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Hereditary optic neuropathies

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Abstract

Aims **To provide a clinical update on the hereditary optic neuropathies.**
Methods **Review of the literature.**
Results **The hereditary optic neuropathies comprise a group of disorders in which the cause of optic nerve dysfunction appears to be hereditable, based on familial expression or genetic analysis. In some hereditary optic neuropathies, optic nerve dysfunction is typically the only manifestation of the disease. In others, various neurologic and systemic abnormalities are regularly observed.**
Conclusion **The most common hereditary optic neuropathies are autosomal dominant optic atrophy (Kjer's disease) and maternally inherited Leber's hereditary optic neuropathy. We review the clinical phenotypes of these and other inherited disorders with optic nerve involvement.**
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Keywords: Leber's hereditary optic neuropathy; autosomal dominant optic atrophy; Kjer's disease; hereditary optic neuropathy; optic atrophy; mitochondrial disease; visual loss

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The hereditary optic neuropathies comprise a group of disorders in which the cause of optic nerve dysfunction appears to be hereditable, based on familial expression or genetic analysis.[1,2] Clinical variability, both within and among families with the same disease, often makes recognition and classification difficult. Traditionally, classification has relied on the recognition of similar characteristics and similar patterns of transmission, but genetic analysis now permits the diagnosis of the hereditary optic neuropathies in the absence of family history or in the setting of unusual clinical presentations. As a result, the clinical phenotypes of each disease are broader, and it is easier to recognize unusual cases.

The inherited optic neuropathies typically present as symmetric, bilateral, central visual loss. In many of these disorders, the papillomacular nerve fibre bundle is affected, with resultant central or cecocentral scotomas. The exact location of initial pathology along the ganglion cell and its axon, and the pathophysiologic mechanisms of optic nerve injury remain unknown. Optic nerve damage is usually permanent and, in many diseases, progressive. Once optic atrophy is observed, substantial nerve injury has already occurred.

In classifying the hereditary optic neuropathies, it is important to exclude the primary retinal degenerations that may masquerade as primary optic neuropathies because of the common finding of optic disc pallor. Retinal findings may be subtle, especially among the cone dystrophies, where optic nerve pallor may be an early finding. The possibility of a primary retinal process should be considered in patients with temporal optic atrophy even when the retina itself is not obviously abnormal. Retinal arterial attenuation and abnormal electroretinography should help distinguish these diseases from the primary optic neuropathies.

Customary classification of the inherited optic neuropathies is by pattern of transmission. The most common patterns of inheritance include autosomal dominant, autosomal recessive, and maternal (mitochondrial). The same genetic defect may not be responsible for all pedigrees with optic neuropathy inherited in a similar fashion. Similarly, different genetic defects may cause identical or similar phenotypes—some inherited in the same manner, others not. Alternatively, the same genetic defect may result in different clinical expressions, although the pattern of inheritance should be consistent. To complicate matters further, single cases are often presumed or proven to be caused by inherited genetic defects, making the pattern of familial transmission unavailable as an aid in classification.

In some of the hereditary optic neuropathies, optic nerve dysfunction is typically the only manifestation of the disease. In others, various neurologic and systemic abnormalities are regularly observed. Additionally, inherited

diseases with primarily neurologic or systemic manifestations, such as the multisystem degenerations, can include optic atrophy.

The hereditary optic neuropathies reflect a number of different inheritance patterns and can be caused by defects in either the nuclear or mitochondrial genomes. As more specific genetic defects are discovered, our concept of the phenotypes of these disorders will likely change, as will our classification. More accurate definition of the underlying genetic abnormalities will aid genetic counselling. Furthermore, identification of the gene defect, elucidation of the gene product and its normal function, and clarification of the abnormality caused by the mutation should improve our understanding of the pathophysiologic mechanisms of optic nerve dysfunction and allow for the development of directed therapies.

Leber's hereditary optic neuropathy

In 1871, Leber[3] first described the disease that bears his name, although similar cases were reported 50 years earlier (e. g., von Graefe[4]). Numerous pedigrees of Leber's hereditary optic neuropathy (LHON) have since been reported worldwide.[5–14] Since the late 1980s, LHON has received notoriety as a maternally inherited disease linked to abnormalities in mitochondrial DNA.[2,7,9,11,14–20] Genetic analysis has broadened our view of what constitutes the clinical presentation of LHON.

Despite multiple studies describing hundreds of patients with LHON worldwide, the actual prevalence and incidence of visual loss from this disorder has been only rarely and geographically selectively investigated. Among individuals in the North East of England, there was a minimal prevalence of visual loss from LHON of 3.22 per 100 000 individuals and a prevalence for harbouring a primary LHON-associated mtDNA mutation of 11.82 per 100 000 individuals.[21,22] In Australia, the disease accounts for about 2% of legal blindness in individuals under age 65 years and for about 11% of all patients with bilateral optic neuropathy of uncertain aetiology.[23–25]

Men are affected with visual loss more frequently than women, with a male predominance of about 80 to 90% in most pedigrees.[6–10] Approximately 20 to 60% of men at risk for LHON experience visual loss.[6,23,24, 26] Among women at risk, the occurrence rate ranges from 4 to 32%.[6,23,24,26] Affected females are more likely to have affected children, especially daughters, than unaffected female carriers.[6,27] Mackey[23,24] reported that approximately 20% of male and 4% of female carriers in Australia lose vision. Mackey and Howell[28] noted that there has been a dramatic decline in the risk of visual loss among pedigrees with LHON in Australia and a definite decrease in penetrance over the past century.

The onset of visual loss typically occurs between the ages of 15 and 35 years, but otherwise classic LHON has been reported in many individuals both younger and older,[5–7,9–11] with a range of age at onset from 2 to 80 years. This age variability occurs even among members of the same pedigree.

Visual loss typically begins painlessly and centrally in one eye. The second eye is usually affected weeks to months later. Reports of simultaneous onset are numerous[5–7] and likely reflect both instances of true bilateral coincidence and those in which initial visual loss in the first eye went unrecognized. Rarely, loss of vision in the second eye occurs after a prolonged interval (more than 12 years) or, even more infrequently, visual loss remains monocular.[11] In general, however, greater than 97% of patients will have second eye involvement within 1 year.[7,9]

The onset of visual loss is usually not associated with other symptoms. Uhthoff's symptom (a transient worsening of vision with exercise or warming) may occur in patients with LHON, as it does in patients with other optic neuropathies. Other reported symptoms at the time of visual loss are usually minor and nonspecific, such as headache; eye discomfort; flashes of light, colour, or both; limb paresthesias; and dizziness.[5–7,9]

The duration of progression of visual loss in each eye also varies and may be difficult to document accurately. Usually, the course is acute or subacute, with deterioration of visual function stabilizing after months.[5–7,11] In one study of molecularly confirmed LHON, progression of visual loss in each eye ranged from 'sudden and complete' to 2 years, with a mean of 3.7 months.[7] Nikoskelainen *et al*[11] described rare patients with slowly progressive visual loss, ultimately with a favourable visual outcome.

