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# The optic nerve: A "mito-window" on mitochondrial neurodegeneration

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ABSTRACT

Retinal ganglion cells (RGCs) project their long axons, composing the optic nerve, to the brain, transmitting the visual information gathered by the retina, ultimately leading to formed vision in the visual cortex. The RGC cellular system, representing the anterior part of the visual pathway, is vulnerable to mitochondrial dysfunction and optic atrophy is a very frequent feature of mitochondrial and neurodegenerative diseases. The start of the molecular era of mitochondrial medicine, the year 1988, was marked by the identification of a maternally inherited form of optic atrophy, Leber's hereditary optic neuropathy, as the first disease due to mitochondrial DNA point mutations. The field of mitochondrial medicine has expanded enormously over the last two decades and many neurodegenerative diseases are now known to have a primary mitochondrial etiology or mitochondrial dysfunction plays a relevant role in their pathogenic mechanism. Recent technical advancements in neuro-ophthalmology, such as optical coherence tomography, prompted a still ongoing systematic re-investigation of retinal and optic nerve involvement in neurodegenerative disorders. In addition to inherited optic neuropathies, such as Leber's hereditary optic neuropathy and dominant optic atrophy, and in addition to the syndromic mitochondrial encephalomyopathies or mitochondrial neurodegenerative disorders such as some spinocerebellar ataxias or familial spastic paraparesis and other disorders, we draw attention to the involvement of the optic nerve in classic age-related neurodegenerative disorders such as Parkinson and Alzheimer disease. We here provide an overview of optic nerve pathology in these different clinical settings, and we review the possible mechanisms involved in the pathogenesis of optic atrophy. This may be a model of general value for the field of neurodegeneration. This article is part of a Special Issue entitled 'Mitochondrial function'.



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## Introduction

In the year 1988, two neuro-muscular disorders were associated with the first pathogenic defects of mitochondrial DNA (mtDNA), starting the molecular era of mitochondrial medicine (Holt et al., 1988; Wallace et al., 1988). Leber's hereditary optic neuropathy (LHON), one of the two, is a form of optic nerve degeneration inherited through the maternal line associated with a point mutation affecting the *MT-ND4* subunit gene of the respiratory complex I (Wallace et al., 1988). Since then, optic nerve atrophy has been recognized as a frequent hallmark of mitochondrial diseases and many neurodegenerative diseases have been discovered to have a primary molecular defect involving mitochondrial proteins (Babcock et al., 1997; Casari et al., 1998; Zuchner et al., 2004). Furthermore, mitochondrial dysfunction has been documented as a key pathogenic mechanism in many neurodegenerative disorders, even in those without a primary mitochondrial etiology (Schon and Area-Gomez, 2010; Vives-Bauza and Przedborski, 2011; Mochel and Haller, 2011). Finally, the introduction of new tools, such as optical coherence tomography (OCT) in ophthalmology, accurately assessed the optic nerve pathology in neurodegenerative diseases, such as Parkinson's disease, revealing patterns suggestive of mitochondrial neurodegeneration (La Morgia et al., 2012). Thus, the eye is a "mito-window" on the brain and this review will consider the retinal ganglion cells (RGCs) and related axons composing the optic nerve as a model system for mitochondrial neurodegeneration.

## Optic neuropathy in mitochondrial diseases: clinical features

### *Non-syndromic: Leber's hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA)*

LHON and DOA are both characterized by an extreme selectivity of their tissue expression, which is limited to the RGCs and their axons in the optic nerve, with a preferential involvement of the small fibers in the papillomacular bundle that subserve central vision (Carelli et al., 2004; Yu-Wai-Man et al., 2011).

LHON patients, mostly young-adult males, typically undergo rapid and painless loss of central vision, which is bilateral in most cases, or involves sequentially one eye first and subsequently the other. The visual loss usually begins with defective color vision and central scotoma on the visual field. Loss of visual acuity stabilizes within the first year after onset, leaving the patient, in most cases, legally blind. Fundus changes characteristic of the subacute stage include peripapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the optic disk (pseudoedema) and lack of leakage on fluorescein angiography (in contrast to true edema). The optic disk appears hyperemic and eventually axonal loss in the papillomacular bundle leads to temporal pallor of the disk. In time, the optic disk turns completely pale.

