A DEARTH of literature exists regarding detailed histopathologic or morphometric descriptions of optic nerve hypoplasia (ONH) and Leber hereditary optic neuropathy (LHON), much less a comparison of these early and late forms of intrinsic axonal loss.

Optic nerve hypoplasia was first recognized in 1915; however, detailed clinical descriptions were not available until the 1960s. Initially, ONH was thought to be a rare anomaly; more recently, it has been regarded as a fairly common cause of blindness in children. Optic nerve hypoplasia is a nonprogressive congenital defect that can occur unilaterally or bilaterally, either in isolation or in association with other central nervous system malformations and endocrine malfunctions. The incidence of ONH is equal in males and females. It can manifest in complete, incomplete, or segmental forms. Optic nerve hypoplasia is usually idiopathic, although the use of several toxins, medications, and alcohol during pregnancy, as well as maternal diabetes mellitus, all have been associated with children born with ONH. The characteristic clinical features range from severely decreased vision usually discovered in infants to an incidental finding without visual loss with or without mild visual field abnormalities and reduced pupillary response to light in adults. Results of funduscopic examination reveal a small optic disc and often the so-called double ring sign.

Unilateral or asymmetrical cases of ONH may be misdiagnosed as simple primary strabismus and amblyopia. Bilateral cases may be erroneously diagnosed as being one of the hereditary congenital forms of optic atrophy but should be primarily differentiated from Leber congenital amaurosis and achromatopsia, which may have similar clinical features. Leber congenital amaurosis is not to be confused...
MATERIALS AND METHODS

In this study, 3 optic nerves were carefully examined. The first was obtained from a 42-year-old woman without a history of any neurologic or ophthalmic problems who had died of hepatic failure. The second optic nerve was obtained from a 33-year-old woman with ONH who had been blind since birth. Her medical records from 1964 to 1973 indicated that she was initially misdiagnosed at age 20 years with “Leber disease” (some of the physician’s notes incorrectly implied LHON rather than ONH). However, the same records revealed that her visual acuities had been fairly stable (20/100 OD and 20/200 OS) since early childhood. Her fundus examination results were described as bilateral optic nerve atrophy. However, results of a skull x-ray (performed in 1970) were negative, and there was no family history of any neuro-ophthalmologic disease. At age 53 years, the patient died of extensive third-degree thermal injuries, and there remained a statistically significant difference between cases of LHON and ONH occurring in the second or third decade of life.15 Although the visual loss affects both eyes and is roughly symmetrical, the onset is usually not absolutely simultaneous.

Previous histopathologic reports4,6,7,15,16 of LHON have been largely limited to describing loss of the retinal ganglion cells and an associated decreased optic nerve diameter and axonal loss.

In the present investigation, we examine and compare the histopathologic and morphometric findings in optic nerves from a healthy control patient, a congenitally blind patient shown on pathologic examination results to have ONH, and a patient with the 11778 primary mutation of LHON. We characterize and histologically compare these 2 optic neuropathies, which differ in that ONH reflects either underdevelopment or early apoptosis of retinal ganglion cells and their axons and LHON occurs in the second or third decade of life and may involve different pathophysiological mechanisms.

RESULTS

Light microscopic and morphometric analysis of the control optic nerve revealed a diameter of 2.1 mm (Figure 1), a normal nerve fiber size spectrum, and a total count of 1.2 million fibers (Table). Results of gross examination of the brain of the patient with ONH showed hypoplastic changes in the corpus callosum limited to the posterior portion (spleen). Results of gross examination of the eyes revealed (1) a peripheral cataract, (2) some atrophic changes in the ciliary bodies, and (3) flat and pale optic nerves with sclerotic vessels at the optic nerve head.

Results of light microscopy revealed severe axonal depletion largely limited to a large, inferonasal sector (Figure 2, left) that contained an anomalous small artery distinct from the central artery (Figure 2, right). Only a small supertemporal sector contained axons compacted to a near normal appearance. The remaining sectors consisted of sparse scattering of axons with extensive proliferation of astrocytes, with no apparent with LHON, a disorder that usually manifests in adulthood. Leber hereditary optic neuropathy was first described by von Graefe in 1858 but was more clearly defined and established by Leber in 1871 as a late-onset hereditary optic atrophy. Results of recent studies13,14 demonstrate that LHON is inherited maternally and is usually associated with point mutations in the mitochondrial DNA at nucleotide positions 11778, 3460, 15257, and 14484, which leads to mitochondrial dysfunction. The clinical features of LHON include acute, bilateral loss of central vision, which affects primarily men in the second or third decade of life.13 Although the visual loss affects both eyes and is roughly symmetrical, the onset is usually not absolutely simultaneous.

