review Board for the publication of this report was obtained from the family.

2.1. Mitochondrial DNA common mutation analysis

The proband’s peripheral blood sample was screened for common mtDNA point mutations (m.3243A>G, m.3460G>A, m.8344A>G, m.8356T>C, m.8993T>G, m.8363G>A, m.11778G>A, m.3460G>A, m.13513G>A, m.13514A>G, m.14459G>A, and m.14484T>C) by multiplex PCR/allele-specific oligonucleotide (ASO) dot-blot analysis as previously described [12,13]. ARMS (allele refractory mutation system) qPCR targeted to the m.11778G>A mutation was performed to quantify the mutation heteroplasmy [14]. mtDNA deletions and rearrangements were analyzed by restriction enzyme digestion followed by Southern blot analysis [13].

2.2. Sequence analysis

Sequencing of the PDHA1, POLG1, PC, SURF1, NDUF52, NDUF58, NDUF57, NDUF51, NDUF53, NDUF56, NDUF54, NDUFA2F, NDUFA1, NDUFA4F, NDUFA7, and NDUFS5 genes was performed on the proband’s peripheral blood sample. All coding exons plus 50 basepairs of the flanking introns were PCR amplified using sequence specific primers covalently linked at the 5’ end to M13 universal primers. The entire mitochondrial genome was amplified from the proband’s skeletal muscle sample using 24 pairs of sequence specific overlapping primers [11,15,16].

2.3. Electron transport chain enzyme analysis

Spectrophotometric analysis of the respiratory chain complexes was performed on the proband’s skeletal muscle sample. The electron transport chain enzymes were assayed at 30 °C using a temperature-controlled spectrophotometer (Tecan M200 Microplate Reader, Durham, NC). The activities of complex I (NADH:ferricyanide reductase), complex II (succinate dehydrogenase), rotenone sensitive complex I + III (NADH:cytochrome c reductase), complex II + III (succinate:cytochrome c reductase), and complex IV (cytochrome c oxidase) were measured using appropriate electron acceptors/donors [17]. Each assay was performed in duplicate [18,19].

2.4. Mitochondrial DNA copy number analysis

Mitochondrial DNA copy number in the proband’s muscle sample was determined using real-time quantitative PCR as previously reported [20]. All samples were assayed in triplicate. Fluorescent signal intensities of PCR products were recorded and analyzed on a 7900HT Fast RT_PCR system (Applied Biosystems, Foster City CA). The mtDNA content (referred to as the mtDNA copy number relative to single copy nuclear genes) was calculated based on the difference in threshold cycle numbers between the nuclear and mitochondrial single copy nuclear genes respectively.

Sequencing reactions were performed on purified PCR products using the BigDye Terminator Cycle Sequencing kit, and analyzed on an ABI3730XL automated DN sequencer. Sequences were analyzed using Mutation Surveyor version 3.20. GenBank sequences NM_000284.1, NM_002693.1, NM_000920.3, NM_003172.2, NM_004550, NM_002496.3, NM_024407.4, NM_007103.2, NM_004551.1, NM_004553.3, NM_002693.1, NM_004550, NM_002496.3, NM_007103.2, NM_004551.1, NM_004553.3, NM_002495.2, NM_174889.3, NM_004541, NM_014165.1, NM_005001.2, NM_004551.1 and NC_001807.4 were used as reference sequences for PDHA1 POLG1, PC, SURF1 NDUF2, NDUF8, NDUF5, NDUF51, NDUF53, NDUF56, NDUF54, NDUFA2F, NDUFA1, NDUFA4F, NDUFA7, NDUFS5 and the whole mitochondrial genome respectively.
2.5. PDHC enzyme activity

The activity of PDHC in skeletal muscle was performed at the Center for Inherited Disorders of Energy Metabolism (CIDEM) at the Department of Pediatrics, Rainbow and Children’s Hospital, Cleveland, Ohio. PDHC activity was assayed on skeletal muscle by thiamine pyrophosphate dependent decarboxylation of 1-14C-pyruvate in the presence of CoASH and NAD+, following activation (dephosphorylation) by pre-incubation with dichloroacetate/flouride as previously published [22,23].