Visual acuities at the point of maximum visual loss range from no light perception to 20/20, with most patients deteriorating to acuities worse than 20/200.[5–7,9,11] Colour vision is affected severely, often early in the course, but rarely before significant visual loss.[11] The Farnsworth-Munsell 100-Hue test may be the earliest indicator of optic nerve dysfunction, but subtle abnormalities of colour vision can be demonstrated in asymptomatic family members.[29] Pupillary light responses may be relatively preserved when compared with the responses in patients with optic neuropathies from other causes,[11,30] although others have not confirmed this finding.[31]

Visual field defects are typically central or cecocentral[6,7,11,29] (Figure 1). Apparently unaffected eyes may show subtle cecocentral scotomas only to red test objects or as mild depression on central automated

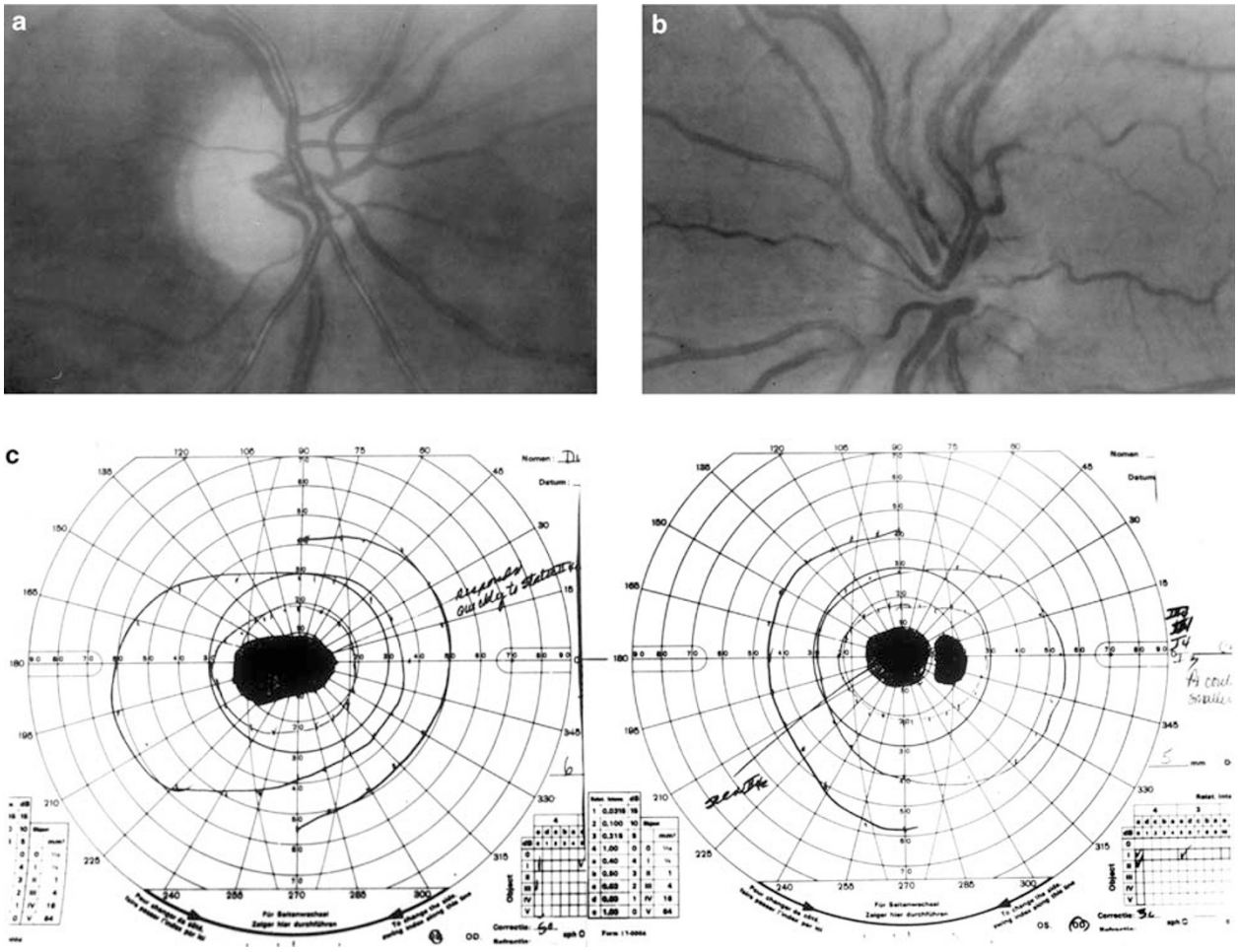

Figure 1 Leber's hereditary optic neuropathy. (a and b) Optic nerve appearance in a patient with bilateral visual loss. (a) The right optic nerve is pale consistent with visual loss of several months' duration. (b) The left optic nerve appears hyperaemic without true disc oedema at the time of visual loss. There are papillary telangiectasias. (c) Goldmann visual fields showing central defects in both eyes.

perimetry. Field abnormalities mimicking the bitemporal configuration of chiasmal defects have also been reported.[32,33] In a few of these cases, the defects have strictly respected the vertical meridian.

Even the earliest descriptions of this disease noted funduscopic abnormalities other than optic atrophy.[3] Especially during the acute phase of visual loss, hyperaemia of the optic nerve head, dilation and tortuosity of vessels, retinal and disc haemorrhages, macular oedema, exudates, retinal striations, and obscuration of the disc margin were recognized in some cases. In 1973, Smith *et al*[34] reported a triad of signs believed pathognomonic for LHON: circumpapillary telangiectatic microangiopathy, swelling of the nerve fibre layer around the disc (pseudoedema), and absence of leakage from the disc or papillary region on fluorescein angiography (distinguishing the LHON nerve head from truly oedematous discs)[34] (Figure 1). Nikoskelainen *et al*[11] observed these funduscopic changes in all of their symptomatic patients with LHON, some of their 'presymptomatic' cases, and in a significant proportion of asymptomatic maternal relatives. However, having abnormalities of the peripapillary nerve fibre layer does not necessarily predict visual loss. Furthermore, some patients with LHON never exhibit the characteristic ophthalmoscopic appearance, even if examined at the time of acute visual loss.[7,9,10] In one review, 22 of 52 patients did not have any abnormal funduscopic findings.[7] In another review, 36% of 33 patients examined within 3 months of visual loss did not have retinal microangiopathy.[9] The 'classic' LHON ophthalmoscopic appearance may be helpful in suggesting the diagnosis if recognized in patients or their maternal relatives, but its absence—even during the period of acute visual loss—does not exclude the diagnosis of LHON. As the disease progresses, the

telangiectatic vessels disappear and the pseudo-oedema of the disc resolves. Perhaps because of the initial hyperaemia, the optic discs of patients with LHON may not appear pale for some time. This feature, coupled with the relatively preserved pupillary responses and the lack of pain, has led to the misdiagnosis of nonorganic visual loss in some LHON patients.[33] Eventually, however, optic atrophy with nerve fibre layer dropout most pronounced in the papillomacular bundle supervenes. Nonglaucomatous cupping of the optic discs or arteriolar attenuation may also be seen in patients with symptomatic LHON.

