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REVIEW

A Review of Mitochondrial Optic Neuropathies: From Inherited to Acquired Forms

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Abstract In recent years, the term mitochondrial optic neuropathy (MON) has increasingly been used within the literature to describe a group of optic neuropathies that exhibit mitochondrial dysfunction in retinal ganglion cells (RGCs). Interestingly, MONs include genetic aetiologies, such as Leber hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA), as well as acquired aetiologies resulting from drugs, nutritional deficiencies, and mixed aetiologies. Regardless of an inherited or acquired cause, patients exhibit the same clinical manifestations with selective loss of the RGCs due to mitochondrial dysfunction. Various novel therapies are being explored to reverse or limit damage to the RGCs. Here we review the pathophysiology, clinical manifestations, differential diagnosis, current treatment, and promising therapeutic targets of MON.

PALABRAS CLAVE
neuropatía óptica;
mitocondria;
células ganglionares de la retina;
Neuropatía Óptica Hereditaria de Leber;
deficiencias nutricionales

Revisión de las neuropatías ópticas mitocondriales: de las formas hereditarias a las adquiridas

Resumen En los últimos años, se ha incrementado el uso en la literatura del término neuropatía óptica mitocondrial (MON), para describir un grupo de neuropatías ópticas que presentan una disfunción mitocondrial en las células ganglionares de la retina (RGC). De manera interesante, las MON incluyen etiologías genéticas, tales como Neuropatía Óptica Hereditaria de Leber (LHON) y Atrofia Óptica Dominante (DOA), así como etiologías adquiridas derivadas del consumo de drogas, deficiencias nutricionales y etiologías mixtas. Independientemente de que la causa sea hereditaria o adquirida, los pacientes presentan las mismas manifestaciones clínicas, con pérdida selectiva de RGCs debido a la disfunción mitocondrial. Se están explorando diversas terapias novedosas para revertir o limitar el daño a las RGC. En este documento revisamos la

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patofisiología, las manifestaciones clínicas, los diagnósticos diferenciales, el tratamiento actual y los prometedores objetivos terapéuticos de las MON.

Introduction

With advances in the understanding of optic nerve diseases, a new term has emerged within the literature to describe a group of diseases caused by mitochondrial dysfunction of the optic nerve: mitochondrial optic neuropathy (MON).

MON describes a group of optic neuropathies with similar clinical features and the same pathophysiology of mitochondrial dysfunction. Regardless of the underlying inherited or acquired cause, MONs share the common feature of mitochondrial dysfunction in the prelaminar area of the optic nerve. The subsequent selective damage and loss of retinal ganglion cells (RGCs) result in clinical signs of painless, progressive bilateral visual acuity loss, central or cecocentral scotomas, and color vision deficiencies. Although the same clinical features exist in MONs, the prevalence of specific aetiologies varies. In acquired MONs, the disease has no gender, racial, or age prevalence. In contrast, inherited aetiologies often affect children or young adults. Many have the potential to be partially or completely reversed. Furthermore, novel therapeutics appear promising in the treatment of MONs.

Mechanism of Action

Whether from an inherited mutation or an acquired exposure, overwhelming evidence suggests a shared mechanism of mitochondrial dysfunction. The impairment in ATP production *via* alternations in oxidative phosphorylation and the accumulation of reactive oxygen species (ROS) within the mitochondria trigger a decrease in the electrical potential across the mitochondrial membrane. This causes cytochrome C to leak out of the mitochondria into the cytoplasm and bind to the apoptosis activating factor-1 (APAF-1) resulting in apoptosis of the RGC.[1–4] In Leber hereditary optic neuropathy (LHON), mutations within the mitochondrial DNA lead to dysfunction in the mitochondrial complex I and cause accumulation of ROS. Alcohol, tobacco, and other MON-causing toxins can increase exogenous ROS and thereby cause the same pathway to be activated.[1] Whether energy depletion or over-production in ROS precipitates RCG loss remains to be understood and explains the variation in therapeutic targets used.

Susceptibility of prelaminar RGC in MON

MON selectively damages the RGCs within the prelaminar area of the papillomacular bundle (PMB). The unique anatomical features of the pre-laminar area make the PMB vulnerable to mitochondrial dysfunction in different ways.[5] First, the pre-laminar area contains a high number of mitochondria compared to the post-laminar area, demonstrating that the PMB has a high energy need.[6] Secondly, PMB fibers contain a large number of unmyelinated RGC axons compared to the post-laminar area which contains predominantly myelinated axons.[2,5] This means that prelaminar axons do not conduct electrical potential in an efficient way compared post-laminar axons which uses saltatory conduction. Thirdly, the PMB fibers are narrow in caliber, which further contributes to decreased energy conduction.[5] The high-energy requirement of the PMB in conjunction with the low energy production and slow axoplasmic transport leads to susceptibility of the PMB when mitochondrial dysfunction occurs in MON.[2,5,7,8]

Examination

Clinical Presentation

Clinical manifestations of MON are summarized in Table 1. Patients with MON typically present with bilateral, painless ''fog'' at the center of fixation. Visual acuities range approximately from 20/25 to 20/200.[9] Only in rare cases such as in methanol toxicity, can vision reach hand motion to no light perception. While visual acuities range widely depending on the severity of the disease, symmetry in visual acuity and ophthalmological findings in both eyes is a hallmark feature of MON.

The loss of color vision, especially of red color, is a prominent feature of MON. Color vision loss may be more severe than visual acuity loss.[2] Hardy Rand and Rittler (HRR) and Fansworth D-15 are most useful because they establish blue-yellow or red-green deficits, whereas Ishihara only assesses red-green defects. Red cap test between two eyes is normal due to the symmetrical nature of genetic or acquired MON. Pupils react equally normal or slightly sluggish to light. Similarly, no relative afferent pupillary defect (RAPD) is observed due to the symmetry of the disease. Reduced contrast sensitivity at high spatial frequencies has been found in sub-clinical cases of MON.[10]

Ophthalmic fundus evaluation varies depending on the extent of the disease. In early stages of MON, the optic nerves may appear normal, oedematous, or hyperemic. Peripapillary hemorrhages may be present. As the disease progress, PMB loss and temporal optic disc pallor occurs. In patients with longstanding MON, diffuse bilateral optic disc pallor and atrophy is apparent.

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