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Uncommon Leber "Plus" Disease Associated With Mitochondrial Mutation m.11778G>A in a Premature Child

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Abstract

Leber hereditary optic neuropathy is a well-known mitochondrial disorder that leads to bilateral subacute visual failure. Although visual impairment is often the sole clinical feature, additional and severe neurologic abnormalities also have been documented for this disease. We report on a 13-year-old boy who has presented with severe visual failure since early childhood in a context of prematurity. In the first years of his life, clinical features included delayed psychomotor development and ataxia. The clinical presentation, which was initially attributed to prematurity, worsened thereafter, and the child developed acute neurologic degradation with the typical radiological findings of Leigh syndrome. The mitochondrial DNA point mutation 11778G>A was identified in the ND4 gene. The probable influence of environmental background on clinical expression of Leber optic neuropathy, particularly those of prematurity and oxygen therapy, is discussed in our manuscript.

Keywords

Leber optic neuropathy, phenotypic variability, Leigh syndrome, oxygen therapy, prematurity

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Leber optic neuropathy is a maternally inherited form of bilateral optic nerve atrophy associated with central vision loss. The disorder results from mitochondrial DNA mutations of various genes that encode for complex I subunits of the mitochondrial respiratory chain. Approximately 90% of affected individuals exhibit 1 of the following 3 mitochondrial DNA point mutations: 11778G>A in the *ND4* gene, 3460G>A in the *ND1* gene, or 14484T>C in the *ND6* gene. Causal mitochondrial DNA mutations have shown significantly reduced and gender-dependent penetrance. Males have approximately a 50% lifetime risk of developing visual loss, in comparison with 10% for females. The 11778G>A mutation was the first to be described and is the most common mutation, typically associated with severe visual impairment and a small likelihood of recovery.[1,2] Generally, pathology is limited to the optic nerve, and visual impairment is the sole clinical manifestation of the disease. However, additional neurologic features have been documented in several cases, including movement disorders, multiple sclerosis–like illnesses, peripheral neuropathy, postural tremor, and seizures.[3-5] Radiologic findings of brainstem and basal ganglia involvement have been observed. Thus, in rare cases, the

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associated neurologic presentation suggests Leigh syndrome, a severe neurodegenerative disorder with a very poor prognosis.[6-9] Leber optic neuropathy accompanied by additional neurologic signs has been described as Leber "plus."

Gender- and age-dependent penetrance, as well as the variable clinical expressivity of the identified mutations, are still poorly understood. Various factors, including hormonal context, additional pathogenic mitochondrial DNA mutations, various mitochondrial DNA haplogroups, environmental factors, and X-linked or autosomal nuclear modifier genes act synergically with the primary mutation and modify the Leber optic neuropathy phenotype.[10-15] With respect to environmental factors, tobacco and alcohol have been suspected to modulate or precipitate clinical manifestations.[16,17] Moreover, exposure to industrial toxins and psychological stress have also been implicated in anecdotal reports.[18,19] To our knowledge, no reports have yet focused on the potential role of prematurity and oxygen therapy in the clinical expression of Leber optic neuropathy.

Case Report

We report on a 13-year-old boy who is the second child of healthy and nonconsanguineous white parents. No ophthalmologic problems have previously been reported in the family.

Our patient was born at 29 weeks of gestation in the context of preeclampsia and acute fetal distress. His birth weight was 820 g, and the Apgar score was 7/8/8. Hyaline membrane disease required surfactant administration and high-frequency ventilation for 4 days. At this time, continuous oxygen therapy was administered with a maximum of 56% oxygen for a few hours. The patient then required 1-month nasal continuous positive airway pressure therapy, with 21% oxygen. Eye fundus examination performed during the patient's 3-month stay in the neonatal unit revealed no signs of retinopathy. At 2 months, he developed coagulase negative staphylococcus septicemia and responded favorably to antibiotics. Indomethacin was used to treat persistent ductus arteriosus. Neonatal transfontanellar ultrasonography was normal. At 2 years of age, magnetic resonance imaging (MRI) did not reveal periventricular leukomalacia sequelae but indicated subtle substantia nigra alterations. Yet brain imaging at 6 years did not show any abnormalities.

