Leber Hereditary Optic Neuropathy and Longitudinally Extensive Transverse Myelitis

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Abstract Leber Hereditary Optic Neuropathy is an inherited optic neuropathy caused by mitochondrial DNA point mutations leading to sudden, painless loss of vision. We report a case of an 8-year-old boy presenting with a radiological phenotype of longitudinally extensive transverse myelitis on a background of severe visual impairment

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secondary to Leber Hereditary Optic Neuropathy (LHON). He was found to have dual mitochondrial DNA mutations at 14484 (*MTND6* gene) and 4160 (*MTND1* gene) in a family with a severe form of LHON characterised by not only an unusually high penetrance of optic neuropathy, but also severe extra-ocular neurological complications. The m.14484T>C mutation is a common LHON mutation, but the m.4160T>C mutation is to our knowledge not reported outside this family and appears to drive the neurological manifestations. To our knowledge there have been no previous reports of spinal cord lesions in children with LHON.

Introduction

Leber Hereditary Optic Neuropathy (LHON) (OMIM #535000) is a mitochondrial disorder in which the primary manifestation is visual loss due to the degeneration of retinal ganglion cells. LHON is one of the most common inherited optic neuropathies, with a prevalence in Europe of between 1 in 30,000 and 1 in 50,000 (Man et al. 2003; Spruijt et al. 2006; Puomila et al. 2007). LHON is caused by point mutations in mitochondrial DNA (mtDNA) genes encoding subunits of complex 1 of the respiratory chain, particularly those encoding the ND1 (OMIM 516000), ND4 (OMIM 516004) and ND6 (OMIM 516006) subunits (Mackey et al. 1996; Valentino et al. 2004). 90% of LHON cases harbour one of three point mutations in mtDNA, m.3460G>A (*MTND1* gene, OMIM 516000), m.11778G>A (*MTND4* gene OMIM 516004) and m.14484T>C (*MTND6* gene OMIM 516006) (Newman 2005). Penetrance is incomplete, and as 80–90% of affected individuals carry homoplasmic mutations, heteroplasmy alone is not responsible for the decreased pene-

trance in LHON (Man et al. 2003; Harding and Sweeney 1995). Our patient belongs to a large Queensland family (Qld1, OMIM 535000) reported to have a severe LHON phenotype characterised by high penetrance of visual loss (with visual loss developing in approximately 100% of male and at least 60% of female family members in the maternal line) and a high incidence of neurological phenotypes (Wallace 1970; Mackey and Buttery 1992; Mackey 1994).

LHON was originally considered an isolated ophthalmic disorder, caused by selective degeneration of the retinal ganglion cells (Carelli et al. 2004; Man et al. 2009). However, extra-ocular neurological manifestations have been reported, including movement disorders, peripheral neuropathy, brainstem and basal ganglia involvement and multiple sclerosis-like syndromes. These have been termed “LHON plus syndromes”, some of which have been linked to mtDNA point mutations other than the three common mutations seen in LHON, but which also affect mitochondrial respiratory chain complex 1 activity and present with optic neuropathy in the majority of affected carriers (Wallace 1970; Jun et al. 1994; Paulus et al. 1993).

Longitudinally extensive transverse myelitis (LETM) is a magnetic resonance imaging diagnosis defined as intramedullary hyperintense T2-weighted signal abnormality spanning three or more vertebral segments (Wingerchuk et al. 2006). The differential diagnosis of LETM is broad, including compressive, infective, demyelinating/inflammatory, vascular and neoplastic causes (Mirbagheri et al. 2016), although use of this terminology commonly implies a demyelinating/inflammatory aetiology. We now report a paediatric patient from the LHON Qld1 family with extensive myelopathy resembling LETM.

Case Report

A molecular diagnosis of LHON was confirmed in our patient at 6 years of age, with testing performed in the context of visual deterioration and a family history. Visual acuity was measured at 4/60 using a Snellen chart bilaterally and he required the use of a cane to aid mobility.

