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Minireview

Optic atrophies in metabolic disorders

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Abstract

Optic nerve involvement in metabolic disorders often results from apoptosis of cells that form or support the optic nerve, the retinal ganglion cell (RGC) axons, the myelin-forming oligodendrocytes, or the supporting vascular system. Given their high energy demands and the long course of their axons, RGCs are particularly sensitive to intracellular metabolic defects. Defects in energy metabolism, formation of reactive oxygen species, and storage of metabolites can all cause apoptosis of RGCs, decreased myelin formation of oligodendrocytes and increased pressure on the optic nerve. Clinically, the loss of RGC axons manifests as pale optic nerves. In general, the ophthalmologist can identify the underlying cause of an optic atrophy by careful examination, neuro-imaging, and family history. In some cases, however, the diagnosis proves elusive. In these instances, and especially when optic atrophy is accompanied by other systemic involvement, a metabolic disorder should be considered. Here, we review the underlying mechanisms of optic atrophy and its significance in metabolic disorders. Early identification of optic atrophy aids the diagnosis and subsequent management of the underlying condition, including anticipation of symptoms, genetic counseling, and possible therapeutic interventions. For many metabolic disorders, molecular testing is available.
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Introduction

Optic atrophy is a form of optic nerve disease resulting from the loss of ganglion cell axons that form the optic nerve, and/or a loss of the supporting microvascular tissue surrounding the optic nerve [1–4]. Symptoms of optic atrophy include decreased visual acuity (ranging from no light perception to mild decreases in visual acuity), visual field defects, and/or abnormalities in color vision and contrast sensitivity [1–5]. The hallmark clinical sign of optic atrophy is optic nerve pallor. Optic neuropathy is a more general term for optic nerve dysfunction, and includes the early phase of the disease, before clinical signs of optic atrophy may be present.

Possible causes of optic atrophy range from traumatic optic nerve injuries to nutritional deficiencies (such as vitamin B12 or folic acid) or toxicities (such as ethambutol or cyanide) to congenital systemic disease [1–6]. No effective treatment exists for most of these disorders, although correction of an underlying nutritional deficiency or elimination of an offending medication may halt progression. Optic nerve damage is usually permanent and, in many diseases, progressive.

Genetic defects are responsible for a substantial portion of the cases of optic atrophy; the inheritance patterns can be autosomal dominant, autosomal recessive, X-linked recessive, or maternally inherited (mitochondrial). In some diseases (primary optic atrophies), the only manifestation of the disease is optic atrophy. In other disorders (primary optic neuropathies with secondary symptoms), various neurological and systemic abnormalities are present.

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Secondary optic atrophies refer to inherited diseases with primary neurological or systemic manifestations, in addition to optic atrophy. Several excellent but primarily ophthalmology-oriented reviews are available concerning the genetics and underlying mechanisms of primary optic atrophies [5–8]. However, the significance of optic atrophy in metabolic disorders and its underlying mechanisms is under-represented in the literature [9,10].

In this review, we address the underlying pathology and frequency of optic atrophies in metabolic diseases by describing and classifying selected disorders. This information may aid ophthalmologic, genetic, neurological, and metabolic investigators to recognize early clues to the presence of optic atrophy in a metabolic disorder and to the presence of a metabolic disorder when optic atrophy has been discerned. Such early diagnosis can aid anticipation of symptoms, genetic counseling, and possible therapeutic interventions.

Pathology of the optic nerve

The process of vision involves light entering the eye and triggering chemical changes in the retina, creating nerve impulses that travel to the brain via the optic nerve. The optic nerve consists of more then one million optic nerve fibers (axons). Each fiber is derived from one retinal ganglion cell (RGC), whose cell bodies are located in the inner retina. Retinal ganglion cell bodies receive input from dendrites in the inner plexiform layer of the retina and extend their axons, via the nerve fiber layer, through the optic nerve head (Fig. 1). These axons become myelinated after they exit the eye and synapse with cells in the lateral geniculate nucleus of the thalamus [1,4,6]. Therefore, an optic neuropathy could be caused by defects in cellular metabolism within each RGC, in intra- and inter-cellular communication, or in myelination. Clinically, ganglion cell loss would appear as pale optic nerves (Fig. 2).