Postnatal ophthalmologic evaluations, which were available from the age of 2 years onwards, revealed divergent strabismus, nystagmus, and oculomotor disorder with multidirectional paresis with the exception of abduction. Fundus examination revealed bilateral optic disc pallor and showed that visual acuity had been severely reduced to 1/10. Electroretinogram at 4 years was normal.

The patient presented with psychomotor delay. He was able to remain in a sitting position at the age of 15 months and could walk at 2 years. Because of the ataxia, his gait was unsteady, and he showed fine motor disturbances and movement coordination disorders. Language development was normal, but weak cognitive skills and learning disabilities required educational support. Hearing screening was normal despite medical history of transtympanic drainage. Treatment with risperidone and methylphenidate was administrated in order to control anxiety and agitation. During the first years of his life, his visual impairment and psychomotor difficulties were attributed to prematurity and interpreted within that context.

The patient was referred for genetic evaluation at 9 years of age. Clinical examination did not reveal any evident dysmorphic features. He had a long face, large and up-slanting palpebral fissures, and a shawl scrotum. He also presented with a short soft palate and nasal speech. Karyotyping and comparative genomic hybridization microarrays analysis (agilent 44 K) showed normal results. The metabolic diagnostic workup, which included plasma amino acids, urine organic acids, acylcarnitine profiles, as well as vitamin E, alpha-fetoprotein, cholesterol, and thyroid hormone levels, were all unremarkable.

At 11 years of age, neurologic degradation occurred over a few months' period, subsequent to a febrile episode. Oculomotor disorder worsened with the development of abduction paresis of the left eye and convergent strabismus, as well as right hemiparesis and dysmetria. Gait and balance disturbance increased, which led to frequent falls. A few weeks later, the patient was no longer able to walk independently and complained of increasing asthenia. Neurologic examination was notable for severe ataxia, pyramidal syndrome, bilateral clonus, stiffness, and hyperextension associated with axial hypotonia. The boy had a tendency to tilt his head to the right and to walk on his tiptoes. Speech deteriorated with the appearance of oral motor difficulties, dysarthria, and hyper-sialorrhea. Brain magnetic resonance imaging indicated a T2-hyperintense signal in the brainstem, right cerebellar peduncles, and right dentate nucleus (Figure 1A, C). Lesions in midbrain and medulla oblongata were characterized by a central hypointense signal on fluid attenuated inversion recovery sequences, which corresponded to necrotizing lesions with cavitation (Figure 1B, D). Lesions in the posterior part of the pons appeared to be more active with a decreased diffusion coefficient. No signal abnormality was noticed in basal ganglia, supratentorial white matter, and cerebral cortex. This cluster of lesions strongly supported a Leigh syndrome diagnosis. Four months later, brain magnetic resonance imaging showed an increase in lesion size (Figure 1E, F). Further investigation, including serological analyses, excluded the possibility of Epstein-Barr virus, cytomegalovirus, and toxoplasmosis infections. Very-long-chain fatty acid profile and biotinidase activity were normal. Cerebrospinal fluid and serum lactate levels, as well as lactate-pyruvate ratio, were normal. Protein electrophoresis in the blood and the cerebrospinal fluid did not detect any specific oligoclonal bands. Visual evoked potentials were unremarkable. Cardiac and abdominal ultrasounds, as well as the electrocardiogram, were normal. A skeletal muscle biopsy revealed a moderate increase in neutral lipids with hypotrophic fibers, but no ragged-red or necrotic fibers. Spectrophotometric analysis of mitochondrial respiratory chain complexes performed on muscle and hepatic samples, as well as cultured fibroblasts, did not detect any deficiencies. However, central nervous system lesions associated with visual impairment raised suspicions of mitochondrial dysfunction as the potential etiology. The most common mitochondrial DNA mutations associated with