2.6. Mitochondrial immunofluorescence assay

The pattern of expression of specific respiratory chain complex proteins was determined using standard immunohistochemical methods. The primary antibody cocktails included the following antibodies to respiratory chain enzyme complex proteins: Complex I (30 kDa NDUF53, IgG1), Complex II (30 kDa FeS protein, IgG2a), Complex III (core 2, IgG1), Complex IV subunit I (IgG2a), Complex IV subunit IV (IgG2a), Complex V (OSCP, IgG1), and pyruvate dehydrogenase (PDH E1α, IgG1). Antibodies to porin (anti-porin IgG 2b) served as reference control for mitochondrial density and distribution. The secondary antibody cocktail included Alexa Fluor 594 goat anti-mouse IgG2b specific antibody and either Alexa Fluor 488 GAM IgG1 for complexes I, III, V and PDH or Alexa Fluor 488 GAM IgG2a for complexes II and IV. All primary antibodies were from Mitosciences, Eugene, Oregon.

2.7. Case report and results

The proband presented at 5 years of age to Texas Children’s Hospital with a 9-month history of increasing lethargy, fatigue, difficulty in walking and a weight gain of 20 kg. Prior to this 9-month period, she had normal motor and cognitive development. During this time period, she exhibited a voracious appetite alternating with nausea, vomiting, and nocturnal enuresis. The patient also developed a moon facies, a buffalo hump, acne, and hair thinning prompting the diagnostic consideration of Cushing syndrome. There was no significant past medical history, and no known family history of neurological disease including encephalopathy, epilepsy, ophthalmoplegia, or cardiomyopathy, although the parents were not available to answer questions about the family history.
She was born at full term gestation via cesarean section secondary to failure to progress with a birth-weight of 2.7 kg to nonconsanguineous parents of Northern European descent. The pregnancy history was only remarkable for maternal methamphetamine and nicotine use.

Physical exam revealed a height of 113 cm (75th percentile), a weight of 38.9 kg (>95th percentile) which was increased from 20 kg nine months prior, and a BMI of 30.5. Her neurological examination was notable for fatigue. The remainder of her neurological examination was

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**Fig. 4.** Immunofluorescence images illustrating variable expression of ETC complexes including regions of normal expression for complexes I (A), II (C), III (E), IV-I (G), V (I) and regions of reduced expression for complexes I (B), II (D), III (F), IV-I (H) and V (J), respectively. [Magnification A, B, G, H ×400; C, D, E, F, I, J ×100.]
otherwise unremarkable including normal extraocular movements, deep tendon reflexes and power, and no ataxia.

A low dose dexamethasone suppression test and a TSH level were obtained as part of the initial diagnostic work-up to evaluate the patient’s physical features and rapid weight gain. The TSH level was mildly elevated to 10 μIU/mL (0.32–5.00). The low dose dexamethasone suppression test was abnormal, with a mildly elevated ACTH level of 54 pg/mL (6–48), with an AM cortisol level of 13.4 μg/dL (it should be <2 if there is a normal response). A repeat low dose dexamethasone test was obtained 2 months later and was normal, with an AM cortisol level of 0.7 μg/dL.

MRI of the brain at the time of the initial presentation was within normal limits and CT of the abdomen revealed no adrenal masses. Two months after the initial evaluation she was noticed to be increasingly lethargic with the appearance of drowsiness. At that time, a repeat MRI of the brain revealed a non-enhancing T2/Flair hyperintense, T1 hypointense signal abnormality in the hypothalamus, medial thalami, periaqueductal region, the dorsolateral medulla, and cerebellar nodules. The presence of these extensive bilateral CNS lesions prompted the consideration of atypical Leigh syndrome as a working diagnosis (Figs. 1 and 2).

A metabolic diagnostic work-up that included plasma amino acids, urine organic acids, and an acylcarnitine profile was normal. The serum venous lactate was 2.2 mmol/L (0.2–2.0). Given the brain MRI findings suggestive of atypical Leigh syndrome, a blood sample was obtained to perform a panel of common mtDNA point mutations and single deletions. The results of this screen revealed an apparently homoplasmic mtDNA mutation, m.11778G→A, most commonly associated with LHON. A suspicion of mitochondrial dysfunction as an underlying cause of her symptoms led to the initiation of carnitine and coenzyme Q10 supplementation. Since the patient improved clinically, she was discharged home. One month later, her symptoms worsened, and she presented with increasing lethargy, tachycardia, fever to 105 °F and shortness of breath. Her respiratory compromise required intubation. Echocardiogram was normal. A positive nasal adenovirus test was noted. The serum venous lactate level was 0.8 mmol/L (0.2–2.0). Further work-up included a repeat MRI of the brain that showed no significant interval change in the signal abnormalities that had been previously visualized and a normal MRA of the brain. Brain MR spectroscopy revealed elevated lactate peaks in the basal ganglia and thalami (Fig. 3).