Figure 1. Cross-section of control retrobulbar optic nerve (1% paraphenylene diamine solution, × 80).
degenerated profiles or macrophages detected (Figure 2, right). Results of morphometric analysis revealed a reduced overall diameter of the ONH compared with the control (1.5 mm vs 2.1 mm) and a total fiber population of only 98,000, representing a 90% reduction compared with the control optic nerve ($P$, .001) (Table).

In contrast, results of light microscopic examination of the LHON revealed a diffuse and general depletion of fibers involving all of the central portion, with residual axons limited to peripheral clusters superiorly and temporally (Figure 3, left). The central portion of the optic nerve, significantly depleted of axons, consisted of fibrocytic scarring and scattered degeneration dust associated with macrophages (Figure 3, right). In contrast to the ONH case, the LHON displayed profiles of degenerated axons, fewer astrocytes, and an increased number of fibroblasts.

Results of morphometric analysis showed a reduced overall diameter of the LHON compared with the control (1.6 vs 2.1 mm) and a total fiber count of only 48,000, representing a 95% reduction compared with the control optic nerve ($P$<.001) (Table).

### Table: Histological and Morphometric Comparison of Control, Optic Nerve Hypoplasia (ONH), and Leber Hereditary Optic Neuropathy (LHON) Optic Nerves

<table>
<thead>
<tr>
<th>Optic Nerve</th>
<th>Control</th>
<th>ONH</th>
<th>LHON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counted fiber population*</td>
<td>1,200,000</td>
<td>98,000</td>
<td>48,000</td>
</tr>
<tr>
<td>Total cross-sectional area, mm²</td>
<td>3.5</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Pattern of axonal distribution</td>
<td>Normal</td>
<td>Mostly superotemporal and a thin sector inferiority</td>
<td>Peripheral clusters superiorly and temporally</td>
</tr>
<tr>
<td>Degeneration pattern</td>
<td>No degeneration</td>
<td>No degeneration</td>
<td>Scattered “degeneration dust” and some 1% paraphenylene diamine solution–verified degeneration</td>
</tr>
<tr>
<td>$P$ (fiber population vs normal optic nerve)</td>
<td>...†</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Axon + myelin.
†Ellipses indicate no data to be entered.

**Figure 2.** Left, Cross-section of retrobulbar optic nerve with optic nerve hypoplasia showing axonal depletion in a large inferonasal sector (arrows) (1% paraphenylene diamine solution, original magnification × 80). Right, High-power picture from an axon-depleted area showing no apparent axonal degeneration or macrophages (1% paraphenylene diamine solution, original magnification × 800). This area also contains an anomalous small artery with elastin distinct from the central artery (arrow).
Results of morphometric comparisons of the nerve fiber counts and nerve fiber diameter spectra in ONH, LHON, and control optic nerves revealed a significant shift of fiber diameters to smaller sizes in LHON optic nerves (histogram). The line diagram (inset) in Figure 4 shows the relationship between the modes of each nerve fiber spectrum, with a shift to the left in LHON.

Earlier studies of ONH and LHON optic nerves provided only limited histopathologic descriptions. Reports of ONH eyes have described subnormal optic nerve diameters and depletions of retinal ganglion cells and axons in the nerve fiber layer and optic nerve.6,20

Regarding LHON, previous reports revealed a reduction of the optic nerve diameter, a central depletion of axons with residual peripheral clusters of axons, and fibrillary gliosis16 without detectable inflammatory profiles.21 We previously reported a reduction of the optic nerve diameter, a central axonal loss, and minimal inflammatory changes in an optic nerve from a patient with the 11778 primary mutation of LHON.15 Kerrison et al22 also recently examined an optic nerve from a patient with LHON. They showed that optic nerve atrophy did not appear more prominent centrally than peripherally, and they did not detect any inflammatory changes.22 They described calcium inclusion bodies as possible evidence of mitochondrial involution. However, we failed to corroborate this.23