The endpoint of LHON is usually optic atrophy with permanent loss of central vision and relative sparing of the pupillary light responses. Spontaneous recovery of visual acuity has been reported occasionally, with contraction of the scotoma or reappearance of small islands of vision within it (fenestration). The most favorable prognostic factors are young age of onset and type of pathogenic mutation, the 14484/*MT-ND6* mutation being most commonly associated with spontaneous recovery (Carelli et al., 2011a). The chronic stage of LHON may be characterized by a further slowly progressing deterioration of visual functions, difficult to be objectively measured, but subjectively reported by patients and documented in a few cases studied post-mortem as evidence of still ongoing neurodegeneration (Carelli et al., 2002, 2004).

The recent use of OCT to measure retinal nerve fiber layer (RNFL) thickness provided anatomical quantitative features describing the subacute and chronic stages of LHON, as well as the unaffected mutation carriers and the recovery of vision. The crucial timing of LHON subacute conversion, detailed by OCT serial studies, demonstrated a precise pattern of axonal swelling followed by reduction, starting from the infero-temporal sector (papillo-macular bundle), followed by the superior and only lastly by the nasal quadrants, the latter usually the most spared by degeneration (Barboni et al., 2010a). This pattern matched that observed by the few postmortem studies of optic nerve specimens (Sadun et al., 2000; Carelli et al., 2002, 2004, 2009). In chronic LHON OCT showed a consistent decrease of RNFL thickness in all quadrants, which was significantly less severe in those patients recovering vision (Barboni et al., 2005). In unaffected mutation carriers the OCT showed a consistent increase of RNFL thickness (swelling) in the temporal/inferior quadrant, indicating a subclinical diseases of papillomacular bundle (Savini et al., 2005). Finally, the conformation of the optic nerve head has been substantiated by OCT as an "anatomical" risk factor for LHON, the small "at risk" disk being associated with conversion to affected status and a more severe final outcome (Ramos et al., 2009).

DOA patients, differently from LHON, present with slowly progressive, bilateral loss of central vision in childhood, accompanied by centrocaecal scotomas, impairment of color vision, temporal pallor of the optic disks and relative preservation of the pupillary reflex. The disease affects both sexes and is frequently so mild as to be recognized only during routine vision testing (school or driving license eye screenings). Its progression may vary within the same family, ranging from mild cases with visual acuity that stabilizes in adolescence, to slowly but relentlessly progressing cases, to severe cases with congenital optic atrophy. A distinct subgroup of LHON cases with childhood onset, especially if presenting with a slowly progressive clinical course, may pose serious problems of differential diagnosis with DOA (Barboni et al., 2006).

Despite the remarkably different clinical course, the endpoint of the pathological process in DOA is clinically indistinguishable from that in LHON, with a possible end-stage optic disk excavation, which may also be reported in LHON. The spontaneous recovery of visual acuity in DOA patients has not been reported, with a rare exception (Carelli et al., 2004; Yu-Wai-Man et al., 2011; Cohn et al., 2008; Cornille et al., 2008).

OCT studies in DOA defined quantitatively the optic atrophy, showing a decreased RNFL thickness, with a smaller average optic disk size, which suggests a reduced complement of axons at birth, compatible with severe congenital disease as a frust form of optic nerve hypoplasia (Barboni et al., 2010b; Barboni et al., 2011). The very few post-mortem studies of DOA showed selective loss of RGCs, particularly in the macular area, optic nerve axonal loss and demyelination, especially in the temporal aspect suggesting vulnerability of the papillomacular fibers as in LHON (Kjer et al., 1983).

An interesting feature shared by LHON and DOA is the occurrence, in a subset of cases, of white matter lesions, which may be indistinguishable from multiple sclerosis (MS) in terms of clinical and laboratory expression (Harding et al., 1992; Verny et al., 2008). This association of MS-like features with mitochondrial optic neuropathies seems to be causally related and not merely a coincidental occurrence of two overlapping diseases (Carelli and Bellan, 2008).

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