In most patients with LHON, visual loss remains profound and permanent. However, not uncommonly, recovery of even excellent central vision occurs years after visual deterioration.[6,7,9,11,35] The recovery may occur gradually over 6 months to 1 year after initial visual loss or may suddenly occur up to 10 years after onset.[36] It may take the form of a gradual clearing of central vision or be restricted to a few central degrees, resulting in a small island of vision within a large central scotoma.[35] Recovery is usually bilateral but may be unilateral. Those patients whose vision improves most substantially appear to have a lower mean age at the time of initial visual loss.[9,11] In the review by Riordan–Eva *et al*[9] of 79 cases from 55 families, good visual outcome was strongly correlated with age at onset, all those with onset before 20 years having a final visual acuity better than 20/80. Furthermore, the particular mitochondrial DNA mutation also influences prognosis, with the 11778 mutation carrying the worst prognosis for vision, and the 14484 mutation the best (see below). Recurrences of visual failure are extremely rare among those patients both with and without visual recovery.

In the majority of patients with LHON, visual dysfunction is the only significant manifestation of the disease. However, some pedigrees have members with associated cardiac conduction abnormalities, especially the pre-excitation syndromes.[37–41]

Minor neurologic abnormalities, such as exaggerated or pathologic reflexes, mild cerebellar ataxia, tremor, movement disorders, myoclonus, seizures, muscle wasting, distal sensory neuropathy, motor neuropathy, and migraine, have been reported in patients with LHON.[6,42,43] Less commonly, pedigrees have been described in which multiple maternal members demonstrate the clinical features of LHON in addition to more severe neurologic abnormalities. We have termed these pedigrees 'Leber's Plus'.[16] The maternal members of a large Australian family demonstrate varied combinations of optic atrophy, movement disorders, spasticity, psychiatric disturbances, skeletal abnormalities, and acute infantile encephalopathic episodes.[44] A Leber's-like optic neuropathy has been associated with dystonia and basal gangliar lesions in several pedigrees.[45–50] Leigh-like encephalopathy, periaqueductal syndrome and other brainstem involvement have also rarely been reported.[51–53]

Disease clinically indistinguishable from multiple sclerosis may occur in families with LHON.[9,42,54,55] Harding *et al*[54] reported molecularly confirmed 11778 pedigrees of LHON with individuals, especially females, exhibiting symptoms and signs of demyelinating disease combined with nonremitting visual loss typical of LHON. Cerebrospinal fluid and MR imaging findings were characteristic of multiple sclerosis. Subsequent population surveys have not found the primary mutations associated with LHON to be overrepresented among multiple sclerosis patients.[56,57] However, among multiple sclerosis patients selected specifically because of their prominent early optic neuropathy, the primary LHON mutations may be found more frequently.[56] It is possible that this association between LHON and multiple sclerosis is no greater than the prevalence of the two diseases. An underlying LHON mutation, however, may worsen the prognosis of optic neuritis in patients with multiple sclerosis.[55,57,58]

Ancillary tests, aside from genetic analysis, are generally of limited usefulness in the evaluation of LHON. CT scanning and MR imaging of the brain are typically normal in patients with LHON.[7,59] Exceptions include those patients with additional symptoms suggestive of multiple sclerosis and those pedigrees with dystonia and basal gangliar lesions. One boy with LHON-visual loss but no symptoms or signs suggestive of demyelinating disease was found to have extensive T2-hyperintense periventricular white matter changes.[60] Two LHON patients were reported with distended optic nerve sheaths on orbital ultrasonography, CT scanning, and MR imaging.[61,62] MR imaging of the optic nerves of symptomatic LHON patients typically reveals normal nerves in the acute phase of visual loss, often followed by high T2 signals in the intraorbital portions of the nerves after several months.[9,59,63–65] Rarely, gadolinium enhancement and enlargement of the optic nerves and even chiasm may be demonstrated during the acute phase of visual loss.[66–68]

In no case do we have optic nerve pathology from the early stages of the disease; hence, the location and nature of the initial injury remain uncertain. Kerrison *et al*[69] noted marked atrophy of the nerve fibre and retinal ganglion cell layers and the optic nerves on a post-mortem study of an 81-year-old affected woman from the large Australian family with 'Leber's Plus'.[44] Electron microscopy demonstrated retinal ganglion cell inclusions consisting of calcium circumscribed by a double membrane, suggesting intramitochondrial

calcification. Histopathologic and morphometric analysis was performed on optic nerves from three other LHON patients, again years remote from the time of acute visual loss.[70,71] Findings consisted of severe generalized depletion of optic nerve fibres (95–99% reduction), with sparing of only peripheral clusters of fibres, primarily those of larger diameter. There was fibrocytic scarring, scattered 'degeneration dust', and evidence of minimal inflammation. These authors propose a selective loss of the ganglion cell P-cell population.[70,71]

All pedigrees clinically designated as LHON have a maternal inheritance pattern, confirming the disease's association with point mutations in the mitochondrial genome (see the accompanying article in this volume on the molecular genetics of optic neuropathies).[9,15,17,19,20,72] Three point mutations in the mitochondrial DNA (mtDNA), the so-called 'primary' LHON mutations, are believed to cause 90 to 95% of cases of LHON worldwide. They are located at mtDNA positions 11778 (69% of cases), 3460 (13% of cases), and 14484 (14% of cases). Several other mtDNA mutations may be 'primary', but account individually for only a few pedigrees worldwide.[72] Other mtDNA point mutations have been associated with LHON, but their pathogenetic significance remains less clear.

Genetic analysis allows a broader view of what constitutes the clinical profile of LHON.[2,16] Most striking are the number of patients without a family history of visual loss. Although there is undoubtedly a referral bias for the unusual cases, it is still quite remarkable that singleton cases constituted 57% of one series of molecularly confirmed LHON.[7] In contrast, Mackey[23] reported only a small proportion of singleton cases in Australia, suggesting ascertainment difficulties or low penetrance in America. The use of high-resolution mtDNA haplotypes to aggregate multiple apparently unrelated pedigrees affected with LHON into single large maternal lineages descending from the same founder[73,74] may decrease the number of true singleton cases. Some of these singleton cases are women, some outside the typical age range for LHON, some without the classic ophthalmoscopic appearance.[33] Clearly, the diagnosis of LHON should be considered in any case of unexplained bilateral optic neuropathy, regardless of age of onset, sex, family history, or funduscopic appearance.

