Letters to the Editor

Brainstem involvement in Leber's hereditary optic neuropathy: association with the 14 484 mitochondrial DNA mutation

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease leading to severe bilateral visual loss. It has recently been associated with several mitochondrial DNA (mtDNA) point mutations. Three major primary pathogenic mutations are located at nucleotide positions 11 778, 3460, and 14 484. Whether two other mutations at positions 4160 and 15 257 are primary pathogenic mutations remains controversial.1

An association between LHON and various other neurological diseases has long been suggested. However, non-fortuitous combinations of neurological disorders and genetically established LHON seem to be rare. Most of them are cases of "multiple sclerosis-like" illness in patients with LHON and with the 11 778 or 3460 mtDNA mutations.2 We report a case of brainstem involvement in a patient with LHON harbouring the 14 484 mtDNA mutation, and none of the other above mentioned mutations.

A 30 year old man (IV-5) had a strong family history of LHON. This disease was diagnosed by academic ophthalmologists in six other members of his family (fig 1). Four of them (III.2, III.4, III.5, IV.3) were young at onset (9 to 14 years of age) and had good recovery of vision. None had a neurological complaint. Patients III.4 and IV.1 were personally seen: neurological examination and brain MRI were normal in both.

At the age of four years, the patient had bilateral visual loss, which never recovered. At the age of 16, he had vertigo, dizziness, and vomiting that were diagnosed as "central vestibular disorder"3 at the local hospital. Symptoms resolved spontaneously, but recurred 10 years later. In April 1992, he experienced difficulty in looking down, progressing over 48 hours. Vertical gaze palsy was noted by local neurologists. Cranial CT was normal. The diagnosis of multiple sclerosis was suspected and the patient received intravenous methylprednisolone, with no benefit. He was admitted to our department in July 1992. Visual acuity was 1/10 OD and 4/10 OS. There was bilateral optic atrophy. He had a combined vertical gaze ophthalmoplegia, bilateral eyelid ptosis, and bilateral gaze evoked nystagmus. His neurological examination was otherwise normal.

Brain MRI showed a symmetric area of increased signal on T2 weighted images in the dorsal midbrain (fig 2), and no other abnormalities. Brainstem auditory evoked potentials (BAEPs) and somatosensory evoked potentials were normal. Results from analysis of CSF were normal. Standard blood tests showed a mild previously known increase in liver function. Because of a past transient drug addiction, viral serological tests were performed and were negative for hepatitis B and HIV, but positive for hepatitis C. Serum thiamine concentration was normal.

In September 1992 and January 1993, he had subacute worsening of his symptoms, leading eventually to global gaze palsy and bilateral tinnitus. The brainstem lesion was larger on MRI (fig 2). His BAEPs showed prolongation of the I-III interpeak interval. Other investigations were normal. During the subsequent months, symptoms improved spontaneously. In January 1994, he complained of stiffness of both legs. On examination, he had a moderate spastic ataxia. Tendon reflexes were very brisk in all limbs and there was bilateral ankle clonus. Plantar responses were flexor. He still had combined vertical gaze ophthalmoplegia.

Brain MRI showed a pronounced decrease in the size of the brainstem lesion. Results from cerebral and dorsal spinal cord MRI were normal. Again, symptoms improved progressively, and six months later ataxia had partly resolved, tinnitus had almost disappeared, and ophthalmoplegia was limited to a downgaze paresis. One year later, clinical features and brain MRI were unchanged.

DNA was extracted from venous blood by standard techniques and analysed for the mtDNA mutations at positions 3460, 4160, 11 778, and 15 257 using the polymerase chain reaction (PCR) and restriction endonuclease digestion, as previously described.4 The T to C mutation at position 14 484 was detected using PCR amplification of a 115 bp segment spanning the mutation site, with oligonucleotide primers 14 390-14 419 (forward) and 14 513-14 486 (reverse). The reverse primer was modified by introduction of a mismatch (substitution of A for C at position 14 487) in the wild type sequence. This creates a restriction site for Bsr I in mutant mtDNA. The patient harboured the 14 484 mutation and was heteroplasmic for it (~70% of mutant mtDNA). He did not harbour any of the four other mutations. Members III.4 and IV.1 were tested for the 14 484 mutation. They were also heteroplasmic (~70% of mutant mtDNA in both).

