TOP IRDS TO WATCH: STARGARDT DISEASE

An overview of the most common juvenile macular dystrophy.

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Stargardt disease, the most common juvenile inherited macular dystrophy, has an estimated prevalence of one in 10,000 people.[1] It is most frequently caused by mutations in the *ABCA4* gene and is inherited in an autosomal recessive pattern. Dysfunction of *ABCA4* leads to the accumulation of toxic byproducts, including lipofuscin, which contributes to the classic phenotype of juvenile-onset bilateral macular flecks and atrophy.[1] More than 900 pathogenic mutations have been identified in the *ABCA4* gene, explaining the wide phenotypic heterogeneity observed in Stargardt disease. Several cases of Stargardt-like dystrophy have been linked to autosomal dominant mutations, most notably in *ELOVL4*.[2]

CLINICAL PRESENTATION

Patients with Stargardt disease usually present in childhood or early adulthood with blurry vision or central scotomas. Photophobia is common, as is dyschromatopsia. Visual acuity can range from 20/20 to 20/200 or worse. Ophthalmoscopic findings also vary with disease severity and range from mild retinal pigment epithelium (RPE) abnormalities and yellow-white pisciform flecks to, in more advance cases, chorioretinal atrophy (Figure A).[3] The pisciform flecks, which are pathognomonic for Stargardt disease, are present at the level of the RPE and result from the accumulation of lipofuscin. These flecks are more readily visualized during fundus examination with green light illumination. The macula can also have a "beaten bronze" appearance due to lipofuscin accumulation. The disease typically affects the macula and extends to the midperiphery, while the far peripheral retina remains mostly unaffected.

MULTIMODAL IMAGING

Although the clinical presentation is often indicative of the diagnosis, multimodal imaging provides additional insights into the structural changes associated with Stargardt disease.

OCT is particularly useful for demonstrating ellipsoid zone disruption, photoreceptor layer disorganization, and outer retinal loss in the macula, which is useful for monitoring progression (Figure B). OCT facilitates the early detection of foveal outer retinal degeneration, and central foveal

AT A GLANCE

- Stargardt disease is the most common juvenile inherited macular dystrophy with an estimated prevalence of one in 10,000 people.
- Patients with Stargardt disease usually present in childhood or early adulthood with blurry vision or central scotomas.
- Vision rehabilitation is strongly recommended to help patients with Stargardt disease adapt to their visual impairment and maintain their quality of life.

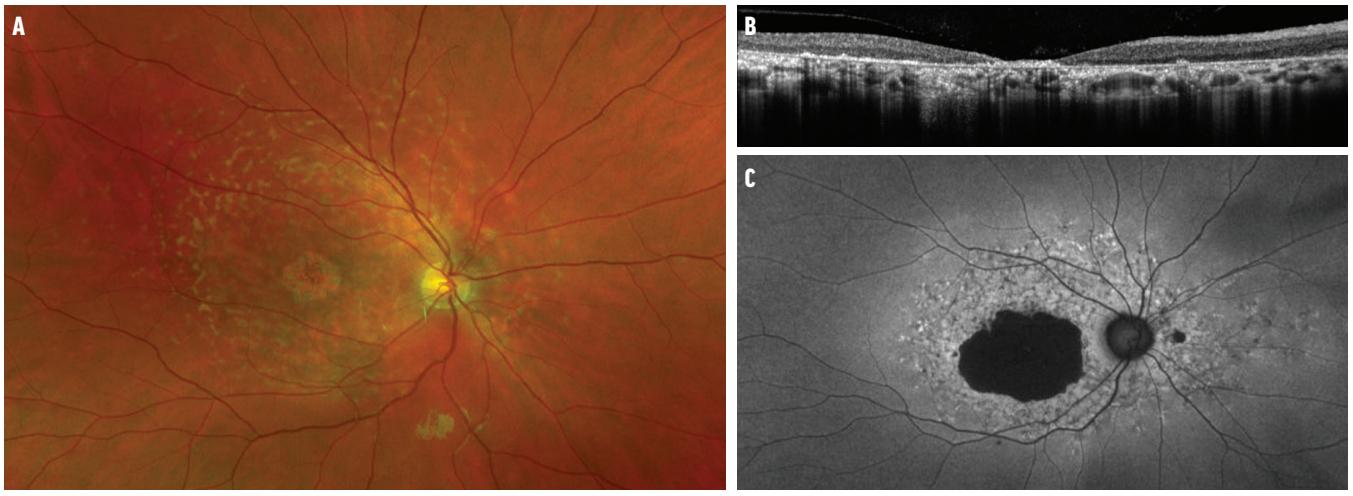

Figure. A color fundus photograph of the eye of a patient with Stargardt disease demonstrates the presence of yellow-white pisciform flecks in the perifoveal region, along with central foveal atrophy (A). OCT shows significant outer retinal loss centrally (B). FAF reveals foveal hypoautofluorescence with surrounding flecks and peripapillary sparing (C).