Many questions remain unanswered regarding the determinants of phenotypic expression in LHON. For instance, does the specific mtDNA mutation dictate particular clinical features? Although those pedigrees with LHON 'plus' demonstrate that certain mtDNA mutations may result in specific disease patterns of Leber's–like optic neuropathies with other neurologic abnormalities,[20] few significant clinical differences have been demonstrated to date among those LHON patients positive for the 11778 mutation, those with other mtDNA mutations, and those as yet genetically unspecified. One major exception is the difference in spontaneous recovery rates among those patients with the 11778 mutation and those with the 14484 mutation. Among 136 patients with the 11778 mutation, only five (4%) reported spontaneous recovery,[35] compared with 37–65% of 14484 patients.[9,11] Furthermore, the ultimate visual acuities in patients with the 14484 mutation are significantly better than those with the 11778 and 3460 mutations.[9]

Except for rare examples of *de novo* occurrence of a primary LHON mutation,[75] a mtDNA mutation will be present in all maternally related family members of patients with LHON, even though many will never become symptomatic. Hence, whereas the presence of an mtDNA mutation may be necessary for phenotypic expression, it may not be sufficient. Heteroplasmy for the primary LHON mutations has been demonstrated in several affected and unaffected individuals, and the degree of heteroplasmy may correlate with the risk of visual loss.[76] However, in most large reviews of molecularly confirmed LHON patients, heteroplasmy is documented in the blood of a minority of affected individuals.[7,22,27]

Other genetic factors besides the specific mtDNA mutation and the presence and degree of heteroplasmy may play a role in expression. Although some investigators have claimed that multiple LHON-associated mtDNA mutations may be necessary for visual loss, this has not been corroborated in several studies.[9,11,77] Indeed, case reports of unaffected individuals who even harbour two primary mutations[78,79] make this claim improbable. Similarly, although the underlying mtDNA haplotype may influence the presence, penetrance, or expression of an mtDNA point mutation,[80] this is unlikely to be the major factor in phenotypic expression. Nuclear–encoded factors modifying mtDNA expression, mtDNA products, or mitochondrial metabolism may influence phenotypic expression of LHON. Although most studies have not been able to confirm X-linkage as an explanation of the male predominance of visual loss in LHON, the X-linkage hypothesis may still be viable.[20]

Tissue energy utilization and reserve in an individual may also determine the timing and extent of visual loss. Mitochondrial energy production decreases with age,[81] and the timing of visual loss in patients at risk for LHON may reflect the threshold at which already reduced mitochondrial function deteriorates to a critical level. Immunologic factors have also been proposed, especially to explain the association of LHON with multiple sclerosis,[54,55] but conclusive evidence is lacking. Finally,

environmental factors, both internal and external, may play a role. Systemic illnesses, nutritional deficiencies, medications, or toxins that stress or directly or indirectly inhibit mitochondrial metabolism have been suggested to initiate or increase phenotypic expression of the disease. However, widespread nutritional deficiency in Cuba did not appear to increase the expression of LHON in one large 11778-positive pedigree.[82] Similarly, although anecdotal reports suggest a possible role for tobacco and excessive alcohol use as precipitants of visual loss, one lare case–control study of sibships[83] failed to confirm this. Other agents known to be toxic to the optic nerve, such as ethambutol,[84,85] or to mitochondrial function, such as antiretroviral therapy,[86–88] may have a heightened toxicity in patients with the LHON mutations and already compromised mitochondrial function.

Theories on the pathogenesis of LHON must reconcile how multiple different mtDNA mutations located in different genes encoding different proteins result in an essentially identical clinical phenotype that is expressed only in the optic nerve, suddenly and bilaterally.[72,89–91] Pathogenetic theories include reduction in ATP-production and/or free-radical damage with resultant apoptosis of retinal ganglion cells. Selective involvement of the ganglion cell or its axon may be explained on a vascular, mechanical, or regional basis, with several studies suggesting a high degree of mitochondrial respiratory activity within the unmyelinated, prelaminar portion of the optic nerve.[72] This portion of the visual system may be particularly vulnerable to mitochondrial dysfunction, especially abnormalities of complex I.[92] Further elucidation of the genetic and environmental triggers of the pathologic cascade in susceptible individuals will require more genetic, biochemical, physiological, and pathologic studies.[72]

In light of the possibility for spontaneous recovery in some patients with Leber's disease, any anecdotal reports of treatment efficacy must be considered with caution. Reports from Japan advocated craniotomy with lysis of chiasmal arachnoid adhesions in patients with LHON, with 80% of more than 120 patients reporting visual improvement.[93,94] Although the data are impressive, it is difficult to support a surgical therapy logistically removed from the site of ocular neurovascular changes. Some manifestations of other mitochondrial diseases, specifically the mitochondrial cytopathies, may respond to therapies designed to increase mitochondrial energy production.[95] Most of the agents used are naturally occurring cofactors involved in mitochondrial metabolism, while others have antioxidant capabilities. Therapies tried include coenzyme Q_{10}, idebenone, L-carnitine, succinate, dichloroacetate, vitamin K_1, vitamin K_3, vitamin C, thiamine, vitamin B_2, and vitamin E. Mashima *et al*[96] reported on 28 LHON patients, 14 of whom were treated with idebenone (a quinol that stimulates ATP formation) combined with vitamin B_2, and vitamin C. There was no significant difference in the number of eyes with visual recovery, although the authors claimed that the treatment seemed to speed recovery when it occurred. Topical agents deemed neuroprotective or antiapoptotic for ganglion cells could be administered directly to the eye.[97] It remains to be seen whether any of these agents alone or in combination will prove consistently useful in the treatment of acute visual loss in LHON, in the prevention of second eye involvement, or in the prophylactic therapy of asymptomatic family members at risk.

A promising form of gene therapy known as *allotypic expression* may play a future role in the therapy of LHON and other mitochondrial diseases.[98] In this approach, a nuclear-encoded version of a gene normally encoded by mtDNA (in this case the ND4 gene containing nucleotide position 11778) is made synthetically, inserted via an adeno-associated viral vector, and codes for a protein expressed in the cytoplasm that is then imported into the mitochondria. This protein increased the survival of cybrids harbouring the 11778 mutation three-fold and restored ATP synthesis to a level indistinguishable from that in cybrids containing normal mtDNA. The relative accessibility of the eye and its ganglion cells may provide the ideal setting in which to test this nuclear solution of a mitochondrial problem.[99]

Nonspecific recommendations to avoid agents that might stress mitochondrial energy production have no proven benefit in LHON, but are certainly reasonable. We advise our patients at risk for LHON to avoid tobacco use, excessive alcohol intake, and environmental toxins. An ECG should be obtained and any cardiac abnormalities treated accordingly. Considering the degree of visual acuity loss, it is remarkable that van Senus[6] reported 82% of patients gainfully employed despite their visual handicap. Low vision assessment may be helpful, especially because much of the useful peripheral vision may remain intact. Finally, the importance of genetic counselling in this disease should not be underestimated.