Mitochondrial DNA polymerase chain reaction restriction fragment length polymorphism (PCR RFLP) analysis was performed. The following mutations were detected: MT-ND1:p.L285P (c.854 T>C) (m.4160T>C) homoplasmic and MT-ND6:p.M64V (c.190 A>G) (m.14484T>C) homoplasmic. These mutations, a primary mutation in ND6 (m.14484T>C) and a secondary mutation (m.4160T>C), are those described in the Qld 1 pedigree (Wallace 1970; Mackey 1994). The known pedigree omitting paternal descendants is shown in Fig. 1. Our patient's maternal grandmother's death at age 58 was said to be secondary to Leigh syndrome. The patient has one sister aged 11 who currently has normal vision and is in good general health.

At 8 years of age, the boy presented with an 8-day history of abnormal gait of gradual onset, in the context of 3 weeks of lower limb and back pain. He had episodic profuse diaphoresis, beginning 7 days prior to the abnormal gait and initially associated with 24 h of fever that did not persist. He had a single episode of faecal incontinence at the time of his fever. He was also noted to have a bilateral manual tremor.

At presentation there was asymmetrical proximal lower limb weakness, more prominent on right, resulting in abnormal gait and difficulty rising from the ground and climbing onto a bed. He had normal tone, but absent right lower limb deep tendon reflexes, and an equivocal plantar

Fig. 1 Qld1 known pedigree omitting paternal descendants

response on that side. The patient reported decreased sensation to the left lower limb in a non-dermatomal distribution, and also on the plantar surface of the right foot. Power was only reduced to 4+/5 and he was able to walk with relatively mild gait abnormality, acknowledging that his sensory disturbance and his pre-existing visual impairment may have affected his gait. The patient had evidence of dysautonomia; initial blood pressure was 139/98 mmHg and there was ongoing intermittent hypertension for the first 7 days of the admission. Paroxysmal, sharply demarcated left hemifacial diaphoresis was seen corresponding to the hypertension, although there was no fever or tachycardia. The right visual acuity was 6/360 and the left visual acuity was 6/270.

Magnetic resonance imaging (MRI) revealed extensive but symmetrical increased signal intensity on T2 weighted imaging throughout the spinal cord extending from the conus to the medulla suggestive of myelopathy. There was swelling of the cord at the C4/5 level and at the conus, with no associated enhancement. Diffusion weighted imaging was not performed on the spinal cord, although through the medulla showed symmetrical prominent increased signal within two central rounded areas of the ventral cord. The remainder of the brain was normal, although spectroscopy was not performed. The optic nerves were noted to be small in calibre. These radiographic features were considered to be mitochondrial in aetiology, based on the history of LHON, but with an inflammatory component.

Full blood count, inflammatory markers and complement studies (C3/C4) were normal, aside from a very mild increase in the erythrocyte sedimentation rate (ESR) (10 mm/h). There was a speckled antinuclear antibody (ANA) titre of 40. A mild elevation in aspartate transaminase (AST) and alanine transferase (ALT) was noted and the lactate was normal. Anti-MOG (myelin oligodendrocyte glycoprotein) and anti-NMO (neuromyelitis optica) antibodies were negative. A lumbar puncture was not performed due to the noted cord swelling.

The patient received intravenous immunoglobulin 2 g/kg over 2 days and pulse methylprednisolone 30 mg/kg/day for 5 days, followed by oral prednisolone at 2 mg/kg/day for 2 weeks, weaned off over a further 3 weeks. He was commenced on idebenone at 300 mg three times daily. The autonomic manifestations of sweating and hypertension resolved over a week, and the patient underwent inpatient rehabilitation. By the time he was discharged 11 days after admission, he had only subtle residual asymmetric lower limb weakness but was ambulant.

At follow up 3 months after admission, he had essentially returned to his baseline prior to his illness, but with mild clumsiness in the right leg seen on running, and decreased deep tendon reflexes on that side. There had been a full resolution of sensory and autonomic symptoms.

Repeat MRI demonstrated residual symmetric increased signal intensity on T2 weighted imaging still present extending throughout the spinal cord.

