

Optic atrophy

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[Abstract](#)

[Keywords](#)

[Included diseases](#)

[Excluded diseases](#)

[Definition/Diagnosis criteria](#)

[Differential diagnosis](#)

[Frequency](#)

[Clinical description](#)

[Diagnosis](#)

[Etiology](#)

[Treatment](#)

[References](#)

Abstract

Optic atrophies (OA) refer to a specific group of hereditary optic neuropathies in which the cause of the optic nerve dysfunction is inherited either in an autosomal dominant or autosomal recessive pattern. Autosomal dominant optic atrophy (ADOA), type Kjer, is the most common OA, whereas autosomal recessive optic atrophy (AROA) is a rare form. Prevalence of ADOA ranges from 1:50,000 to 1:10,000. The frequency of AROA is unknown but the disease seems rare. MRI of patients with ADOA reflects the important loss of tissue of the optic nerve due to a dramatic reduction of the retinal ganglion cells. The age at onset of ADOA is usually between 4 and 6 years, although visual symptoms are usually imperceptible until late in life due to the slowly progressive decrease in visual acuity. There is no neurological deficit. However, a mild hearing loss may be encountered. In the pure congenital AROA, optic atrophy is never associated with neurological disorder and visual impairment is severe. Since the visual symptoms are important, AROA can be discovered very early, usually before the age of 4 years. ADOA has been associated with more than 60 mutations in the OPA1 gene. OPA1 maps to 3q28 and encodes an homologue of yeast dynamin-related GTPase, which is ubiquitously expressed in retinal ganglion cells and optic nerve. To date, no causative gene has been identified in the recessive form of OA.

Keywords

Optic atrophy, hereditary optic neuropathy, ADOA, AROA, OPA1 gene

Included diseases

-autosomal dominant optic atrophy, type Kjer;
-autosomal recessive optic atrophy.

-Wolfram syndrome

-Normal tension glaucoma

-Acquired optic atrophies

Excluded diseases

-Leber's hereditary optic neuropathy
-Leigh syndrome

Definition/Diagnosis criteria

Optic atrophies (OA) refer to a specific group of hereditary optic neuropathies in which the cause

of the optic nerve dysfunction is inherited either in an autosomal dominant or autosomal recessive pattern. Autosomal dominant optic atrophy (ADOA), type Kjer, is the most common OA, whereas autosomal recessive optic atrophy (AROA) is a rare form.

Differential diagnosis

[Leber's hereditary optic neuropathy](#), a maternally inherited optic atrophy due to mutations of the mitochondrial DNA, and many other inherited optic atrophies such as Leigh syndrome, Wolfram syndrome, Costeff optic atrophy syndrome, can be differentiated from OA by the clinical findings and family history.

Normal tension glaucoma (NTG) is particularly important to differentiate from OA since it leads also to an optic atrophy and may have a genetic basis. The characteristic enlargement of the optic is not specific of NTG and it can be observed in the course of OA. Thus, it is not possible to rule out the diagnosis of AO with slow visual impairment when such optic disc enlargement is observed. High value must be attributed to the visual field defects or to vascular manifestations. In addition, it has been stated that polymorphisms of the OPA1 gene could be associated with NTG.

Frequency

The frequency of each OA varies depending on their pattern of inheritance. Prevalence of ADOA ranges from 1:50,000 to 1:10,000. The frequency of AROA is unknown but the disease seems rare.

Clinical description

OA are characterized by a primary degeneration of retinal ganglion cells, the axons of which join to form the optic nerve. This degeneration leads to ascending atrophy of the optic nerve and is responsible for the clinical manifestations of the OA, which consist mainly in a decreased visual acuity, abnormalities of the central visual field and a typical color vision defect.

Dominant form

ADOA is characterized by a selective degeneration of the retinal ganglion cells and fibers of the papillo-macular bundle. This involvement of the smallest fibers of the optic nerve is not specific to ADAO since it may be also encountered in all genetic and acquired optic neuropathies resulting from mitochondrial dysfunction. The age of onset is usually between 4 and 6 years, but ADAO rarely causes severe impairment of vision in childhood. Acuity ranges from 20/20 to 20/200 in 85% of young adult patients and is lower than 20/200 in the remaining 15%. But, visual impairment can major quickly in adults. Thus visual symptoms

are usually mild until late in life due to the slowly progressive decrease in visual acuity. In most cases, visual acuity is equally reduced in both eyes. Intra or interfamilial phenotypic variations are important. Although the entire optic disc may be affected, it sometimes only displays temporal pallor with an absence of vessels or capillaries. Visual field exhibits central or paracentral scotomas. A blue-yellow dyschromatopsia is characteristically observed in color vision testing in ADOA patients. MRI of patients with ADOA reveals a significant thinning of the optic nerve along its length, confirming the important loss of tissue of the optic nerve due to a dramatic reduction of the ganglion cells. There is no neurological deficit. Hearing loss may be encountered during the course of ADOA. But this deficit is usually mild.

Recessive form

In the pure congenital AROA, visual impairment appears very early and is present at birth or appears in the first year of life. In addition, visual impairment is severe, leading to visually disabled or to blind children. Since the visual symptoms are important, AROA is discovered very early, usually before the age of 4 years. Sensory nystagmus is the rule. At fundus examination, normal retina contrasts with the diffuse pallor of the optic disc. A cupping may develop with age. However, in very young children, it might be difficult to differentiate AROA from Leber's congenital amaurosis or other retinal degenerations, since narrowing of retinal vessels and abnormalities of retinal pigmentation, which are characteristic of these congenital retinal disorders, are delayed in juvenile forms. Electrophysiological testing enables the diagnosis to be confirmed. Electroretinogram (ERG) is normal in pure congenital AROA, whereas no responses are obtained in congenital retinal degenerations. Visual evoked potentials are absent in AROA, confirming the pathology of the optic tract. Visual field testing, when possible, shows a central scotoma. This form of optic atrophy is never associated with neurological disorder.

Diagnosis

Diagnosis of OA forms is established on the basis of clinical findings and family history.

Etiology

Linkage analysis revealed genetic heterogeneity in ADOA. Two loci have been identified, one located on chromosome 3 (3q28-qter) and the other one on chromosome 18 (18 q12.2-q12.3). *OPA1*, the gene mapping to 3q28, is responsible for most ADOA cases. This *OPA1* gene comprises 28 coding exons and 8 mRNA isoforms have been reported, due to the

alternative splicing of 3 different exons. More than 60 OPA1 mutations have been described. OPA1 encodes a protein which shares a high homology with a yeast mitochondrial dynamin-related GTPase, Msp1. This Msp1 protein is essential for the maintenance of mitochondrial DNA. The OPA1 protein is ubiquitously expressed, especially in retinal ganglion cells and optic nerve. It is imported into mitochondria and is responsible for the maintenance of mitochondrial inner membranes and cristae. It has been suggested that OPA1 mutations lead to a loss of protein function and haplotype insufficiency, or are responsible for a dominant negative effect. This leads to the hypothesis that OPA1 mutations could induce the changes in mitochondrial structure or distribution that are thought to be implicated in loss of retinal ganglion cells.

To date, no causative gene has been identified in the recessive form of OA.

Treatment

Treatment is not currently available.

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