Chapter 25

Leber Hereditary Optic Neuropathy

25.1 Clinical Features and Laboratory Investigations

Leber hereditary optic neuropathy (LHON) is a maternally inherited disorder that causes acute or subacute loss of bilateral central vision. The onset is usually asymmetrical, but the interval between involvement of the two eyes is usually less than a few months. Monocular involvement is extremely rare. Men are affected much more frequently than women and the age at onset is usually lower in males than in females. The male preponderance ranges from 80% to 90% in most white pedigrees to approximately 60% in Japanese families. The onset of visual loss typically occurs between the ages of 15 and 35 years, with an age range of 5–70 years. In most patients visual acuities deteriorate to worse than 2/20 in the course of several months, stabilizing thereafter. The loss of vision is usually permanent, but spontaneous improvement or recovery can occur. Transient worsening of vision with exercise or heat may occur (Uhthoff's symptom). Visual field defects are typically central or cecocentral, but may also be bitemporal. Headache, eye discomfort, and flashes of light may occur at the time of vision loss. Color vision is affected severely, often early on in the course of vision loss.

The first sign of the disease, peripapillary telangiectatic microangiopathy, is ophthalmoscopically visible in the presymptomatic stage. At the onset of visual loss, the optic disc is swollen and there is marked dilatation and tortuosity of the peripapillary retinal vessels. However, vessels do not leak fluorescein on fluorescein angiography. The typical ophthalmoscopic findings may also be present in asymptomatic family members, but some patients with LHON never exhibit these characteristics, even if examined at the time of acute vision loss. After the development of visual loss, a capillary-poor retina with attenuated arterioles and a pale optic disc remain.

In the majority of patients with LHON, visual dysfunction is the only significant manifestation of the disease. In some pedigrees additional cardiac conduction abnormalities occur, in particular pre-excitation syndromes such as Wolff–Parkinson–White syndrome. Minor neurological abnormalities such as hyperreflexia, Babinski signs, mild ataxia, or peripheral neuropathy have been reported. Several pedigrees have been described in which some of the patients experience more severe neurological problems. An extrapyramidal movement disorder with bilateral lesions of the basal ganglia on MRI has been reported in several patients. Association with a Leigh-like encephalopathy with brain stem and basal ganglia involvement on MRI has also been observed. The most frequently observed association is with a multiple sclerosis-like disease, and multiple studies have shown that the association is more than coincidental. Episodic neurological abnormalities occur with partial or complete recovery. Apart from optic neuropathy, frequently observed signs include spasticity, cerebellar ataxia, sensory disturbances, vertigo, diplopia, internuclear ophthalmoplegia, and urgency of micturition. The clinical features are indistinguishable from those of multiple sclerosis, except for their occurrence in the context of a family history of LHON. Presence of severe and bilateral visual signs justifies considering the possibility of LHON in otherwise typical multiple sclerosis patients.

Laboratory tests are of limited use in LHON. Fluorescein angiography is helpful for the illustration and confirmation of the LHON funduscopic features. VEP studies confirm the absence of any response or presence of responses with prolonged latencies and decreased amplitudes. ERG is typically normal. In patients in whom the disease course resembles that of multiple sclerosis, CSF analysis may reveal an elevation of the IgG index and presence of oligoclonal bands. ECG may reveal conduction abnormalities. In the past, a definitive diagnosis depended on a positive family history, age at onset of the vision loss, and the characteristic circumpapillary microangiopathy of the optic disc in the acute stage. Demonstration of a point mutation in mitochondrial DNA in affected individuals confirms the diagnosis; DNA confirmation of the diagnosis can also be obtained in atypical or sporadic cases.

25.2 Pathology

In LHON severe axonal degeneration with myelin loss of the central part of the optic nerve and pregeniculate pathway is found. The nature of the cerebral multiple sclerosis-like white matter lesions has not yet been investigated.