Discussion

While LHON was originally considered an isolated ophthalmic disorder, coexisting neurological disorders and other features such as kyphosis and cardiac conduction abnormalities are relatively common, and many of these additional findings are unsurprising given the underlying complex 1 respiratory chain defect (Nikoskelainen et al. 1995; Paulus et al. 1993). In one Finnish study of 46 patients with LHON vision loss from 24 families, 59% were found to have neurological abnormalities in addition to LHON. “LHON plus” neurological manifestations include tremor, dystonia, migraine, seizures, progressive encephalopathy with basal ganglia involvement, peripheral neuropathy, myoclonus and cerebellar ataxia (Nikoskelainen et al. 1995; Murakami et al. 1996; Funalot et al. 2002).

Our patient belongs to a large Queensland family (Qld1) reported to have a severe LHON phenotype. Significant neurological complications have been described in this LHON Qld1 family, including dysarthria, ataxia, spastic paraplegia, and a severe acute infantile or childhood encephalopathy in at least nine family members with a fatal outcome in at least three. There was no definite evidence of a demyelinating process, including at autopsy in two of these cases (Wallace 1970). Modern imaging was not available at the time of Wallace’s report; however, none of the described cases appears readily attributable to an isolated spinal cord process. The combination of m.14484T>C and m.4160T>C mutations is to our knowledge not reported outside this family. The m.4160T>C mutation is not described elsewhere, aside from a single entry in the Genbank database, in an unaffected individual. A third mutation m.4136A>G, in the ND1 gene, has been reported in a branch of the Qld 1 family, and appeared to be homoplasmic in the family members tested. It has been proposed to be an intragenic suppressor mutation, ameliorating the biochemical and clinical manifestations in this branch of the family (Howell et al. 1991). Several family members outside this small branch tested negative, but none of our patient’s antecedents appears to have been tested (Howell et al. 1991).

Our patient’s episode of extensive spinal cord pathology could represent a separate coincidental issue, however; the coexistence of two relatively rare disorders seems particularly unlikely, given that numerous cases of apparent demyelination have been reported in LHON (Pfeffer et al. 2013; Shiraishi et al. 2014; Harding et al. 1992; Parry-Jones et al. 2008; Perez et al. 2009). This syndrome, known as LHON-multiple sclerosis (LHON-MS), is essentially clini-

cally and radiologically indistinguishable from multiple sclerosis, but with less ocular pain and a poorer visual prognosis (Pfeffer et al. 2013; Matthews et al. 2015). The pathophysiology of multiple sclerosis is also incompletely understood, and has been postulated to involve a complex I defect, with biochemical evidence of complex I deficiency having been noted in muscle in MS patients as well as in animal models (Sadeghian et al. 2016; Kumleh et al. 2006). LHON-MS has not been reported in childhood, and while spinal cord changes have been noted on MRI in these patients, they rarely occur without concurrent white matter lesions in the brain (Pfeffer et al. 2013; Matthews et al. 2015; La Russa et al. 2011). Our patient had extensive spinal cord changes suggestive of demyelination but negative anti-AQP4 antibodies, and did not meet the diagnostic criteria for neuromyelitis optica, which is an inflammatory demyelinating disorder which causes optic neuritis and myelitis (Crout et al. 2016). Table 1 summarises 15 cases of LHON and spinal cord MRI changes, of which m.14484T>C mutations account for 6, or 40%, including our patient with dual mutations.