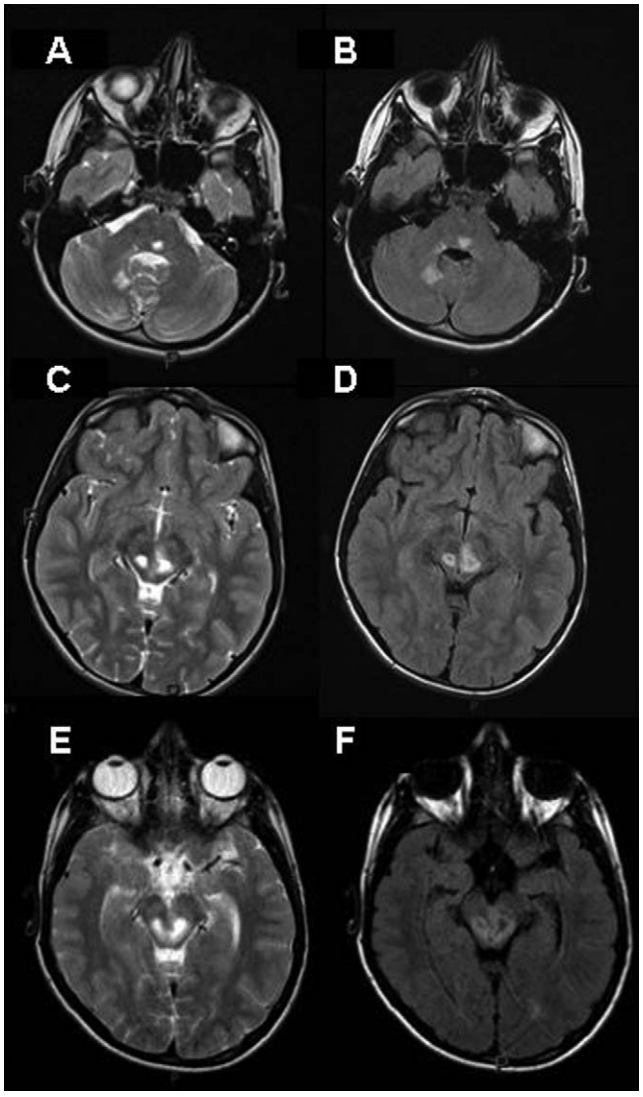

Figure 1. Serial magnetic resonance imaging (MRI). Axial T2-weighted (A, C, E) and axial T2-weighted fluid attenuated inversion recovery sequences (B, D, F) show an increased bilateral signal in the brainstem involving the tegmentum mesencephali, periaqueductal region, and, at left, the red nucleus, posterior, and paramedian region of the pons, as well as the paramedian region of medulla oblongata. Lesions are also visible in the superior and middle right cerebellar peduncles and right dentate nucleus. Central hypointense signal on fluid attenuated inversion recovery sequences corresponds to necrotizing lesions with cavitation. Four months later, brain magnetic resonance imaging showed an increase in lesion size (E, F).

Leber optic neuropathy were sought out in leukocytes. A duplicate analysis was performed and revealed the homoplasmic mitochondrial DNA mutation 11778G>A in the *ND4* gene. The result correlated with visual impairment. To establish the potential relation between other mitochondrial DNA mutations or variants and neurologic manifestations, additional blood and urine sample screening was performed for the 8993T>G and 8993T>C mutations in the mitochondrial *ATP6* gene, which have been frequently reported in Leigh syndrome, as well as for the 3243A>G and the 8344A>G mutations, described in mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes syndrome, and myoclonic epilepsy with ragged-red fibers. Moreover, mitochondrial tRNA Leu (UUR), Lys, and Ser genes were sequenced, and the multiplex ligation-dependent probe amplification technique (kit P125, MRC Holland) was employed to seek out mitochondrial DNA deletions. We did not detect any additional mitochondrial DNA abnormalities. To determine whether the 11778G>A mutation was inherited or originated de novo, molecular analysis was performed on the asymptomatic mother's blood sample, which revealed heteroplasmy for the mutation. Conversely, the mutation was not found in a blood sample of the patient's maternal aunt. Dead maternal grandmother could not be tested.

Treatment with vitamin B_1, B_2, carnitine, and ubiquinone (coenzyme Q10) was initiated. The child benefited from multidisciplinary rehabilitation, which included intensive physical and occupational therapy, as well as speech support. Symptoms stabilized over the next months. Axial tonus improved slightly, and the boy's ability to walk recovered with appropriate support. Nevertheless, severe ataxia and ophthalmoplegia persisted, and abnormal paroxystic movements emerged. Treatment with biperiden was initiated, and based on recent studies supporting idebenone's beneficial effect on Leber optic neuropathy, this latter medication replaced ubiquinone.[20-22]

Discussion

In 1871, Leber described some of the associated neurologic signs in his so-called Leber optic neuropathy patients.[23] More recently, several studies have reported various neurologic features associated with visual failure, such as dystonia, tremors, parkinsonism, multiple sclerosis–like illness, peripheral neuropathy, and hearing loss.[3-5,24] Furthermore, brain magnetic resonance imaging revealed brainstem or basal ganglia involvement in some of the affected patients.[6-9] Cardiac conduction defects, such as preexcitation syndrome, cardiomyopathy, diabetes mellitus, and skeletal changes in the form of kyphoscoliosis have been documented as extraneurologic manifestations of the disease.[5,25-28] Therefore, Leber optic neuropathy can be a systemic disorder that is much more severe than an isolated visual impairment.