In the present family, four of the seven affected members had a young age of onset and good recovery of vision, whereas three did not recover. A good recovery of vision has often been reported in patients with LHON harbouring the 14 484 mutation.5 It seems to be strongly correlated with an early age of onset and not with the degree of heteroplasmia in affected members. Paradoxically, our patient had the earliest age of onset but did not recover. He was the only one that experienced symptoms of CNS involvement. In fact, it is the first time that the 14 484 mutation has been unequivocally associated with CNS involvement in a patient with LHON, although this mutation has already been reported in an LHON pedigree with neurological features. A large

4. Figure 1 Pedigree of the LHON family, showing a clear maternal transmission of the optic neuropathy. Circle = female; square = male; oblique lines = deceased; filled symbols = affected; open symbols = unaffected; arrow = patient.
5. Figure 2 Axial T2 weighted MRI, showing a symmetric lesion of the dorsal midbrain (maximum size, January 1993).
Queensland LHON family was found to harbour two mtDNA mutations, at positions 14 484 and 4160 (the second being found in this family only). Many family members were affected by a severe neurological disorder, which has not been reported in any other family with LHON until now. To date, the neurological disorder in the Queensland family seems to be related to the presence of the 4160 mutation. The 14 484 mutation is likely to be the cause of the optic neuropathy in this kindred.

The nature of the midbrain lesion found in our patient remains hypothetical. In most cases, patients with LHON and CNS involvement are females affected by a multiple sclerosis-like illness. In our patient, some of the clinical features (global paralysis of gaze, tinnitus, MRI, BAEP, and CSF findings) do not support the diagnosis of multiple sclerosis. Involvement of the CNS can occur in drug addicts, but it has never been reported in patients that had stopped taking drugs for years. Hepatitis C infection has not been associated with this kind of brainstem lesion until now. Interestingly, a very similar lesion of the dorsal midbrain has been reported in a German patient with LHON. This male patient had vertical gaze palsy, oculopupillary myclonus, and harboured the 3460 mtDNA mutation. The brainstem lesion also decreased on successive MRI. The clinical and MRI features shared by this patient and ours suggest the existence of a separate type of CNS involvement in LHON, characterised by clinical symptoms of brainstem involvement (in particular, supranuclear ophthalmoplegia) and a dorsal brainstem lesion on MRI.

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Pure sensory deficit with crossed oro-crural topography after pontine haemorrhage

Sensory deficits involving one half of the body and restricted to the hand and mouth region or the face are unusual clinical findings associated with contralateral lacunae. The posterior tibial nerves (findings considered compatible with Charcot-Marie-Tooth disease). Brainstem auditory evoked potentials and blink reflex studies were normal.

Nine months later, the numbness in the tongue and lips on the left side had gradually reduced, but continuous burning dysaesthesia in the right lower limb persisted. The left intraorbital and perioral sensory loss had resolved; a considerable decrease in pain and temperature sensations remained in the lower abdomen and leg on the right side, but tactile and proprioceptive sensations were preserved. At this time, T1 and T2 weighted MRI showed pronounced hypointensity in the left lateral pontine tegmentum reflecting haemosiderin deposition (figure, B), and no cryptic vascular malformation was detected.

What is most conspicuous in this case is the presence of trigeminal sensory changes ipsilateral to the pontine haemorrhage accompanied by abnormal sensation in the contralateral lower limb. A similar crossed sensory pattern occurs, although not isolated but in combination with other neurological dysfunction, after vascular lesions in the lateral aspect of the pons and medulla. It is noticeable that our patient showed decreased pinprick and temperature senses without impaired vibration or position senses in a crural distribution. This restricted sensory deficit presumably occurred as the result of damage to the lateral side of the spinothalamic tract where the leg representation area is situated, whereas sensory fibres from the arm are most medi ally projected. Our patient also had dysaesthesia and diminished intraoral perception of pinprick sparing facial sensation. The present case is consistent with the clinical findings of Graham et al. suggesting that the rostral spinal trigeminal nucleus in the pons

or haemorrhages in the pontine tegmentum. We describe the first case of pontine stroke leading to pure sensory deficit with crossed distribution reminiscent of the sensory pattern occurring with Wallenberg’s lateral medullary syndrome.

A 71 year old man with a history of hypertension and diagnosed as having Charcot-Marie-Tooth disease, suddenly experienced left frontal headache, vomiting, and numbness on the left side of the tongue and peribuccal area, followed by a tingling sensation over the right leg. On admission, there was no weakness of the limbs or ataxia, and cranial nerve palsy was not present. Pain and temperature sensations were diminished on the left side of the tongue and lips, and were abolished on the right side of the body below T12. Response to tactile stimulation and vibration was slightly disturbed on the right leg, but position sense was spared. Brain MRI performed two weeks after the onset of symptoms showed a lesion of high intensity in the left pontine tegmentum on both T1 and T2 weighted images (figure, A), the upper part of the medulla being spared. The somatosensory evoked potentials were normal on both sides after median nerve stimulation, and showed symmetric normal latencies with significantly reduced amplitudes when stimulating the trigeminal nerve on the left side.