The pathology underpinning the spinal cord and brain pathology in patients with LHON and features resembling MS and LETM remains unclear. Only three cases of LHON with spinal cord involvement have been reported with post-mortem pathological data. A case of posterior column spinal cord degeneration was reported in a 39-year-old woman with subacute bilateral visual failure 5 years previously and m.3460G>A homoplasmy. The picture was of a subacute metabolic axonopathy with additional features of a Leigh-like syndrome on brain MRI, with no evidence of demyelination or remyelination at autopsy after her unexpected death 2 months later (Jaros et al. 2007). Neuropathology was also performed in a case of atypical MS-like disease in a patient with homoplasmic m.14484T>C mutations and spinal cord (cervical gracile fasciculus) as well as cerebral white matter changes (Kovács et al. 2005). Post-mortem studies demonstrated axonal damage, active demyelination, cystic necrosis, inactive demyelinated areas and vacuolated white matter (Kovács et al. 2005). This suggests metabolic injury including demyelination in the pathology of at least some patients with this pattern of disease. A third pathological study was performed in the pre-molecular era on a 58-year-old LHON patient who was otherwise neurologically normal aside from bilateral impaired position sense in the toes. Demyelination and gliosis were noted in the optic tracts and also the gracilis columns of the cervical spine. A slight degree of myelin sheath destruction was described in the peripheral nerves of the lower extremities. The spinal and peripheral changes were postulated to be related to severe malnutrition secondary to the cardiac failure which

resulted in his death; however, impaired position sense in the patient's brother increased the uncertainty about whether it was LHON-related (Kwittken and Barest 1958). It has been postulated that tissue injury in LHON patients may provoke an immune response in susceptible individuals, for example by liberation of mitochondrial proteins (autoantigens) (Palace 2009). It is, however, by no means certain that there is an inflammatory or autoimmune component to the demyelination seen in this disorder, as white matter pathology including demyelination is seen in other disorders involving complex I deficiency (Filosto et al. 2007).

Longitudinally extensive transverse myelitis is a radiological descriptor encompassing a broad variety of differential diagnoses which may be narrowed down by specific imaging features, history, clinical findings and other investigations. Metabolic myelopathy is an important differential diagnosis. Mitochondrial disorders including LHON should be considered as part of the broad differential in adults and children presenting with LETM, even when appearances are typical of demyelination. To the best of our knowledge there are no reported cases of demyelinating disease or spinal cord lesions in children with LHON mutations, with the youngest reported patient with LHON-MS being 18 years at onset of non-visual manifestations (Pfeffer et al. 2013).

In summary, we present a unique case of extensive subacute myelopathy in a child with early onset visual loss due to LHON in a family reported to have a high rate of neurological manifestations. Neurological complications have not been reported for several decades in this family, although our patient's grandmother is said to have died from complications of Leigh syndrome. Such cases challenge and extend current knowledge of this disorder, as well as highlighting the need to consider mitochondrial disorders as a cause of myelitis or myelopathy.

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Synopsis

Extensive myelopathy in a child with LHON; an unusual extraocular manifestation.

Authors' Contributions

Carolyn Bursle is a metabolic fellow who was involved in patient care and drove manuscript development.

Kate Riney is a neurologist who was involved in patient care and manuscript development.

Table 1 Reported LHON cases with spinal cord involvement

	LHON genotype	Age at presentation of spinal cord pathology (after visual onset)	Clinical features (i.e. NMO)	Reported spinal imaging features	CSF oligoclonal bands	Anti-NMO antibodies	Treatment	Additional diagnosis if made, outcome	Reference
Case 1	m.11778G→A	20 (3 years)	Two episodes bilateral lower limb paralysis and hypoaesthesia, brisk DTRs	T2 hyperintensity T1–T6 level No gadolinium enhancement	Neg	Positive	Steroids	NMO, partial recovery, ambulant	Shiraishi et al. (2014)
Case 2	m.3460G→A	25 (7 years)	Lower limb sensory changes, weakness, urinary dysfunction	Lesions T8–9, T11, gadolinium enhancement	NA	NA	NA	NMO, incomplete recovery	Ghezzi et al. (2004)
Case 3	4216 and 4917	31 (7 years)	Three episodes lower limb weakness, urinary dysfunction, C4 sensory level	T2 hyperintense lesion C4–T4, with expansion, later atrophy	Neg	NA	Steroids	Relapsing NMO, good recovery, walking independently	Celebisoy et al. (2006)
Case 4	m.14484T→C	65 (–1 year)	Lower limb pain, weakness, gait imbalance, axonal polyneuropathy	T2 hyperintensity posterior columns entire C spine, no enhancement	Neg	Negative	Not reported	NMO, deficits stable for 1 year, followed by optic neuropathy	McClelland et al. (2011)
Case 5	m.3460G→A	39 (5 years)	Pyramidal pattern lower limb weakness, nystagmus, absent ankle jerks	T2 hyperintensity dorsal columns	Neg	NA	Not reported	Unexpected death – Leigh-like subacute degeneration at autopsy brain and spinal cord	Jaros et al. (2007)
Case 6	m.14484T→C	38 (13 years)	Left leg weakness, paraesthesiae, ataxia, urinary retention	NA, brain only	Neg	NA	Steroids – improvement noted	Secondary progressive MS? Death due to bronchopneumonia. Pathology: active demyelination in cerebral white matter lesions, axonal degeneration in cervical gracile fascicle and dorsal roots of spine	Kovács et al. (2005) and Horváth et al. (2000)
Case 7	m.14484T→C	35 (approx. 10 years)	Lower limb weakness, hypoaesthesia	Diffuse T2 hyperintensity T6–T11, gadolinium enhancement	Pos	NA	Steroids	RRMS, moderate improvement, recurrence after 4 months	La Russa et al. (2011)