Dominant optic atrophy

Autosomal dominant optic atrophy, type Kjer (McKusick no. 165500, gene symbol OPA1), is believed to be the most common of the hereditary optic neuropathies. The estimated disease prevalence is 1 : 50 000 or as high as 1 : 10 000 in Denmark.[100,101]

In addition to the cases described by Kjer,[102,103] numerous other studies have established the clinical profile of patients with dominantly inherited optic

atrophy.[101,104–113] It is generally agreed that dominant optic atrophy (DOA) is an abiotrophy with usual onset in the 1st decade of life. Kjer[102,103] noted that many of his patients were ignorant of the familial nature of their disease and, in fact, did not realize that they, themselves, had visual dysfunction. No individual in the series by Kline and Glaser[106] could identify a precise onset of reduced acuity. In Hoyt's series,[107] the majority of affected patients dated the onset of visual symptoms between 4 and 6 years of age, although a few severely affected individuals were noted to have a visual disturbance, primarily because of nystagmus, prior to beginning schooling. Smith[104] reviewed the literature up to 1972 on this subject and collected 554 clear–cut cases, of whom 442 were actually examined. He emphasized that of this large group, only 15 patients (2.2%) were actually observed to have optic atrophy before age 10 years. Similarly, Johnston *et al*[113] reported visual symptoms before the age of 10 years in only 58% of their 47 affected individuals. Three of the patients (12.5%) examined by Kline and Glaser,[106] seven of Hoyt's[107] patients (22.6%), and five of the patients reported by Elliott *et al*[108] (25%) were unaware of visual difficulties and were discovered to have optic atrophy as a direct consequence of examination of other affected family members. These phenomena attest to the usually imperceptible onset in childhood, often mild degree of visual dysfunction, absence of night blindness, and absence of acute or subacute progression.

Kjer[102,103] emphasized that visual acuity was usually reduced to the same mild extent in both eyes. Visual acuity remained between 20/20 and 20/60 throughout life in 40% of his cases, with severe visual loss (20/200 to 20/600) occurring in only 15%. None of the 200 patients examined by Kjer[102] had visual acuity reduced to hand motion or light perception levels. His findings are in accordance with the cases collected by Smith,[104] who found that 37% had visual acuity of 20/60 or better; 46% had visual acuity between 20/60 and 20/200; and only 17% had visual acuity below 20/200. Other studies support this wide range of visual acuities from 20/20 to light perception.[106–112] In an analysis of 87 affected patients from 21 molecularly confirmed families with DOA,[111] the mean visual acuity was 20/120. In all studies, a few patients have been found with striking asymmetry between the acuities of the two eyes, and there is considerable interfamilial and intrafamilial variation in acuities.[111]

Kjer[102,103] was able to obtain follow–up data on 98 patients, 75 of whom were observed for at least 5 years. Some progression occurred in about 50% of the patients. In addition, in Kjer's[103] series, no patients below 15 years of age had visual acuity below 20/200, but 10% of patients 15–44 years of age and 25% of patients 45 years and older had vision below 20/200. In a study of 20 patients with a mean follow–up of 16 years,[108] visual acuity remained stable in both eyes of 13 patients (65%), decreased in one eye in three patients (15%), and decreased in both eyes in four patients (20%). There was no correlation between the rate of visual loss and initial visual acuity or individual pedigrees. Votruba *et al*[111] documented deterioration of visual acuity with age in one-third of their 21 families. These figures suggest a mild, slow, insidious progression of visual dysfunction in some patients. The observation that some families have a marked decline in visual acuity with age while others do not has important implications for counseling.[111] Spontaneous recovery of vision is not a feature of this disorder.

In the patients studied by Kjer,[102,103] there was often an inability to perceive blue colours. Some studies[104,106,107] subsequently claimed that tritanopia is the characteristic colour vision defect in patients with dominant optic atrophy; however, other studies suggest that a generalized dyschromatopsia, with both blue–yellow and red–green defects, is even more common than an isolated tritanopia.[108,111] This mixed colour defect accounted for more than 80% of the colour deficits documented in a large study of 21 pedigrees.[111]

Visual fields in patients with dominant optic atrophy characteristically show central, paracentral, or cecocentral scotomas. In patients with acuities of 20/50 or better, static perimetry is often necessary to identify the defects. The peripheral fields are usually normal in these patients. Smith[104] collected 22 cases of 'bitemporal hemianopia' detected with coloured test objects. In the large study performed by Votruba *et al*,[111] 66% of the visual field defects in 50 affected patients were predominantly in the superotemporal visual fields (Figure 2). This pattern of visual field involvement has been demonstrated using a variety of techniques of field testing, and fixation has been monitored with scanning laser ophthalmoscopy,[111] suggesting that these superobitemporal defects are not an artefact of the testing procedures or of eccentric fixation.

The optic atrophy in patients with dominantly inherited optic neuropathy may be subtle,[103] temporal only,[104,114] or involving the entire optic disc.[103] Kline and Glaser[106] found the most characteristic change was a translucent pallor with absence of fine superficial capillaries of the temporal aspect of the disc, with a triangular excavation of the temporal portion of the disc (Figure 2). In the Votruba *et al* analysis,[111] wedge-shaped temporal pallor of the disc was documented in 44% of 172 eyes, total atrophy in another 44%, and subtle diffuse pallor in 12%. Other ophthalmoscopic findings reported in these patients included peripapillary atrophy, absent foveal reflex, mild macular pigmentary changes, arterial