The possible underlying mechanisms previously suggested regarding ONH have, in the absence of ultrastructure, been partially speculative. Most early investigators thought that ONH resulted from a failure of the retinal ganglion cell layer to differentiate between the 13- and 17-mm stage of embryonic development.1,9,20,24 In 1957, Mann25 suggested that when retinal ganglion cell axons fail to form central connections, these axons then degenerate, which, in extreme cases, results in ONH. In 1978, Moiser et al6 examined the eyes of a child with hydranencephaly and ONH and found in the retinas normal amacrine and horizontal cells; they argued that failure of retinal ganglion cell differentiation as a cause of ONH was unlikely because all 3 cell types arise from the same stem cells. Alternatively, in 1978 Frisen and Holmegaard4 suggested that ONH is a consequence of degeneration of ganglion cells and their axons caused by an insult to the developing visual pathway. This would not be contradictory to the general concepts of Mann25 regarding the process of retinofugal specificity acquisition. However, despite these theories, the pathogenesis of ONH remains incompletely understood.

Leber hereditary optic neuropathy was initially believed to be a rare, X-linked genetic disorder. However, recent studies have confirmed that the pathogenesis of LHON is caused by point mutations in the mitochon-
drial DNA, producing mitochondrial dysfunction. Harding et al. suggested that optic nerve damage in LHON could be immunologically mediated and that mitochondrial genes might contribute to susceptibility of multiple sclerosis. Results of our histopathologic examination did not reveal any signs of perivasculitis, and the detectable inflammatory changes were minimal. Hence, we could not corroborate the suggestion of Harding et al. of an immunologic component for optic nerve damage in LHON.

In the present study, results of light microscopic examination of the optic nerve from our patient with ONH revealed sectoral axonal loss without any detectable degenerated profiles, consistent with the more limited descriptions in the literature. The present study of an optic nerve with LHON showed central axonal loss with detectable fibrocytic scarring and scattered degeneration dust with minimal inflammatory profile, contrary to previous findings. The data from morphometric analysis and comparison of control, ONH, and LHON are summarized in the Table. Morphometric comparison of nerve fiber diameters from healthy, ONH, and LHON reveals a significant shifting of nerve fiber diameters to the smaller size in LHON, notwithstanding the fact that the nerve fiber diameter is expected to be of greater caliber in the peripheral portions of the optic nerve. On the other hand, the nerve fiber diameter spectrum in ONH was similar to that of the control optic nerve. The shifting of the nerve fiber diameter in LHON is intriguing. We had anticipated a shift in the opposite direction insofar as clinically, LHON involves a selective loss of the smaller papillomacular fiber. One possible explanation is that surviving axons diminish in caliber.

The corpus callosum (splenium) anomaly in our patient with ONH suggests a more generalized neurodevelopmental impairment, consistent with the study by Novakovic et al. Our patient with ONH was originally misdiagnosed as having Leber disease. Such confusion probably stems from the difficulty in differentiating ONH from Leber congenital amaurosis (the name Leber has been applied to 2 forms of optic neuropathy).

Yet, as our study results show, ONH and LHON are distinguishable not only clinically but also histopathologically. Each has a clearly distinctive pattern of nerve fiber distribution and axonal dropout. The histopathologic findings in ONH did not reflect evidence of axonal degeneration. These findings and the previously accumulated experimental and clinical data suggest that ONH may be the result of excessive “apoptosis” of the retinal ganglion cells during the development of visual pathway, which fits in well with Mann’s concept of the overproduction of retinal ganglion cells and their axons, followed by the dying back (or apoptosis) of those that fail to establish the correct terminal connections. Alternatively, as Frisen and Holmegaard suggested, it is possible that ONH is caused by an insult directly to the developing anterior visual pathway, which leaves only a small number of nerve fibers intact.

Conversely, in LHON, mutational-induced mitochondrial dysfunction directly leads to axonal degeneration and an associated minimal inflammation, presumably implicating a more degenerative process with a mild reactive immunologic component in LHON.

The association between ONH and LHON probably reflects 2 distinct pathogenetic mechanisms: the result of apoptosis and the result of specific degenerative processes, respectively.

The present study had 2 important limitations. Pathologic condition described at the end of a long life may not reflect the processes that occurred 6 decades earlier. Only 1 optic nerve was available as a sample of each of
these optic neuropathies. Further histopathologic and morphometric comparison of the retina, lateral geniculate nucleus, and other primary visual nuclei from the patients with ONH and LHON might, compared with healthy controls, provide more information regarding the pathogenesis of these clinical entities.

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REFERENCES


Announcement

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