Principles and Practice of Clinical Electrophysiology of Vision

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PART XVII

Optic Nerve and Central Nervous System Dysfunction

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Leber's Hereditary Optic Atrophy

Thomas A. Berninger

In 1871 Leber[4] described a hereditary optic atrophy characterized by acute visual loss, circumpapillary telangiectatic micropathy, tortuosity of the retinal vessels, and edema in the retinal nerve fibers; 85% of those affected are male, but affected fathers do not transmit the condition to their children. The onset of Leber's optic atrophy (LOA) is usually in the second and third decade in males and, more rarely, in the fourth and fifth decade in females; however it has been observed as late as 70 years in a male.[12]

INHERITANCE

While there was no doubt that LOA was a hereditary disorder, the manner of transmission was not clear since male-to-female (to-male) transmission was not seen in the families who had been studied, and, therefore, the criteria for x-linked recessive inheritance was not fulfilled. This issue was clarified by Nikoskelainen et al.'s observation of enlarged subsarcolemmal mitochondria in patients with LOA.[9, 10] They proposed that mitochondrial DNA inheritance explained the hereditary patterns seen in LOA families, since all of zygote's viable mitochondria is contributed by the ovum. Mitochondrial inheritance in LOA was confirmed by Wallace et al. who found a mitochondrial DNA replacement mutation.[17]

FUNDUS

In 1973 Smith et al.[14] described the typical signs and appearance of fluorescein angiography. The fundus shows a glistening opacity of the peripapillary nerve fiber layer due to dilatation of the ganglion cell axons, blurred disc margins, tortuous retinal vessels, and irregular telangiectatic dilation of capillaries in peripapillary and prepapillary networks. Despite the vascular changes, fluorescein angiography does not show evidence of abnormal vascular permeability. The telangiectatic microangiopathy of the peripapillary arterioles and capillaries has also been observed in asymptomatic males and females of the female line.[8] As the disease progresses, the microangiopathy disappears. Optic atrophy develops with attenuation of retinal vessels and atrophy of the whole fiber layer.

RETINAL FUNCTION

Visual Acuity

Reports concerning visual acuity are contradictory. Carroll and Mastaglia[2] stated that there is no visual improvement after the initial deterioration to 6/60. However, there are several reports about spontaneous improvement in up to 45% of members with the typical patterns of LOA.[6, 13, 15, 16]

Color Vision

Severe color vision defects are reported in patients with LOA. Color vision defects—mainly of the tritan axis—are also observed in suspected carriers.[1, 5, 7]

Visual Fields

The first observation is of a relative centrocecal scotoma. This progresses to a large absolute centrocecal scotoma that breaks through to the periphery, usually upward or inward.[11] An improvement of the

visual field has frequently been observed prior to improvement in color vision and visual acuity.[15]

ELECTROPHYSIOLOGY

Electroretinograms and electro-oculograms have been reported to be normal in patients with LOA.[15] Some patients show supranormal ERG b-waves (unpublished, Heckenlively).

Visual Evoked Cortical Potential

The first abnormalities in the visual evoked cortical potential (VECP) consist either of an increase in the P100 latency or a VECP waveform with a double, positive peak (PNP complex).[1, 3] In advanced cases with markedly reduced visual acuity the responses are immeasurably small.[2]

Pattern Electroretinography

Normal P50 components were recorded in patients with LOA, while the N95 component was extinguished.[1] Substantially reduced amplitudes in two recently affected cases were found by Heckenlively (unpublished data).

Associated Neurological Findings

Many subsequent reports have described neurological involvement, including epilepsy and spastic quadriparesis.[1]

PATHOGENESIS

Wallace et al.[17] determined in several families with LOA that a mitochondrial DNA replacement mutation occurs that converts an arginine to a histidine at codon 340 in the reduced necotincimide adenine dinucleotide subunit 4 gene and eliminates an Sfa NI site. Although there is an excellent correlation between LOA and the loss of the Sfa NI site between the maternal lineages, there is a much less clear association between the loss of the Sfa NI site and the optic atrophy. Thus environmental stresses that reduce respiratory capacity (e.g., cyanide), might augment expression of the mutation.[1, 17–19]

TREATMENT

Currently, no definite treatment is known for LOA. One current theory suggests a putative role of cyanide, and Syme et al. proposed 4 to 8 g cystine orally per day together with 1,000 μg hydroxocobalamin intramuscularly 3 times weekly.[15] Thirty-five percent of their patients acheived a visual acuity of 6/18 and better. With the mutation site known, diagnostic blood tests will become available to determine if a patient is at risk, to whom prophylactic therapy can be directed.[14a]

DIFFERENTIAL DIAGNOSIS

The major differential diagnosis of LOA is papillitis. However, the case history and the clinical findings (especially fluorescein angiography) are so typical in LOA that LOA should be easily differentiated from papillitis.

LEBER'S OPTIC ATROPHY IN JAPAN

LOA seems to be more than one entity. Japanese patients especially seem to belong to another entity. The sex distribution (40% affected females) is different from that in Europe. There are also definite signs of inflammation observed in histopathological cases in Japan, while in no European study was such seen.

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