Multisystemic manifestations are typical of mitochondrial diseases. Adenosine triphosphate (ATP) synthesis via the mitochondrial respiratory chain is an ubiquitous metabolic pathway that provides most organs and tissues with energy.[29,30] Consequently and unsurprisingly, genetic defects in the respiratory chain can lead to a wide variety of clinical symptoms.[31] However, a mitochondrial respiratory chain complex defect is not always clearly detected in affected patients' tissue analyses.[32] Therefore, the absence of in vitro abnormalities in the mitochondrial respiratory chain does not exclude a Leber optic neuropathy or Leber "plus" diagnosis, as in the case of our patient.

It is unclear why identical genotypes are associated with such variable expressivity, even within the same family. Initially, different case reports attempted to establish a link between a particular causal mutation and a distinguishing neurologic presentation.

For example, mitochondrial DNA mutation 14459G>A in the *ND6* gene, which encodes for a complex I component of the mitochondrial respiratory chain, was linked to "Leber optic neuropathy plus dystonia" or "pediatric onset dystonia."[33-35] Nevertheless, this mutation was described not only in dystonic patients but also in asymptomatic carriers and in patients with isolated visual impairment or other neurologic signs.[36] Furthermore, isolated Leigh disease cases were reported with this mutation.[37,38] Clinical heterogeneity was reported progressively for all of the most common primary mutations. Therefore, it is now well established that a primary Leber optic neuropathy mutation is not correlated with a specific and unique clinical presentation.

Variable expressivity concerns not only symptom severity but also the age at disease onset. Visual impairment and potentially associated neurologic signs usually occur during young adult life. In rare cases, and for reasons that are poorly understood, symptoms are detected during childhood. In our present case, the patient experienced early onset of severe visual failure. In fact, he developed severe neurologic features suggestive of Leigh syndrome. So far, only a few cases with similar neurologic presentation have been reported in pediatric patients with the mitochondrial DNA mutation 11778G>A. McFarland et al[6] described a 22-year-old woman with this mutation who had developed symptoms of atypical Leigh disease at the age of 17 months. Fruhman et al[7] reported the case of a 5-year-old girl who also presented with atypical Leigh syndrome associated with mitochondrial DNA mutation 11778G>A. She suffered from increasing lethargy, difficulty walking, and central Cushing syndrome, without the associated visual impairment. Cerebral magnetic resonance imaging revealed extensive bilateral lesions, which suggested the presence of Leigh disease. Finally, Grazina et al[8] reported the case of a 12-year-old girl with the mitochondrial DNA mutation 11778G>A who began suffering from visual impairment at 8 months of age.Neurodevelopment was normal until the age of 14 months, at which time she developed refractory epilepsy and began the progressive development of neurologic deficits. Brain imaging at 42 months showed bilateral symmetric lesions involving the thalamus, cerebral cortex, and basal ganglia.

Because Leber optic neuropathy primary mutations can manifest themselves in a diverse array of phenotypes at variable ages, many authors have suspected other factors to interact with the primary mutation and thus modulate the phenotype. Among these factors, heteroplasmy, gender, and various environmental and genomic factors are thought to play a role. Considering genomic factors, the existence of "secondary" mitochondrial DNA mutations, which are able to modify disease presentation through synergic interaction with the primary mutation, was proposed. For example, Li et al[39] attributed a modifier role to mitochondrial DNA mutation 15951A>G (tRNAThr) in a 3-generation Chinese family, which likely worsened the penetrance and expressivity of visual impairment caused by primary mitochondrial mutation 11778G>A. Mitochondrial DNA mutation 4435A>G (tRNAMet) is another example of a secondary mutation that can modulate the phenotypic expression and worsen the mitochondrial dysfunction associated with primary mitochondrial DNA mutation 11778G>A.[40] However, "secondary" mitochondrial mutations do not always explain phenotype variability, which suggests that other genomic factors can be responsible, such as specific combinations of mitochondrial DNA polymorphic variants or nuclear modifier genes.[15] Recessive/X-linked susceptibility genes could explain the predominance of males affected by the disease.[10-14] Nevertheless, these genetic modifier factors are poorly defined, and their interpretation remains complex. In our patient, as complete mitochondrial DNA sequencing was not undertaken, the potential role of mitochondrial DNA variants or secondary mutations on the phenotype cannot be precisely evaluated. However, the most common mitochondrial syndromes were excluded, and gene sequencing commonly implicated in mitochondrial encephalomyopathy did not reveal any additional mutations.