Although the proband’s brain MRI and MRS findings were suggestive of ongoing mitochondrial dysfunction in the central nervous system, on the other hand, the patient’s clinical phenotype did not fit the classical LHON phenotype caused by the m.11778G→A mutation. Serial ophthalmological examinations revealed no papilepdaema, ocular signs of elevated intracranial pressure or optic nerve atrophy. In order to determine whether there were additional biochemical and molecular causes for the observed atypical Leigh encephalopathy, a skeletal muscle biopsy was performed. Results revealed a moderate predominance of type II fibers, moderately increased neutral lipids, and a mild to moderate increase in the number of mitochondria. No abnormalities of the cristae or paracrystalline inclusions were observed. Focal to regional reduced immunostaining for complexes I, II, III, IV (subunits COI and COII) and V was also observed (Figs. 4 and 5). However, deficiencies in the mitochondrial electron transport chain enzyme activities were not noted (Table 1). To establish if other mtDNA mutations or variants were present, the whole mitochondrial genome from skeletal muscle was sequenced. The results confirmed the presence of the apparently homoplasmic m.11778G→A mutation and haplogroup H in this patient. However, additional deleterious mtDNA mutations were not detected (Table 2). In addition, real-time quantitative PCR was performed on the muscle sample to estimate mtDNA copy number and was found to be 84% of the mean value for age and tissue matched controls, ruling out mtDNA depletion. Array Comparative Genomic Hybridization (aCGH) (Baylor version 8.0) did not detect any copy number variants in nuclear encoded genes. Sequencing of the genes encoding the E1 alpha subunit of the pyruvate dehydrogenase complex (PDHA1), pyruvate carboxylase (PC), DNA polymerase gamma (POLG1) and surflet locus protein 1 (SURF1) did not show any deleterious mutations. In addition, sequence analysis of a panel of genes encoding complex I proteins including NDUFS2, NDUFS8, NDUFS7, NDUFS5, NDUFS6, NUDF54, NDUFA2, NDUFA1, NDUFA4, NDUFA7, and NDUFS5 did not detect deleterious mutations either. Pyruvate dehydrogenase complex (PDHC) activity was measured in the muscle biopsy sample, and was 50% of the mean of the control values, a value in the low normal range but not consistent with PDHC deficiency.

To determine if the patient’s asymptomatic mother also carried the m.11778G→A mutation, real-time Allele Refractory Mutation System (ARMS) qPCR was performed on her blood sample. These studies showed that the patient’s mother’s blood is 56% heteroplasmic for the m.11778G→A mutation. Additional matrilineal relatives were not available for testing.

3. Discussion
Leber hereditary optic neuropathy (LHON) is a degenerative eye disease characterized by bilateral, painless, subacute visual failure that occurs usually in young adult life. There is variable penetrance, and males are more likely to be affected than females [24,25]. Affected subjects are typically asymptomatic until visual blurring develops affecting the central visual field in one eye, with similar symptoms appearing in the other eye about eight weeks later. The vast majority of cases of LHON fall under one of four mutations in the genes encoding different protein subunits of the mitochondrial NADH dehydrogenase (complex I of respiratory chain): m.3460G→A (p.A52T) in the MTND1 genes, m.11778G→A (p.R340H) in the MTND4 gene, m.14484T→C

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Table 1
Electron transport chain enzymatic activities — skeletal muscle.

<table>
<thead>
<tr>
<th>Electron transport chain enzymatic activities</th>
<th>ETC complexes</th>
<th>Patient (% of mean)</th>
<th>Control +/− SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NADH:ferricyanide dehydrogenase</td>
<td>I (114)</td>
<td>239 +/− 82.5</td>
<td></td>
</tr>
<tr>
<td>NADH:cytochrome c oxidase</td>
<td>I + III</td>
<td>60.0 (73)</td>
<td>82.2 +/− 16.2</td>
</tr>
<tr>
<td>Succinate dehydrogenase</td>
<td>II (129)</td>
<td>7.22 +/− 1.32</td>
<td></td>
</tr>
<tr>
<td>Succinate:cytochrome c reductase</td>
<td>II + III</td>
<td>3.43 (66)</td>
<td>5.21 +/− 2.63</td>
</tr>
<tr>
<td>Cytochrome c oxidase</td>
<td>IV (64)</td>
<td>24.4 +/− 9.9</td>
<td></td>
</tr>
<tr>
<td>Citrate synthase</td>
<td>26.1 (108)</td>
<td>242 +/− 68</td>
<td></td>
</tr>
</tbody>
</table>

ETC: electron transport chain.