25.3 Pathogenetic Considerations

A number of mitochondrial DNA mutations have been described in association with LHON. The mutations can be distinguished into high-risk mutations, called class I or primary mutations, and low-risk mutations, called class II or secondary mutations. The most frequent class I mutations include a mutation at nucleotide position 11778 in the mitochondrial gene encoding subunit 4 of complex I, present in 50% of European patients to 95% of Asian LHON patients; a mutation at nucleotide position 3460 in the gene encoding subunit 1 of complex I, present in about 15% of European patients; a mutation at position 14484 in the gene encoding for subunit 6 of complex I, present in about 15% of European patients; and a mutation at position 14459 in the gene encoding for subunit 6 of complex I. In addition, several class II mutations are known, the pathogenic role of which is much less clear. Generally, only one class I mutation occurs in a LHON pedigree and individuals harboring this mutation have a relatively high probability of vision loss. Class I mutations are not observed in the normal population. Class II mutations occur at a much higher frequency among LHON patients than among the normal population. When present in LHON patients, they occur in combination with other class I or II mutations. They may serve as additional predisposing or exacerbating genetic factors that increase the probability of expressing LHON. It is probably the synergistic effect of multiple mitochondrial DNA mutations that, by their accumulative effect on the oxidative phosphorylation, produces a pathogenic reduction in ATP-generating capacity.

For all class I mutations variable penetrance is observed among apparently homoplastic LHON pedigrees. About 50% of males and 10% of females harboring a pathogenic mutation actually develop LHON. In spite of sharing the same mutations, males have a 4–5 times higher risk of being affected than females. About 15% of the patients are heteroplasmic for a class I mutation, and in about 35% of the families at least one heteroplasmic individual can be identified, but heteroplasmy is not sufficient to explain the observed phenotypic variation. Therefore, class I mutations appear to be necessary but not sufficient for the clinical manifestation of LHON. Additional genetic (nuclear or mitochondrial), environmental, or physiological factors may play a significant role in the expression of LHON. Both internal and external environmental factors may play a role. Systemic illnesses, nutritional deficiencies, and toxins that stress or inhibit the body's mitochondrial respiratory capacity could conceivably initiate or increase phenotypic expression of the disease. Adverse effects of tobacco smoke (cyanide present in tobacco smoke inhibits cytochrome-*c* oxidase activity) and alcohol have been suggested but never proven. The male preponderance and earlier onset for males suggest a recessive susceptibility gene on the X chromosome acting in synergy with the mitochondrial DNA mutation. Affected females heterozygous for the X-chromosomal susceptibility gene may be involved because of unfortunate X chromosome inactivation.

Almost all class I mutations alter mitochondrial DNA-encoded subunits of complex I. The LHON mutations do not alter the amount, assembly, and stability of complex I. However, various mutations have been shown to affect complex I function, resulting in altered electron transport capacity, respiration rate, and ATP production. It is suggested that the decline in oxidative phosphorylation capacity caused by a combination of influences (class I and class II mutations, X-linked nuclear factor, other genetic factors, environmental factors, effects of aging) may result in optic atrophy, cardiac conduction abnormalities, and neurological disease. With regard to those pedigrees with LHON and neurological disease, it would appear that certain mitochondrial DNA mutations may be particularly responsible. The mutation at position 14459 is frequently associated with a combination of LHON and dystonia. Females with the 11778 mutation are especially likely to develop clinical and neuroimaging findings indistinguishable from multiple sclerosis.

25.4 Therapy

No effective treatment to prevent or halt LHON has as yet been found.

25.5 Magnetic Resonance Imaging

In patients with LHON, optic nerve abnormalities can be shown with STIR (short tau inversion recovery) sequences. Increased signal intensity of the mid and posterior intraorbital section of the optic nerve is seen, sparing the anterior portion. In most patients brain MRI is normal. In LHON associated with dystonia, bilateral putamen lesions have been found. In patients with a Leigh-like presentation, additional brain stem lesions are found. Cerebellar atrophy has also been reported. In patients with a multiple sclerosis-like disease, multiple small white matter lesions are seen as in multiple sclerosis (Fig. 25.1). The lesions are found in the periventricular and deep white matter of the cerebral hemispheres, in the brain stem, and in the cerebellum. The periventricular white matter is predominantly involved. On the basis of MRI only, differentiation between LHON and multiple sclerosis is not possible. In MRS we found no elevation of lactate in LHON.

