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Mini Review

Eye and Mitochondrial Diseases

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Abstract

Mitochondria represent the powerhouse of the eukaryotic cells, being responsible of energy production and cell survival. The retina, in particular retinal ganglion cells and photoreceptors, which requires great amount of energy to perform daily activity, have a strong dependence on mitochondria function. In mitochondria diseases, the retina and optic disc are affected, with the typical manifestations of tapeto-retinal degeneration and optic atrophy. Leber hereditary optic neuropathy (LHON) is the most popular mitochondrial retinopathy, with bilateral involvement, characterized by vascular and nervous retinal impairment. In the acute phase the retinal nerve fibers (RNFL) swelling is typically reported, which is later substituted by a RNFL thinning, corresponding to enlargement of centrocecal scotoma and vision impairment. Autosomal dominant optic atrophy (DOA) is the most common inherited optic neuropathy, whose diagnosis is usually made accidentally at a follow up visit. The characteristic aspect of fundus is almost similar to LHON. The natural course could consider a steady situation, a steep worsening or a slow and progressive evolution. In chronic progressive external ophthalmoplegia (CPEO) the posterior segment of the eye is infrequently involved, while the extraocular muscles are the typical targets, leading to ptosis, ocular motility impairment and diplopia. Although many nuclear genes could be responsible of CPEO, a sporadic single deletion in the mtDNA is the most common finding. The typical diagnosis is made following a skeletal muscle biopsy, revealing the characteristic feature "ragged red fibers." CPEO may show an extremely mild phenotype or being part of a more severe condition, defined Kearns – Sayre syndrome (KSS). The acronym NARP refers to the triad, neurogenic muscle weakness, ataxia and retinitis pigmentosa, which could be found isolated or associated with a severe encephalopathy in the context of maternally inherited Leigh syndrome (MILS). Nowadays, the only approved therapy is the Idebenone, for the treatment of young and adult patients suffering from LHON.

Keywords: Mitochondrial Retinopathies; Leber Hereditary Optic Neuropathy; Autosomal Dominant Optic Atrophy; Chronic Progressive External Ophthalmoplegia; Neurogenic Muscle Weakness; Ataxia And Retinitis Pigmentosa; Idebenone

Introduction

Mitochondria are responsible of several fundamental activities in the eukaryotic cells, particularly comprehensive of energy production and cells survival regulation. These little cytoplasmatic organelle are provided of multiple circular DNA copies (mtDNA) and a proteins production system. Photoreceptors and retinal ganglion cells (RGCs) are the retinal cells with the highest ATP expense and consequently with a great dependence on mitochondria integrity and activity. In view of this strong connection, mitochondrial dysfunction typically leads to RGCs axons damage, particularly in the papillomacular bundle. The introduction of optical coherence tomography (OCT) in daily clinical activity has provided a huge advantage for both qualitative and quantitative analysis of the retina. Thus, fundus and OCT examination play a crucial role in the study of mitochondrial retinopathies, which typically consist in tapeto-retinal degeneration and optic atrophy.

Leber hereditary optic neuropathy

Leber hereditary optic neuropathy (LHON) is the most popular mitochondrial retinopathy typically caused by point mutations of mtDNA, m.11778G>A, m.3460G>A and m.14484T>C on the genes MTDN1 and MTDN6 [1-5]. Typically, disease onset is single-eye, while the fellow is usually involved six-eight weeks later, and characterized by vascular and nervous retinal impairment with vessel tortuosity, telangiectasia, artero-venous shunts and fluctuation of the RNFL swelling [6,7], Patients complain about centrocecal and central scotoma, colour vision impairment, reduced visual acuity and contrast sensitivity [7-9]. In the chronic phase, the RNFL swelling leave the place to fibers thinning and optic atrophy, well evaluable by OCT analysis, while a complete recovery of the vascular system is observed [10]. The central scotoma enlarges progressively along the natural course of the disease, associating with a remarkable central vision impairment, with only few islands of restored visual field [11].

Autosomal dominant optic atrophy

Autosomal dominant optic atrophy (DOA) is the most common inherited optic neuropathy, due to mutations in a nuclear gene, OPA1, encoding for a GTPase, which has been found in the retina, brain and cochlea [12]. OPA1 has been proved to result crucial in mitochondrial integrity, in the respiratory chain and moreover in retinal dendritis preservation [13]. DOA diagnosis is usually made accidentally at a follow up visit, when the patient complains about a symmetrical, bilateral vision impairment, in association with dyschromatopsia and centrocecal scotoma, due to a generalized or sectorial nerve fibers swelling, usually involving the papillomacular bundle [14,15]. Later, RNFL thinning, disc pallor, "saucerization" of the disc, deep optic disc excavation and peripapillary atrophy characterize the chronic phase. The natural course of the disease could be variable, including a steadiness condition, or a steep worsening or few times a progressive evolution [15,16].

Chronic progressive external ophthalmoplegia (CPEO)

The extraocular muscles are the main targets of the chronic progressive external ophthalmoplegia (CPEO), leading to ptosis, ocular motility impairment and diplopia. Occasionally, patients may show optic disc atrophy and retinal involvement, with no visual impairment. Several nuclear genes have been ascribed in the pathogenesis of CPEO, however a sporadic single deletion in the mtDNA is the most common finding [17]. The typical diagnosis is made following a skeletal muscle biopsy, revealing the characteristic feature "ragged red fibers", however it has been reported a good reliability with orbiculari muscle biopsy. CPEO presentation could be sufficiently mild that the diagnosis is made later in life, or it could be associated with pigmentary retinopathy, condition known as Kearns – Sayre syndrome (KSS), which typically appears before twenties. Further possible findings include diabetes mellitus, hearing loss, as primary symptoms, and CNS involvement found by neuroradiological exams [18].

Neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP)

The acronym NARP refers to the triad, neurogenic muscle weakness, ataxia and retinitis pigmentosa, caused by different degree of heteroplasmy trasversion m.8993 T>G, encoding for mitochondrial ATPase 6. Heteroplasmy greater than 70% characterize the most severe pattern, known as maternally inherited Leigh syndrome (MILS), where the classic triad is associated with a severe encephalopathy. An adult onset is reported in case of heteroplasmy lower than 60-70%, while few or no signs are described if it is lower than 40%.

Therapy

While most of the part of mitochondrial retinopathies still lack a targeting therapy, the food and drug administration (FDA),

approved in 2006 Idebenone, a short chain benzoquinone, to treat young and adult patients who suffer from LHON [19]. It directly transfers electrons to complex III, bypassing the complex I, not functional in LHON, restoring the energy production. The reactivation of dysfunctional ganglionar cells leads to block the disease progression and to promote visual recovery. Genetic therapy, which would represent the best and definite solution, has still some limits to overcome, due to the presence of multiple mtDNA copies in each human cell, as well as, to the multiple organs' involvement in these diseases.

Conclusion

Nowadays, the only approved therapy is the Idebenone, for the treatment of young and adult patients suffering from LHON.

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The authors have no financial disclosure to declare.

Conflicts of Interest

The authors have no conflicts of interest.

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