The influence of environmental factors on the described mutations' clinical expressivity was documented in a relatively limited number of series. Risk factor assessment can, however, be relevant with respect to disease prevention. Smoke and alcohol are the most commonly studied environmental factors suspected to precipitate visual impairment in patients carrying a primary mutation.[16,17] To our knowledge, prematurity and oxygen therapy's roles as "triggering" factors for the clinical expression of a Leber optic neuropathy mutation have not yet been reported. These 2 factors characterize our patient's history. On the one hand, alterations in the mitochondrial respiratory chain in cells harboring a pathogenic mutation can give rise to energy deficiency and reactive oxygen species overproduction, both of which are responsible for mitochondrial apoptosis.[41] Moreover, cells of Leber optic neuropathy patients display a higher apoptosis rate than controls.[42] On the other hand, prematurity-associated diseases (retinopathy, periventricular leukomalacia, bronchodysplasia, etc) have been linked to free radical species production and tissue injuries. Oxygen accepts free electrons that are generated during oxidative metabolism within the cell, resulting in reactive oxygen species.[43] Under physiological conditions, these radicals are quickly inactivated and do not induce cell dysfunction and apoptosis.[44] As regards cell production, the balance between free radical production and antioxidant defenses is rather fragile. Under conditions of hyperoxia, ischemia-reperfusion, or in the presence of limited or impaired antioxidant defenses, this balance can be upset. Because of their prolonged oxygen needs and severely reduced antioxidant defense mechanisms, premature infants are particularly sensitive to the toxic effects of oxygen.[43] If a Leber optic neuropathy mutation is responsible for abnormal mitochondrial respiratory chain function and consequently leads to elevated reactive oxygen species production and apoptosis, we hypothesize that prematurity and oxygen therapy potentiate the injurious effects of pathogenic mutations by amplifying reactive oxygen species production and oxidative stress–induced apoptosis. Reactive oxygen species overproduction can result in an imbalance between free radical production and the cells' antioxidant defense mechanisms. This disequilibrium could have played a role in both the early occurrence and the severity of our patient's symptoms. Developing retinas are particularly susceptible to the oxygen-mediated damages that contribute to retinopathy in preterm infants. In our

patient, visual impairment and oculomotor disorders were initially associated with sequelae of prematurity. However, the absence of prematurity-associated retinal changes and periventricular leukomalacia in brain imaging does not support the notion of prematurity as the sole cause of symptoms. The progressive appearance of additional neurologic abnormalities with subacute deterioration led to the identification of a mitochondrial disease as the main etiology.

To our knowledge, this is the first reported case of mitochondrial DNA mutation 11778G>A-related Leber "plus" in an ex-premature infant exposed to oxygen therapy. Our patient presented with an early onset and severe visual impairment that was associated with neurologic signs suggestive of Leigh syndrome. Therefore, prematurity and oxygen therapy can be considered to be additional environmental factors capable of acting synergically with the primary mutation so as to modulate or trigger phenotypic expression. Further cases are required to confirm the causality of this association.

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Author Contributions

SP, the pediatric resident who participated in IM genetic consultations, wrote the first draft of the manuscript. VB, a biologist, performed the genetic testing. CW, a pediatric neurologist, cared for the patient during his first years. MC and FM were the patient's ophthalmologists during his childhood. AC was the neonatologist who cared for the patient at birth and collected neonatal data. DR participated in metabolic investigations, and RVC performed mitochondrial analyses. MCN is the child's current pediatric neurologist and assisted with manuscript revision. IM oversaw the manuscript's preparation and revision.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This manuscript represents a descriptive, retrospective case report without any intervention and therefore did not require an institutional review board's review or approval.

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