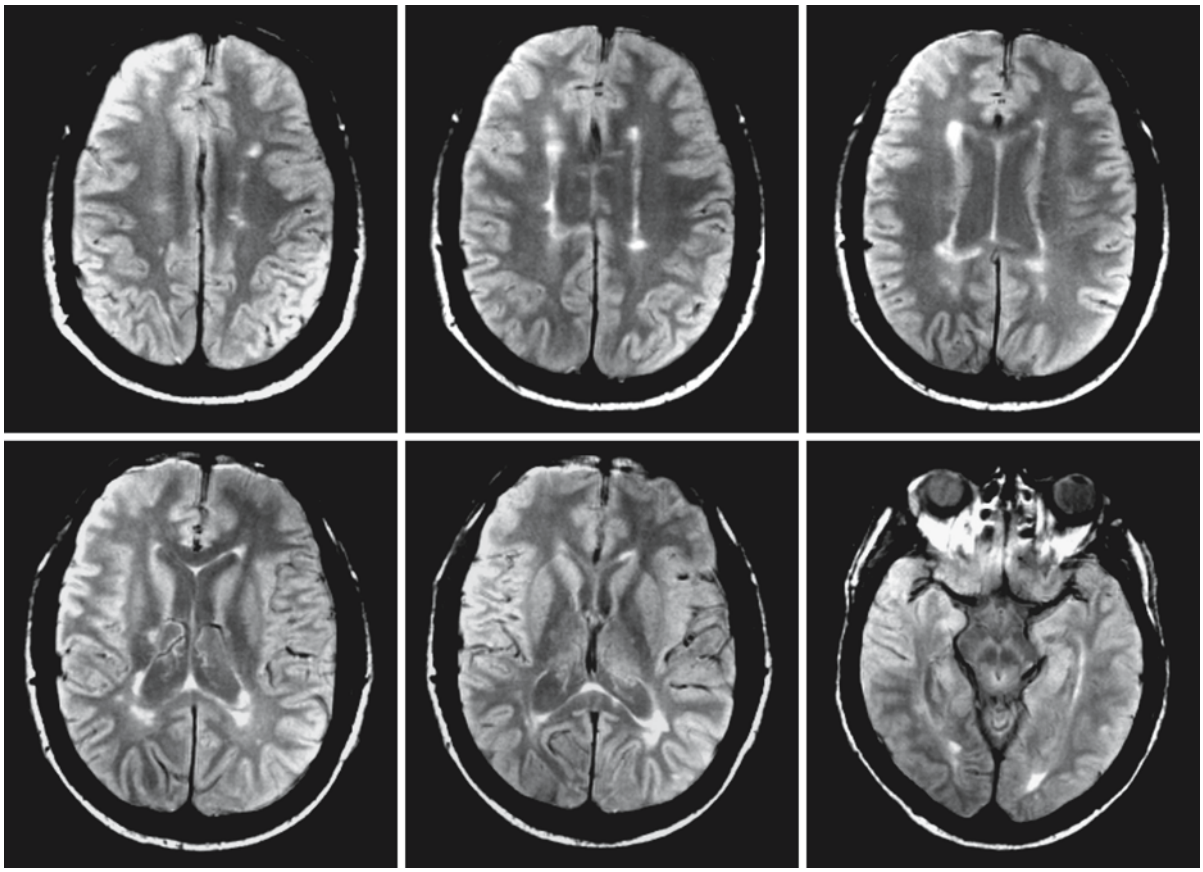

Fig. 25.1. Male patient, 43 years of age, with LHON. The transverse proton density series shows a white rim around the ventricles, involvement of the corpus callosum, and some isolated spots in the centrum semiovale. The ventricles are slightly enlarged