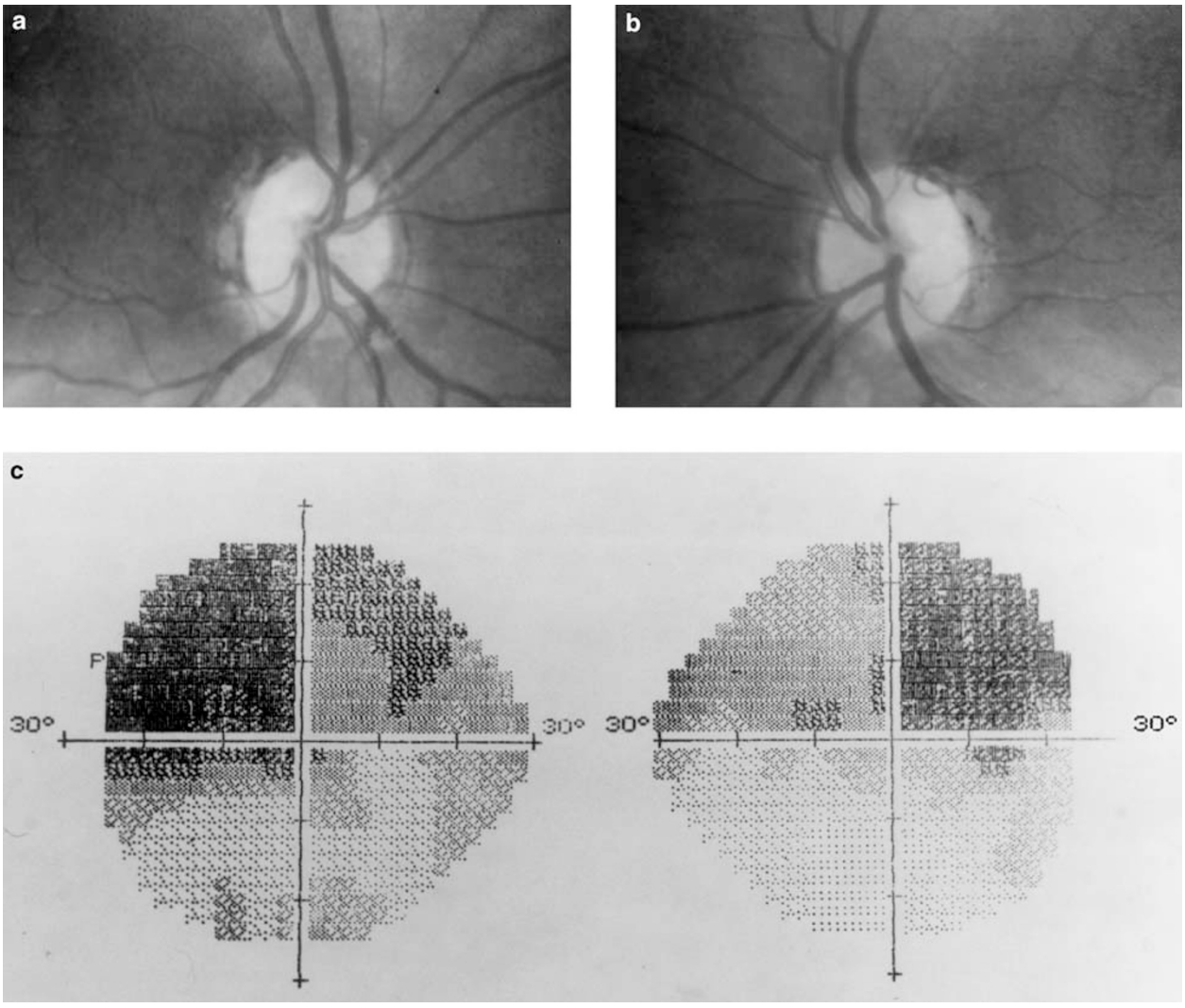

Figure 2 Dominant optic atrophy. (a and b) Bilateral optic nerve pallor in a patient with dominant optic atrophy amd visual acuity of 20/80 OU. There are triangular excavations of the temporal portions of the discs. (c) Goldmann visual fields showing central and superotemporal visual field defects.

attenuation, and nonglaucomatous cupping with absence of a healthy neuroretinal rim and shallow saucerization of the cup.[104,106,108,115] Fournier *et al*[116] emphasized several clinical features that help distinguish patients with DOA from those with normal tension glaucoma, including early age of onset, preferential loss of central vision, sparing of the peripheral fields, pallor of the remaining neuroretinal rim, and a family history of unexplained visual loss or optic atrophy.

Electrophysiologic studies have been performed in several patients with dominant optic atrophy.[106,111,117,118] Visual-evoked responses in affected individuals characteristically show diminished amplitudes and prolonged latencies, the latter usually less profound than in demyelinating disease.[111,117,118] Pattern electroretinograms show a reduced N95 component in keeping with primary ganglion cell dysfunction.[111] Extreme clinical variability among subjects with DOA suggests that on occasion, combined clinical and functional evaluation, with computerized perimetry, tests of contrast sensitivity, and electrophysiologic testing, may be necessary to diagnose the most subtle cases.[118]

Although there are dominantly inherited syndromes of optic atrophy associated with neurologic dysfunction, most of the patients with the syndrome of autosomal dominant optic atrophy have no additional neurologic deficits. Nystagmus in some patients likely reflects early visual deprivation rather than central neurologic involvement. Kjer[102,103] found mental abnormalities in 10% of his cases, but this feature was not confirmed in subsequent studies. Eight of 31 patients described by Hoyt[107] had neural hearing loss, clustering in three of six

families. Only one patient was aware of any hearing difficulties. More severe hearing loss associated with familial optic atrophy may be a genetically distinct syndrome (see below).

Johnston *et al*[105] performed a histologic examination of the eyes and optic nerves of a 56–year–old woman from a family with a typical pedigree of autosomal dominant hereditary optic atrophy. The patient had a long history of bilaterally reduced vision (20/100 in both eyes), bilateral central scotomas, and temporal pallor of both discs. In both eyes, there was diffuse atrophy of the retinal ganglion cell layer associated with diffuse atrophy and loss of myelin within the optic nerves. Johnston *et al*[105] suggested, as did Kjer,[102,103] that dominant optic atrophy is a primary degeneration of retinal ganglion cells. Electrophysiologic studies confirm loss of ganglion cell function predominantly from central retina, but not the exclusive result of either parvocellular or magnocellular cell loss.[111]

One study of a large pedigree of German descent suggested linkage of the gene responsible for dominant optic atrophy with the Kidd blood group antigen, subsequently localized to chromosome 18q12[112,119] (see the accompanying article in this volume on the molecular genetics of optic neuropathies). Further study of this family refined the chromosomal locus to a 3-cM region at 18q12.2–12.3.[112] This family is clinically similar to the other pedigrees of DOA, including its intrafamilial variation, although the median visual acuity was somewhat better at 20/40.

Most of the other pedigrees with DOA, including several from Denmark, the United Kingdom, Germany, France, Cuba, Japan, and the United States, have genetic homogeneity in their linkage to the telomeric portion of the long arm of chromosome 3 (3q28–29).[100,101,120–125] Between 30 and 90% of these families have been found to harbour over 60 different missence and nonsense mutations, deletions, and insertions in a gene within this region that has been designated the OPA1 gene.[122–128] The product of the OPA1 gene is targeted to the mitochondria and appears to exert its function in mitochondrial biogenesis and stabilization of mitochondrial membrane integrity.[122–124] Downregulation of the OPA1 leads to fragmentation of the mitochondrial network and dissipation of the mitochondrial membrane potential with cytochorme *c* release and caspase-dependent apoptosis.[129] These findings demonstrate the crucial role of mitochondria in retinal ganglion cell pathophysiology.[124] Linkage analysis of patients with normal tension glaucoma has shown an association with polymorphisms of the OPA1 gene.[130] Interestingly, there is a mutant strain of mice with dominantly inherited optic atrophy with variable expressivity.[131] The mutation in these mice is located on the mouse chromosome 16, which is homologous to the human chromosome 3.

Other monosymptomatic hereditary optic neuropathies

Compared to LHON and DOA, other monosymptomatic optic neuropathies are extremely rare.[1] They include congenital recessive optic atrophy,[132] apparent sex-linked optic atrophy,[133,134] and possibly an autosomal recessive chiasmal optic neuropathy.[135]

Hereditary optic atrophy with other consistent neurologic or systemic findings

In some pedigrees with inherited optic neuropathies, certain neurologic or systemic manifestations are regularly observed.[1] These include pedigrees with: autosomal dominant optic atrophy and deafness; autosomal dominant optic atrophy with hearing loss and ataxia; hereditary optic atrophy with hearing loss and polyneuropathy; autosomal recessive optic atrophy with hearing loss, spastic quadriplegia, mental deterioration and death (opticocochleodentate degeneration); opticoacoustic nerve atrophy with dementia; diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD or Wolfram's syndrome); progressive encephalopathy with oedema, hypsarrhythmia and optic atrophy; and autosomal recessive complicated hereditary infantile optic atrophy (Behr's syndrome). The most common of these syndromes are Wolfram's syndrome and Behr's syndrome.