Given their high energy demands and the long course of their axons, retinal ganglion cells are sensitive to intracellular metabolic defects. Defects in intracellular energy metabolism, formation of reactive oxygen species (ROS), and storage of metabolites can result in apoptosis of RGCs, decreased myelination of oligodendrocytes, or (theoretically) increased pressure on the optic nerve and/or its supporting vascular system. Defects in intracellular energy metabolism are often a result of mitochondrial dysfunction. Mitochondrial biogenesis within each RGC axon occurs in the retinal, unmyelinated cell body (containing the nucleus) and is regulated by both nuclear and mitochondrial genes. After biogenesis, mitochondria are transported down the axons and distributed asymmetrically; the unmyelinated portions of the axons within the retina have much higher concentrations of mitochondria than the posterior myelinated portions or synaptic terminals of these same axons. This is partly due to the greater energy demands of

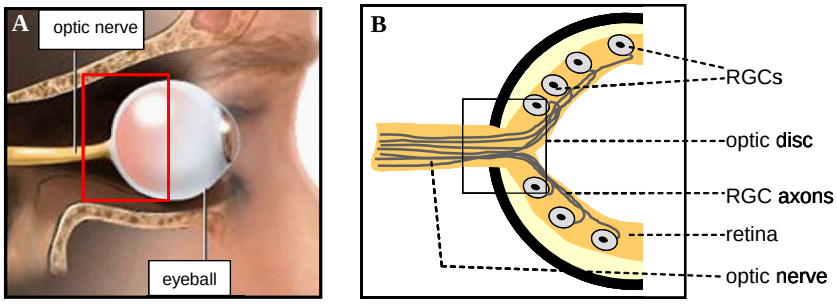

Fig. 1. Schematic, simplified view of the human optic nerve. (A)The optic nerve exits the eye posteriorly. Inset (red) is detailed in (B). (B)The cell bodies of the retinal ganglion cells (RGCs; ~1 million in each eye) are in the innermost cellular layer of retina. An axon extends from each RGC, which grows towards the vitreous interface and the optic nerve head. At the optic nerve head, the axons combine into the optic nerve and exit the eye.

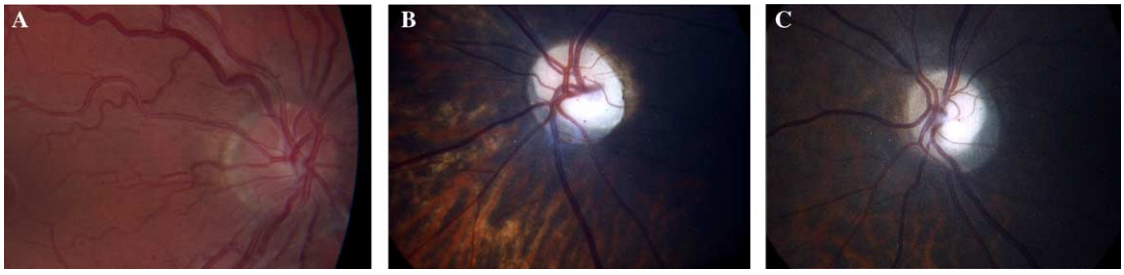

Fig. 2. Fundus photographs showing optic nerve heads of two patients with Costeff syndrome. The optic nerve head normally has an orange-pink color with a central, physiologic cup (A). In patients with Costeff syndrome (due to autosomal recessive *OPA3* mutations), ganglion cell loss is seen at the optic nerve head as bilateral, relatively symmetric pallor (B, left eye patient 1; C, left eye of the brother of patient 1). In these patients, fiber loss has been particularly pronounced in the papillo-macular bundle, leading to temporal pallor.