(continued)

Table 1 (continued)

	LHON genotype	Age at presentation of spinal cord pathology (after visual onset)	Clinical features (i.e. NMO)	Reported spinal imaging features	CSF oligoclonal bands	Anti-NMO antibodies	Treatment	Additional diagnosis if made, outcome	Reference
Case 8	m.14484T→C	28 (concurrent)	Sensory changes thorax and hand	T2 hyperintensity upper C spine odontoid level	Neg	NA	Steroids	MS, incomplete recovery	Bhatti and Newman (1999)
Case 9	m.14484T→C	33 (6 months)	Three episodes limb weakness, sensory changes, urinary frequency and urgency, brisk DTRs	T2 hyperintensity T10	Pos	NA	Steroids	MS, partial recovery	Parry-Jones et al. (2008)
Case 10	m.11778G>A	42 (8 years)	Lower limb weakness, brisk DTRs, extensor plantars	Multiple T2 hyperintensities throughout the cervical and upper thoracic cord	NA	NA	NA	NA	Tran et al. (2001)
Case 10	m.11778G>A	27 (−3 years)	Sensory episodes, Lhermitte symptom	Cervical spine lesions	NA	NA	NA	RRMS	Pfeffer et al. (2013)
Case 11	m.11778G>A	27 (no visual involvement)	Episodes sensory loss, ataxia, weakness, LL spasticity	Cervical spine lesions	NA	NA	NA	RRMS-secondary progressive course after 4 years	Pfeffer et al. (2013)
Case 12	m.3460G→A	27 (2 years)	Recurrent sensory episodes, one episode transverse myelitis	Cervical spine lesions	Neg	NA	NA	RRMS	Pfeffer et al. (2013)
Case 13	m.3460G→A	20 (6 months)	Two episodes weakness, sensory loss, Lhermitte symptom	Cervical spine lesions	NA	NA	NA	RRMS	Pfeffer et al. (2013)
Current case	m.14484T→C, m.4160T>C	8 (2 years)	Lower limb weakness, sensory symptoms, dysautonomia	T2 hyperintensity whole spine, some swelling, no enhancement	NA	Neg	Steroids, idebenone	Near complete recovery	

NMO neuromyelitis optica, OCB oligoclonal bands, RRMS relapsing remitting multiple sclerosis, NA not available, DTR deep tendon reflexes

Josephine Stringer is a neurology fellow who was involved in patient care and manuscript development.

David Moore is a paediatrician involved in patient care and manuscript development.

Glen Gole is a paediatric ophthalmologist involved in patient care and manuscript development.

Lisa Kearns is an orthoptist and genetic counsellor who was involved in the curation of the genetic information for LHON families and was involved in manuscript development.

David Mackey is a genetic ophthalmologist with long-standing research involvement with the family and was involved in manuscript development.