Since 1938,[136] about 300 cases of *Wolfram's syndrome* have been recorded, with a prevalence of one in 770 000 in the United Kingdom.[137–144] Most cases have been classified as sporadic or recessively inherited. The hallmark of all these cases is the association of juvenile diabetes mellitus and progressive visual loss with optic atrophy, almost always associated with diabetes insipidus, neurosensory hearing loss, or both (hence, the eponym DIDMOAD for diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). The progression and development of this syndrome is variable. Symptoms and signs of diabetes mellitus usually occur within the 1st or 2nd decade of life and usually precede the development of optic atrophy. In several cases, however, visual loss with optic atrophy was the first sign of the syndrome. In the early stages, visual acuity may be normal despite mild dyschromatopsia and optic atrophy. In later stages, visual loss becomes severe, usually worse than 20/200, suggesting progression.[137,141] Visual fields show both generalized constriction and central scotomas. Optic atrophy is uniformly severe, and there may be mild to moderate cupping of the disc.

The onset of hearing loss and of diabetes insipidus in this syndrome is equally variable. Both begin in the 1st or 2nd decade of life and may be quite severe. Atonia of the efferent urinary tract is present in 46–58% of patients and is associated with recurrent urinary tract infections and even fatal complications.[138,139] Other systemic and neurologic abnormalities include ataxia, axial rigidity, seizures, startle myoclonus, tremor, gastrointestinal dysmotility, vestibular malfunction, central apnea, neurogenic upper airway collapse, ptosis, cataracts, pigmentary retinopathy, iritis, lacrimal hyposecretion, tonic pupil, ophthalmoplegia, convergence insufficiency, vertical gaze palsy, mental retardation, psychiatric abnormalities, nystagmus, short stature, primary gonadal atrophy, other endocrine abnormalities, anosmia, megaloblastic and sideroblastic anaemia, abnormal electroretinography, and elevated cerebrospinal fluid protein.[137,139,140,143–145] Psychiatric disorders are also seen at an increased frequency among heterozygous carriers.[146] Pathology and neuroimaging in some patients reveal widespread atrophic changes and suggest a diffuse neurodegenerative disorder, with particular involvement of the midbrain and pons.[140,144,147] Median age at death is 30 years, most commonly due to central respiratory failure with brain-stem atrophy.[139,148] When the syndrome is accompanied by anaemia, treatment with thiamine may ameliorate the anaemia and decrease the insulin requirement.[149]

Many of the associated abnormalities reported in Wolfram's syndrome are commonly encountered in patients with presumed mitochondrial diseases, especially those patients with the chronic progressive external ophthalmoplegia syndromes.[150] This has led to the speculation that the Wolfram's phenotype may be nonspecific and reflect a wide array of underlying genetic defects in either the nuclear or mitochondrial genomes, with perhaps a unifying pathogenesis in underlying mitochondrial dysfunction.[151,152] Polymeropoulos *et al*[153] proposed localization of the Wolfram's gene to the short arm of chromosome 4 in several families with presumed autosomal recessive inheritance. This locus was further refined to chromosome 4p16.1 and accounts for many, but not all, DIDMOAD pedigrees.[154,155] The gene responsible at this locus has been designated WFS1, in which multiple point mutations and deletions have been identified.[155] Some of these mutations were subsequently found to be a common cause of inherited isolated low-frequency hearing loss.[156] In one report, the locus on chromosome 4p16 was proposed as a predisposing factor for the formation of multiple mtDNA deletions.[157] DIDMOAD patients were also found to concentrate on two major mtDNA haplotypes that are also over-represented among LHON patients.[158] A phenotypic variant of Wolfram's syndrome with peptic ulcer disease and bleeding secondary to a platelet aggregation defect, but without diabetes insipidus, was noted in four consanguineous Jordanian families and linked to a second locus (WFS2) on chromosome 4q22–24.[143,159]

In 1909, Behr[160] described a syndrome of heredofamilial optic atrophy beginning in early childhood and associated with variable pyramidal tract signs, ataxia, mental retardation, urinary incontinence, and pes cavus. The syndrome has been reported in both sexes,[161,162] and is believed to be autosomal recessively inherited. Visual loss usually manifests before age 10 years, is moderate to severe, and is frequently accompanied by nystagmus. Neuroimaging may demonstrate diffuse symmetric white matter abnormalities. In several Iraqi-Jewish pedigrees of Behr's syndrome, 3–methylglutaconic aciduria was identified, leading to mapping of the gene (designated OPA3) to chromosome 19q13.2–13.3.[163–166] These patients had infantile optic atrophy and an early–onset extrapyramidal movement disorder dominated by chorea. Approximately half of the patients developed spastic paraparesis by the 2nd decade, and the majority of affected individuals were female. Clinical findings in Behr's syndrome may be similar to those in cases of hereditary ataxia. Behr's syndrome is likely heterogeneous, reflecting different aetiologic and genetic factors.[1]

Optic neuropathy as a manifestation of hereditary degenerative or developmental diseases

Inherited diseases with primarily neurologic or systemic manifestations, such as the multisystem degenerations, can include optic atrophy among their signs, typically as a secondary and inconsistent finding. This category of disorders encompasses the hereditary ataxias, the hereditary polyneuropathies, the hereditary spastic paraplegias, the hereditary muscular dystrophies, storage diseases and other cerebral degenerations of childhood, and mitochondrial disorders other than LHON.[1]

Friedrich's ataxia is an autosomal recessive disorder linked to the long arm of chromosome 9 (9q13–q21) involving a GAA trinucleotide expansion in a gene coding for a protein called frataxin, which regulates iron levels in the mitochondria.[167] The disease usually begins during the second decade of life and includes progressive ataxia, dysarthria, loss of joint position and vibratory sensation, absence of lower extremity tendon reflexes, and extensor plantar responses. Scoliosis, foot deformity, diabetes mellitus, and cardiac disease are common. Other manifestations include pes cavus, distal

wasting, deafness, eye movement abnormalities consistent with abnormal cerebellar function, and optic atrophy. The course is progressive, with most patients unable to walk within 15 years of onset, and death from infectious or cardiac causes usually in the fourth or fifth decades. A later-onset, more slowly progressive form has also been described. Evidence of optic neuropathy is present in up to two-thirds of cases of Friedreich's ataxia, although severe visual loss is uncommon.[168–174] A condition resembling Friedreich's ataxia associated with decreased vitamin E levels has been localized to chromosome 8, and also includes some patients with optic atrophy.[175] Vitamin E supplementation of these patients may be efficacious early in the course of the disease.

