Stargardt disease

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Abstract
Stargardt's disease is a form of juvenile hereditary macular degeneration characterized by discrete yellowish round or pisciform flecks around the macula at the level of the retinal pigment epithelium (rpe). Stargardt's disease is the most common hereditary macular dystrophy. Prevalence is estimated between 1 in 8,000 and 1 in 10,000. Disease onset occurs typically in the first or second decade of life and manifests as decreased visual acuity. In the early stages, the macula usually shows discrete rpe changes, followed later by an horizontal ovoid zone of beaten bronze atrophy. In final stages, the macula can be associated with central areolar choroidal dystrophy. Fluorescein angiography reveals the characteristic dark choroid ("silence choroidien"), which probably results from the accumulation of lipofuscin in the rpe. This disease has usually an autosomal recessive inheritance pattern but some dominant pedigrees have been reported. The autosomal type has been associated with mutations in the ABCR gene, which encodes a transmembrane transporter protein expressed by the rod outer segments. There is currently no treatment available for Stargardt's disease.

Keywords
Stargardt, Macula, Fundus flavimaculatus

Disease name and synonyms

- Stargardt's disease
- Fundus flavimaculatus

Excluded diseases

- Cone dystrophy
- X-linked juvenile retinoschisis
- Ceroid lipofuscinosis
- Vitelliform dystrophy (Best disease)
- Pattern dystrophy
- Chloroquine retinopathy

Definition

Stargardt's disease (Stargardt, 1909, 1913, 1916, 1917, 1925; Weleber, 1994; Armstrong *et al*., 1998) is a form of juvenile hereditary macular degeneration characterized by discrete yellowish round or pisciform flecks around the macula at the level of the retinal pigment epithelium (rpe). This condition is also referred to as fundus flavimaculatus (Deutman and Hoyng, 2001).

Frequency

Stargardt's disease is the most common hereditary macular dystrophy. The incidence of Stargardt's disease is unknown. Approximate

estimates place the rate of prevalence between 1 in 8,000 and 1 in 10,000.
Men and women are equally affected and no racial predilection has been observed.

Clinical description
Patients present typically in the first or second decade of life, complaining of decreased visual acuity. Both eyes are generally equally and symetrically affected. Visual acuity usually gradually diminishes to 20/200 (6/60; 0.1) and has a significant correlation with the matching ranges of the Rayleigh equation (Mantyjarvi and Tuppurainen, 1992).
Clinical presentation in Stargardt's disease varies greatly. Early manifestation may only consist of some yellowish flecks and a macula with a snail's slime aspect. In the later stages of the disease, the macula may show a bull's eye pattern with rpe-atrophy or a beaten-bronze atrophy aspect.
The functional changes remain usually restricted to the posterior pole of the eye, but they sometimes also affect the peripheral retina (Stargardt's disease with peripheral degenerative retinopathy or mixed tapeto retinal degeneration). In those cases, the vessels are attenuated, the discs may become pale and pigmentary changes become obvious; the electroretinography (ERG) and electro-oculography (EOG) may become subnormal and the visual fields may be attenuated.
Disease onset is associated with a very slight defect in processing red-green vision in retina. A distinct acquired red (pseudo-protanomalous) defect is observed later in the disease course. In advanced stages, the red defect becomes much stronger (scotopization). A blue defect can also be found.

Management including treatment
Low-vision aids are prescribed and no other treatment is currently available (Fishman *et al*., 1987).

Etiology
Stargardt's disease has usually an autosomal recessive inheritance pattern but some dominant pedigrees have been reported. The autosomal type has been associated to mutations in the *ABCA4* (*ABCR*) gene, which maps to 1p21-p13. *ABCA4* encodes a transmembrane transporter protein that is expressed by the rod outer segments (Cremers *et al*., 1998; Klevering *et al*., 1999; Maugeri *et al*., 2000).
ABCA4 mutations may also lead to autosomal recessive cone rod dystrophy (Cremers *et al*., 2002; Rudolph *et al*., 2002; Fukui *et al*., 2002).
Some ABCR-variant alleles may enhance susceptibility to age-related macular degeneration (AMD) but further studies are necessary (Bernstein *et al*., 2002). Recently Glazer and Dryja presented a three-step explanation for the pathophysiology of Stargardt's disease (Glazer and Dryja, 2002).
1. Defective Rim protein, a protein encoded by the *ABCA4* gene causes an accumulation of protonated N-retinyledine-PE in the rod outer segments.
2. A2-E, a byproduct of N-retinyledine-PE then accumulates in the rpe cells and is toxic to them.
3. Photoreceptors eventually die secondary to loss of the rpe support function.

Diagnosis
Fluorescein angiography plays a key role in the diagnosis of Stargardt's, as it evidences dark choroid ("silence choroidien"), a characteristic sign of the disease that probably results from the accumulation of lipofuscin in the rpe. The retinal vasculature, and especially the retinal capillaries, appear then very clearly against the hypofluorescent choroid.
Functional findings show usually a normal ERG, and a normal or slightly affected EOG.

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