David Coman is a metabolic physician involved in patient care and was instrumental in the manuscript design and development.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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Ethics Approval

N/A.

Patient Consent

The patients' parents consent to publication of this case report.

References

- Bhatti MT, Newman NJ (1999) A multiple sclerosis-like illness in a man harboring the mtDNA 14484 mutation. *J Neuroophthalmol* 19(1):28–33
- Carelli V, Ross-Cisneros F, Sadun A (2004) Mitochondrial dysfunction as a cause of optic neuropathies. *Prog Retin Eye Res* 23:53–89
- Celebisoy N, Akyurekli O, Copur A (2006) Devis's neuromyelitis optica: a case with mitochondrial DNA mutations. *Eur Neurol* 55(2):93–95
- Crout T, Parks L, Majithia V (2016) Neuromyelitis optica (Devic's syndrome): and appraisal. *Curr Rheumatol Rep* 18:54
- Filosto M, Tomelleri G, Tonin P et al (2007) Neuropathology of mitochondrial diseases. *Biosci Rep* 27(1–3):23–30
- Funalot B, Reynier P, Vighetto A et al (2002) Leigh-like encephalopathy complicating Leber's hereditary optic neuropathy. *Ann Neurol* 52(3):374–377
- Ghezzi A, Baldini S, Zaffaroni M et al (2004) Devic's neuromyelitis optica and mitochondrial DNA mutation: a case report. *Neurol Sci* 25:S380–S382
- Harding A, Sweeney M (1995) Pedigree analysis in Leber hereditary optic neuropathy families with a pathogenic mtDNA mutation. *Am J Hum Genet* 57:77–86
- Harding AE, Sweeney MG, Miller DH et al (1992) Occurrence of a multiple sclerosis-like illness in women who have a Leber hereditary optic neuropathy mt-DNA mutation. *Brain* 115:979–989
- Horvath R, Abicht A, Shoubridge E et al (2000) Leber's hereditary optic neuropathy presenting as multiple sclerosis-like disease of the CNS. *J Neurol* 247:65–67
- Howell N, Kubacka I, Xu M, McCullough DA (1991) Leber Hereditary Optic Neuropathy involvement of mitochondrial MDI gene and evidence for an intragenic suppressor mutation. *Am J Hum Genet* 48:935–942
- Jaros E, Mahad DJ, Hudson G et al (2007) Primary spinal cord neurodegeneration in Leber hereditary optic neuropathy. *Neurology* 69(2):214–216
- Jun AS, Brown MD, Wallace DC (1994) A mitochondrial DNA mutation at nucleotide pair 14459 of the NADH dehydrogenase subunit 6 gene associated with maternally inherited Leber hereditary optic neuropathy and dystonia. *Proc Natl Acad Sci U S A* 91(13):6206–6210
- Kovács GG, Höftberger R, Majtényi K et al (2005) Neuropathology of white matter disease in Leber's hereditary optic neuropathy. *Brain* 128(Pt 1):35–41
- Kumleh HH, Riazi GH, Houshmand M et al (2006) Complex I deficiency in Persian multiple sclerosis patients. *J Neurol Sci* 243(1–2):65–69
- Kwittken J, Barest H (1958) The neuropathology of hereditary optic atrophy (Leber's disease); the first complete anatomic study. *Am J Pathol* 34(1):185–207
- La Russa A, Cittadella R, Andreoli V et al (2011) Leber's hereditary optic neuropathy associated with a multiple-sclerosis-like picture in a man. *Mult Scler* 17(6):763–766
- Mackey DA (1994) Three subgroups of patients from the United Kingdom with Leber hereditary optic neuropathy. *Eye* 8:431–436
- Mackey DA, Buttery RG (1992) Leber hereditary optic neuropathy in Australia. *Aust N Z J Ophthalmol* 20:177–184
- Mackey DA, Oostra RJ, Rosenberg T et al (1996) Primary pathogenic mtDNA mutations in multigeneration pedigrees with Leber hereditary optic neuropathy. *Am J Hum Genet* 59:481–485
- Man PYW, Griffiths P, Brown D (2003) The epidemiology of Leber hereditary optic neuropathy in the North East of England. *Am J Hum Genet* 72:333–339
- Man PYW, Griffiths PG, Hudson G, Chinnery PF (2009) Inherited mitochondrial optic neuropathies. *J Med Genet* 46:145–158
- Matthews L, Enzinger C, Fazekas F et al (2015) MRI in Leber's hereditary optic neuropathy: the relationship to multiple sclerosis. *J Neurol Neurosurg Psychiatry* 86:537–542
- McClelland CM, Van Stavern GP, Tselis AC (2011) Leber hereditary optic neuropathy mimicking neuromyelitis optica. *J Neuroophthalmol* 31:265–268
- Mirbagheri S, Eckart D, Zamora CA, Mossa-Basha M, Newsome SD, Izbudak I (2016) Evaluation and management of