thickness has been found to correlate with visual acuity loss. Furthermore, early thickening of the outer limiting membrane may precede the onset of atrophy.[4]

Fundus autofluorescence (FAF) is a valuable imaging modality in staging Stargardt disease.[5,6] It typically reveals a central reduction in autofluorescence, often surrounded by a ring of hyperautofluorescence, resulting in a bull's eye maculopathy-like appearance (Figure C).[7]

The presence of a dark choroid on fluorescein angiography is also pathognomonic for Stargardt disease and can be seen in up to 80% of cases. Lipofuscin-laden RPE cells block choroidal fluorescence and enhance the contrast of retinal vessels.[8] However, with the increasing availability and accuracy of genetic testing, fluorescein angiography is used less often as a primary diagnostic imaging modality.

Microperimetry provides detailed topographical mapping of macular function, although results can be affected by media opacities such as cataracts. Despite its limitation, microperimetry remains a valuable tool for monitoring disease progression and is a reliable and sensitive functional outcome measure in clinical trials.[9]

Full-field electroretinography (ffERG) may demonstrate normal to subnormal scotopic and photopic responses, particularly in early stages. However, a wide range of ffERG abnormalities have been reported.[1] ffERG findings may also have prognostic value, with studies showing that early photoreceptor dysfunction is associated with increased risk of developing more severe visual impairment over time.[10]

MANAGEMENT

Regular follow-up to monitor disease progression is important for patients with Stargardt disease. During these visits, OCT and microperimetry are useful for evaluating structural and functional changes. Genetic testing is crucial for patients who may qualify for and are interested in clinical trials. Patients should avoid excessive vitamin A intake, including supplements and topical retinoids, which may exacerbate the accumulation of lipofuscin and potentially accelerate retinal degeneration.[11] Patients should use ultraviolet light-blocking sunglasses to reduce light toxicity. Vision rehabilitation is strongly recommended to help patients adapt to their visual impairment and maintain their quality of life.

Although uncommon, macular neovascularization has been reported in association with Stargardt disease and should be considered in cases of sudden vision changes.[12,13] Rare cases of subretinal fibrosis and RPE hypertrophy following minor ocular trauma have been described.[14] Lastly, the management of age-related cataracts requires thorough discussion, as postoperative light sensitivity can be bothersome for patients with Stargardt disease and should be carefully weighed against potential benefits of improved clarity.

CLINICAL TRIALS

Several ongoing clinical trials are investigating emerging therapeutic strategies, including the following:

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The phase 1/2 STELLAR study (NCT06467344) is investigating ACDN-01 (Ascidian Therapeutics), an RNA-based exon editing therapy administered via subretinal injection.

The phase 1/2 GARDian study (NCT05956626) involves OCU410ST (Ocugen), a gene-agnostic modifier gene therapy delivered via subretinal injection. It specifically involves human retinoic acid-related orphan receptor alpha.

The now complete phase 2 STARLIGHT study (NCT05417126) involved multi-characteristic opsin (MCO-010, Nanoscope), an optogenetics therapy that targets surviving retinal cells with the goal of improving vision.

The phase 2 TEASE study (NCT02402660) is investigating oral ALK-001 (Alkeus) as a strategy to replace vitamin A and prevent the formation of toxic vitamin A dimers.[11]

A phase 2b study (NCT03364153) of avacincaptad pegol (Astellas), a complement C5 inhibitor, is active for Stargardt.

The phase 2/3 DRAGON II study (NCT0638808) is investigating tinlarebant (LBS-008, Belite Bio), an oral small molecule that reduces the accumulation of toxic vitamin A-derived byproducts.

A phase 1/2 study (NCT04545736) is evaluating metformin in the treatment of *ABCA4*-related retinopathy. ■

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