The *spinocerebellar ataxias* (SCA), previously called olivopontocerebellar atrophy (OPCA) and autosomal dominant cerebellar ataxia (ADCA), comprise a group of hereditary ataxic disorders in which the ataxia is related more to degeneration of the cerebellum than the spinal cord.[167,176] As of 2003, there were at least 23 different genetic loci for the SCAs (SCA1–SCA17).[167] (George Wilmot, 2003, Personal Communication). The combination of SCA1 (chromosome 6p), SCA2 (chromosome 12q), SCA3 (chromosome 14q), SCA6 (chromosome 19p), and SCA7 (chromosome 3p) comprises approximately 80% of the autosomal dominant ataxias.[167] Many of the SCAs are caused by mutations involving the expansion of a CAG trinucleotide repeat in the protein coding sequences of specific genes. Clinically, the SCAs are characterized by signs and symptoms attribuable to cerebellar degeneration and sometimes other neurologic dysfunction secondary to neuronal loss. Loss of vision is usually mild but may be a prominent symptom, occurring in association with constricted visual fields and diffuse optic atrophy.[177] However, it is not clear in some cases whether the primary process is retinal with secondary optic atrophy or primarily involving the optic nerve. Detailed analysis of the prevalence of optic atrophy among the different genotypes now associated with the SCAs has not been performed. Prior to genetic analysis, Harding[178] categorized the ADCAs into four types, with only the first type having individuals with primary optic atrophy (approximately 30% of cases). We now know that ADCA type I encompasses multiple genetic loci, including those pedigrees now classified genetically as SCA1, SCA2, SCA3, and probably SCA4 and SCA5. Initial studies suggest that patients with the SCA2 genotype do not exhibit optic atrophy,[179] whereas the SCA3 patients may have optic atrophy, especially if their ataxia is severe, and there are several SCA1 families with optic atrophy.[177] SCA7 is specifically associated with retinal degeneration.

Among the hereditary polyneuropathies, *Charcot-Marie-Tooth disease* (CMT) encompasses a group of heredofamilial disorders characterized by progressive muscular weakness and atrophy that begins during the first two decades of life.[167] This group of hereditary polyneuropathies accounts for 90% of all hereditary neuropathies, with the prevalence in the United States being about 40 per 100 000. Most forms of CMT begin between the ages of 2 and 15 years, and the first signs may be pes cavus, foot deformities, or scoliosis. There is slowly progressive weakness and wasting, first of the feet and legs, and then of the hands. Motor symptoms predominate over sensory abnormalities. As of 2002, causative mutations for the hereditary peripheral neuropathies have been identified in 17 different genes.[180] Inheritance is most commonly autosomal dominant, although autosomal recessive and also X-linked forms occur. Numerous patients with CMT and optic atrophy have been reported.[181,182] Associated visual loss, if present, is usually mild. However, taking into account both electrophysiologic and clinical data, up to 75% of patients with CMT have some afferent visual pathway dysfunction, demonstrating that subclinical optic neuropathy may occur in a high proportion of patients with CMT.[183] Pedigrees specifically designated CMT type 6 show a regular association of CMT and optic atrophy.[181,182] This type of CMT is as yet genetically unspecified and may prove genetically heterogeneous.[181]

Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive disease that almost exclusively affects Ashkenazi Jews. Abnormalities of the peripheral nervous system cause the clinical manifestations of sensory and autonomic dysfunction. Optic atrophy is very common in patients with familial dysautonomia, usually noted after the first decade of life.[184,185] However, in most cases, early mortality from the disease probably precludes the later development of optic atrophy.[184]

The *hereditary spastic paraplegias* (Strumpell-Lorrain disease) are autosomal dominant disorders characterized by progressive spasticity of the lower limbs and pathological reflexes with degeneration or demyelination of the cortico-spinal system and of the spinocerebellar system. Optic neuropathies with visual acuities ranging from 20/20 to 20/200 have been reported in a small number of patients with this disease.[186]

One of the most common of the hereditary muscular dystrophies, *myotonic dystrophy* is an autosomal dominant disorder with a prevalence of 1 in 20 000, characterized by progressive myopathy, ptosis, cataracts, cardiomyopathy with conduction defects, frontal balding, bifacial weakness, and diabetes mellitus. Most patients with myotonic dystrophy have an expansion of a CTG repeat in a protein kinase gene on chromosome

19q13.3. Less common ophthalmic manifestations include external ophthalmoplegia, pigmentary retinopathy, and optic atrophy.[167]

There are more than 100 inherited metabolic diseases and as yet undefined genetic syndromes with ocular manifestations, including optic atrophy. These include the storage diseases such as the mucopolysaccharidoses and the lipidoses, the hereditary leukodystrophies, including Krabbe's disease, mucosulphatidosis, metachromatic leukodystrophy, adrenoleukodystrophy and adrenomyeloneuropathy, Zellweger syndrome, Pelizeus–Merzbacher disease, infantile neuroaxonal dystrophy, Hallervorden–Spatz disease, Menkes syndrome, Canavan's disease, Cockayne syndrome, cerebro-oculo-facio-skeletal syndrome, Smith–Lemli–Opitz syndrome, Allgrove syndrome, and GAPO (growth retardation, alopecia, pseudoanodontia, and optic atrophy) syndrome.[1]

The prototype for a mitochondrial abnormality resulting in optic nerve dysfunction is, of course, LHON with its classically isolated optic nerve involvement and its causal relationship to mitochondrial DNA point mutations (see above). Additionally, Kjer's dominant optic atrophy likely results from perturbations of mitochondrial function secondary to abnormalities in a nuclear gene whose product is destined for the mitochondria. Other multisystem hereditary disorders with prominent optic nerve involvement, such as Wolfram's syndrome, may also prove to have a final common pathway in mitochondrial dysfunction. Indeed, the seemed selective vulnerability of the ganglion cell or its axon to both hereditary and acquired mitochondrial abnormalities suggests a possible common pathophysiology for these disorders.[187] Given this relative selective involvement of the optic nerve in these disorders, however, it is somewhat surprising that other mitochondrial disorders do not regularly manifest optic neuropathies.

The *subacute necrotizing encephalomyelopathy of Leigh* results from multiple different biochemical defects that all impair cerebral oxidative metabolism.[1,2,188] This disorder may be inherited in an autosomal recessive, X-linked, or maternal pattern, depending on the genetic defect. The onset of symptoms is typically between the ages of 2 months and 6 years, and consists of progressive deterioration of brainstem functions, ataxia, seizures, peripheral neuropathy, intellectual deterioration, impaired hearing and poor vision. Visual loss may be secondary to optic atrophy or retinal degeneration. Many cases have optic nerves with extensive atrophy on pathologic examination.[189] The syndrome of Leigh is likely a nonspecific phenotypic response to certain abnormalities of mitochondrial energy production.

Other presumed mitochondrial disorders of both nuclear and mitochondrial genomic origins may manifest optic atrophy as a secondary clinical feature, often a variable manifestation of the disease.[2,190] Examples include cases of *MERRF, MELAS*, and *chronic progressive external ophthalmoplegia*, both with and without the full Kearns–Sayre phenotype.[1] The other, more constant, phenotypic characteristics of all of these mitochondrial disorders distinguish them from diseases such as Leber's optic neuropathy in which visual loss from optic nerve dysfunction is the primary manifestation of the disorder.

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