- longitudinally extensive transverse myelitis: a guide for radiologists. *Clin Radiol* 71:960–971
- Murakami T, Mita S, Tokunaga M et al (1996) Hereditary cerebellar ataxia with Leber's hereditary optic neuropathy mitochondrial DNA 11778 mutation. *J Neurol Sci* 142:111–113
- Newman NJ (2005) Hereditary optic neuropathies: from the mitochondria to the optic nerve. *Am J Ophthalmol* 140:517–523
- Nikoskelainen E, Marttila R, Houponen K et al (1995) Leber's "plus": neurological abnormalities in patients with Leber's hereditary optic neuropathy. *J Neurol Neurosurg Psychiatry* 59:160–164
- Palace J (2009) Multiple sclerosis associated with Leber's hereditary optic neuropathy. *J Neurol Sci* 286:24–27
- Parry-Jones AR, Mitchell JD, Gunarwardena WJ, Shaunak S (2008) Leber's hereditary optic neuropathy associated with multiple sclerosis: Harding's syndrome. *Pract Neurol* 8:118–121
- Paulus W, Straube A, Bauer W, Harding AE (1993) Central nervous system involvement in Leber's optic neuropathy. *J Neurol* 240:251–253
- Perez F, Anne O, Debruxelles S et al (2009) Leber's optic neuropathy associated with disseminated white matter disease: a case report and review. *Clin Neurol Neurosurg* 111:83–86
- Pfeffer G, Burke A, Yu-Wai-Man P et al (2013) Clinical features of MS associated with Leber hereditary optic neuropathy mtDNA mutations. *Neurology* 81:2073–2081
- Puomila A, Hämäläinen P, Kivioja S et al (2007) Epidemiology and penetrance of Leber hereditary optic neuropathy in Finland. *Eur J Hum Genet* 15:1079–1089
- Sadeghian M, Mastrolia V, Rezaei Haddad A et al (2016) Mitochondrial dysfunction is an important cause of neurological deficits in an inflammatory model of multiple sclerosis. *Sci Rep* 14:333249
- Shiraishi W, Hayashi S, Kamada T et al (2014) A case of neuromyelitis optica harboring both anti-aquaporin-4 antibodies and a pathogenic mitochondrial DNA mutation for Leber's hereditary optic neuropathy. *Mult Scler J* 20(2):258–260
- Spruijt L, Kolbach DN, de Coo RF et al (2006) Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. *Am J Ophthalmol* 141:676–682
- Tran M, Bhargava R, MacDonald IM (2001) Leber hereditary optic neuropathy, progressive visual loss, and multiple-sclerosis-like symptoms. *Am J Ophthalmol* 132(4):591–593
- Valentino ML, Barboni P, Ghelli A et al (2004) The ND1 gene of complex I is a mutational hot spot for Leber's hereditary optic neuropathy. *Ann Neurol* 56(5):631–641
- Wallace DC (1970) A new manifestation of Leber's disease and a new explanation for the agency responsible for its unusual pattern of inheritance. *Brain* 93:121–132
- Wingerchuk DM, Lennon VA, Pittock SJ et al (2006) Revised diagnostic criteria for neuromyelitis optica. *Neurology* 66(10):1485–1489