* nmol/min/mg protein.
Leigh disease and the m.14459G mutations have been reported. Kirby et al. reported 3 patients with neuritis; the onset of neurological features often occurs years after the optic neuropathy. Majority becoming affected in their late 20s to early 30s. Moreover, earliest age of presentation of these individuals is 17 years, with a ratio of males to females with LHON-MSL is approximately 1:2. The well, and presumably carried the m.1178G mutation had not yet developed any visual deficits, which included the 4 common LHON mutations [29]. One of these unrelated Japanese patients with SNHL for 29 common mtDNA mutations and one female with isolated spasticity/dystonia and no signs of optic neuropathy [27]. However, precise measurements of the degree of heteroplasmy were not described in that study. In another family with multiple individuals homoplasmic for the m.14459G-A mutation, the major clinical presentations were spasticity, hemiparesis, dystonia, and dysarthria. Some individuals were completely asymptomatic, and no family members manifested LHON at the time of assessment [28].

Sensorineural hearing loss (SNHL) has also been reported with common LHON mutations with and without additional clinical phenotypes [29,30]. Ceranic et al. reported two patients with LHON caused by the m.11778G-A mutation with progressive auditory neuropathy [30]. One of the patients, a 59 year old male, presented with progressive and significant bilateral hearing loss in addition to LHON. The second patient, a 45 year old female, also had severe optic atrophy yet had a more subtle SNHL and also presented with a multiple-sclerosis-like illness. Recently, Kato et al. screened blood samples from 373 unrelated Japanese patients with SNHL for 29 common mtDNA mutations, which included the 4 common LHON mutations [29]. One of these patients, a 28 year old female, carried the m.11778G-A mutation and had not yet developed any visual difficulties. The patient’s mother, two sisters, and two nieces all suffered from SNHL with no optic atrophy as well, and presumably carried the m.1178G-A mutation, although it was not reported [29].

Harding et al. described 8 female patients with LHON caused by the m.11778G-A mutation, 6 of whom had clinical and brain MRI findings indistinguishable from multiple sclerosis [4]. Thus far, less than 20 subjects with LHON and multiple sclerosis-like (MSL) symptoms have been reported. Eighteen of these individuals are either homoplasmic, or have levels of heteroplasmy above 95%, for the m.11778G-A mutation [31]. Interestingly, unlike the classical LHON phenotype, the ratio of males to females with LHON-MSL is approximately 1:2. The earliest age of presentation of these individuals is 17 years, with a majority becoming affected in their late 20s to early 30s. Moreover, the onset of neurological features often occurs years after the optic neuritis first presents.

A few cases of Leigh disease associated with some primary LHON mutations have been reported. Kirby et al. reported 3 patients with Leigh disease and the m.14459G-A LHON mutation [32]. All three individuals (two male siblings and one unrelated female) first presented at less than one year of age with lactic acidosis, developmental regression, and symptoms of brainstem dysfunction. One of the patients died of respiratory arrest at age 6 years 11 months, the other two died of disease related complications prior to the age of 1 year. No evidence or family history of optic neuropathy or dystonia was noted. Funabiki et al. reported three male subjects with Leigh-like encephalopathy, each of which had visual loss followed by neurological regression and bilateral brainstem lesions on MRI [33]. One patient suffered from vision loss at the age of 4 years, another at the age of 18 years, and the third at age 34 years. All three developed neurological symptoms in their early 30s. Sequence analysis indicated that two of the affected individuals were ~70% and ~40% heteroplasmic for the m.14484T>CA mutation; the third carried a homoplasmic m.3460G-A mutation [33]. The m.3460G-A mutation has also been reported in a 23 year old male who suffered from severe visual impairment followed shortly by the development of palatal myoclonus and vertical gaze palsy, and the appearance of brainstem lesions observed by MRI [34]. Interestingly, the patient’s mother and grandmother were also diagnosed with LHON due to vision loss, yet never suffered the central nervous system deficits observed in the patient. An additional male patient harboring the m.3460G-A mutation with LHON plus spastic ataxia with dystonia, and periventricular multiple sclerosis-like white matter lesions has also been reported [35].

McFarland et al. [40] reported the case of a 22 year old woman who initially presented with signs and symptoms of atypical Leigh syndrome at 17 months of age. These symptoms primarily included progressive dystonia involving the trunk, face, and all four limbs. Her 19 year old brother presented with similar signs and symptoms at 3 years of age and eventually became wheelchair dependent. Brain MRI scans demonstrated bilateral symmetric putaminal necrosis in both individuals. The m.11778G-A mutation was detected at 86% heteroplasmy in the proband’s muscle sample, and at 87% heteroplasmy in a blood sample of her brother. Interestingly, the m.11778G-A mutation was also detected at 85% heteroplasmy in a blood sample of their asymptomatic mother. Both individuals exhibited an atypical clinical course for Leigh disease, surviving well into adulthood and completing school, with the brother going on to college.

The case herein presented is atypical because of the clinical presentation, age, and gender of the patient, in conjunction with the presence of the m.11778G-A mutation. The proband currently at 6 years of age exhibits a normal clinical status. In general, subjects harboring primary mtDNA mutations associated with LHON become symptomatic at a later age. In addition, the penetrance for these mutations is lower in females and in particular for the m.11778G-A mutation [9–11%]. The proband’s mother also harbors the m.11778G-A mutation at 56% heteroplasmy in blood, yet at the age of 44 years is currently asymptomatic. Moreover, based on the results of the real-time qPCR and ETC analyses, mtDNA depletion has been ruled out. Other known

<table>
<thead>
<tr>
<th>Nucleotide number</th>
<th>Gene</th>
<th>Base change</th>
<th>Codon</th>
<th>Amino acid change</th>
<th>Reported in MITOMAP</th>
<th>Base pair ratios as reported in mtDB</th>
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<td>311</td>
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<td>insC</td>
<td></td>
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<td>ATP6</td>
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<td>mtDB: 1115:752</td>
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HV: Hypervariable Region; D-loop: displacement loop 2; OH: Origin of Heavy Strand; CSB2: Conserved Sequence Block 2. mtDB: Human Mitochondrial Genome Database.

(p.M64V) in the MTND6 gene, and m.14459G-A (p.A72V) in the MTND6 gene [3].
possible causes of Leigh syndrome such as defects in PDHC activity and mutations in POLG1, PDHA, PC, SURF1, and nuclear genes encoding complex I proteins have also been excluded in our proband. Immunohistochemistry demonstrated variable focal to regional reduced expression of mitochondrial proteins for complexes I, II, III, IV and V. This reduction reflects a "global" depression of the expression of the major ETC complexes, albeit in a subset of fibers. The proportion of affected fibers was not large enough to reduce the overall biochemical activity of ETC complexes below 30% of the mean activity. Since biochemical assays are often based on non-selective tissue homogenates, they are therefore unlikely to detect reduced protein expression affecting only a small subset of fibers in a tissue.

Since a causative effect of the m.11778A→G mutation cannot be completely proven in our patient, modifying factors such as mitochondrial haplotype, nuclear modifier genes, and possible environmental factors causing atypical Leigh syndrome in this patient may be possible. A synergistic role of mitochondrial variants depending on the haplotype of the individual has previously been proposed in cases of LHON with and without additional clinical phenotypes [5,36]. Studies of two Han Chinese families have suggested that m.4435G→A (tRNA Met) and m.15951G→A (tRNA Thr) may increase the penetrance of LHON caused by the m.11778G→A mutation by decreasing the expression of tRNAs methionine and threonine respectively, leading to altered mitochondrial tRNA metabolism and increased mitochondrial dysfunction [37,38]. As previously noted, the mitochondrial haplotype J, which includes secondary LHON mutations 4216T→C and 13708G→A, increases the risk of visual failure [5]. In contrast, mitochondrial haplotype H has been associated with a decreased risk of visual failure [5]. These data suggest that our patient, who has haplotype H, may actually be at a decreased risk of developing optic atrophy. In the case of the siblings with atypical Leigh syndrome [40], the presence of m.4716G→C (which changes glutamine to glutamic acid at amino acid position 83) was postulated to influence the pathogenicity of the m.11778G→A mutation. However, no other notable variants, including m.4716C→G, were observed in our patient's mitochondrial whole genome (Table 2).

Because LHON mutations are more penetrant among men than women, an X-linked susceptibility gene has been hypothesized. Hudson et al. identified a region of the X chromosome (Xp21–Xq21) that contains a high risk haplotype (markers DXS8090 and DXS106) which may contain a nuclear modifier gene [39]. Males homozygous for the m.11778A→G and 14484T→C mutations and hemizygous for this high risk haplotype on the X chromosome were much more likely to develop visual impairment than those not carrying the haplotype. Females with the m.11778A→G mutation who were homozygous for the high risk haplotype were also much more likely to develop visual impairment than heterozygous females. However, the presence of an X-linked susceptibility locus does not exclude the possibility of autosomal factors having an influence on disease, although to date no such factors have been identified.

In summary, our report adds further evidence to the existing body of literature that atypical Leigh syndrome may also be associated with primary mtDNA mutations typically associated with a LHON phenotype. However, we cannot definitively rule out an as yet unknown nuclear modifier gene interacting with the m.11778A→G mutation leading to an atypical Leigh encephalopathy. Further cases may need to be analyzed in order to establish the causality of this association.

References


