REVIEWS

Stargardt Disease

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Stargardt disease is a slowly progressing macular dystrophy with an onset of disease most commonly in children and young adults. Numerous genes have been found to be associated with this disease, with variants in the retina specific ATP-binding cassette transporter (ABCA4) gene being most common. Each variant may have distinct clinical features, however, patients generally experience bilateral central vision loss and poor visual acuity ranging from 20/70 to 20/200. Diagnosis is often made through clinical presentation and may be assisted by fluorescein angiography (FA), spectral domain optical coherence tomography (OCT), fundus autofluorescence (FAF) or electrophysiological assessment. Currently, there are multiple classification systems of Stargardt disease that include Fishman STGD classification system, groupings due to electroretinography (ERG) findings, and types based on FAF imaging. Though there are currently no clinically proven treatments for Stargardt disease, physicians often recommend patients avoid direct sunlight, smoking cigarettes, and excessive intake of vitamin A. Potential treatments currently under investigation include strategies using gene replacement therapy, stem cell therapy, and pharmacologic agents. The purpose of this paper is to review the current knowledge of the genetics, classifications, and treatments of Stargardt disease, while underscoring the need for further research in potential treatment routes.

Introduction

Stargardt disease is the most common inherited macular dystrophy in adults and children, with a prevalence of roughly 1:8,000-10,000.[1] This disease has an autosomal recessive mode of inheritance and is most often associated with variants in the retina specific ATP-binding cassette transporter (ABCA4) gene.[2] The onset of the disease commonly occurs in childhood with a subsequent peak in early adulthood, and earlier onset often correlates with a worse prognosis. While early-onset Stargardt disease is often associated with moderate to severe mutations in the ABCD4 gene that lead to complete loss of function, late-onset Stargardt disease is associated with milder missense mutations, allowing for retention of partial ABCA4 protein function.[3,4] Early onset Stargardt disease is diagnosed prior to age 10,[5] late onset Stargardt disease is diagnosed at ages above 45, with the late-onset patients being diagnosed either during asymptomatic routine eye exam or presenting with metamorphopsia or oscillopsia without decreases to visual acuity.[6] Though there is much heterogeneity in clinical presentation, course and genetics, patients classically experience a progressive loss of retinal function, manifesting as a loss of central vision over time with preservation of peripheral vision.[7] Patients who presented with visual acuity greater than 20/40 took on average 22 years to develop a visual acuity of 20/200 or worse (consistent with legal blindness). Of the patients that presented prior to 20 years of age, their time

to legal blindness was 7 years on average.[7] Although there are currently no clinically proven treatments available, there are many clinical trials underway to investigate potential treatments for Stargardt disease. There is much current research being conducted on the understanding of the pathophysiology and treatments of Stargardt disease. With the recent advancements in knowledge of the disease, we aim to summarize the current understanding of and treatments for Stargardt disease.

Genetics

Stargardt disease is most often inherited by an autosomal recessive inheritance pattern, and is caused by variants in the ABCA4 gene, a highly polymorphic gene with 50 exons and over 900 disease causing variants identified.[8] This gene encodes an ATP-binding cassette transporter protein, also known as Rim protein, that is expressed on the outer segment of rods to transport potentially harmful substances from the cells. In these mutant Rim proteins, N-retinylidene-PE (N-RPE) accumulates in the rods, and combines with all-trans retinal to form the major component of lipofuscin known as N-retinylidene-N-retinlyethanolamine (A2E), which is suspected to be toxic to rods as it may dissolve cell membranes, and cause secondary photoreceptor cell death.[9] Common variants include 1268 A->G, 5814 A->G, 5844 A->G, and 5603 A->T.[10]

The vast allelic heterogeneity poses a barrier in determining the genotype to phenotype relationship.[11] Studies have shown significant discordance in phenotypic expression among siblings sharing the same ABCA4 variant.[12] Missense variants in the gene generally cause a more mild disease than a null allele, though certain missense mutations may more closely mimic the functional outcomes of null alleles.[13] In addition to the ABCA4 gene, roughly 5% of Stargardt disease is caused by mutations in the STGD4, ELOVL4, and PRPH2 genes.[14]

Clinical characteristics and diagnosis

The clinical features of Stargardt disease vary widely, in part due to the greater than 900 variants associated with the disease.[2] Patients generally present in early childhood or adolescence with bilateral central vision loss and may also experience blurred vision, central scotomas, and dyschromatopsia.[5] Visual acuity often ranges from 20/70 to 20/200.[14] Late onset Stargardt disease (FS-STGD1) is associated with a milder course of disease, better prognosis, and foveal sparing.[15] Early in disease, ophthalmoscopy may show a normal fundus and mild retinal abnormalities, such as the loss of foveal reflex or mild retinal pigment epithelium (RPE) changes.[15] In more advanced cases, the macula may be described as a bullseye pattern with a “beaten bronze metal” appearance.[16] Though, the diagnosis of Stargardt disease may not be possible prior to retinal

imaging with fluorescein angiography (FA), spectral domain optical coherence tomography (OCT), fundus autofluorescence (FAF) or electrophysiological assessment may also be performed.

Once considered the gold standard in diagnosing the disease, FA will show a dark choroid sign resulting from blockage of fluorescence by lipofuscin deposits in RPE. On spectral domain OCT, atrophy of the outer retinal fovea and inner ellipsoid loss may be seen. One of the benefits of OCT is the ability to monitor total and outer retinal thickness, inner segment ellipsoid loss and macular volume over time.[17] As of late there has been an increase in physician preference in the utilization of FAF in diagnosing Stargardt disease because it allows for detection of the disease prior to onset of clinical symptoms. Hyperautofluorescence is initially seen, likely due to lipofuscin accumulation within cells, progressing to hypofluorescence because of the death of RPE.[18]

Classifications

Once diagnosed, Stargardt disease may be organized by the Fishman STGD classification system, groupings due to electroretinography (ERG) findings, and types based on FAF imaging. The Fishman STGD classification system is categorized in three stages (stage 1, stage 2, and stage 3) and is mainly based on fundus appearance, and presence of macula or pisciform flecks.[19] Stargardt disease may also be organized into three groups (group 1, group 2, and group 3) based on ERG findings, by the presence or absence of flash, pattern, cone, and photopic/ scotopic full-field abnormalities. FAF may be used to categorize Stargardt disease into three types as well (type 1, type 2, and type 3), characterized by the presence of a speckled pattern of hypo- or hyper-fluorescence at the fovea, macula or surrounding.[20] Each subsequent stage, group, and type correlates with an increased progression of the disease and burden.

Clinical Management

Currently, there are no clinically proven treatments for Stargardt disease, though physicians often recommend patients avoid direct sun exposure, refrain from smoking cigarettes to minimize toxic exposures, and avoid dietary supplements with excessive vitamin A. Physicians may also recommend visual aids, such as prism based glasses, magnifiers, and microscopic lenses, and adaptations to help alleviate symptoms and to visit a genetic counselor when desiring to have children. There is much ongoing research in identifying potential therapies of this disease, with potential avenues of treatment including pharmacologic, gene replacement and stem cell therapy.

Current Research

The pharmacological interventions have proven difficult to develop due to the complexity of the various disrupted pathways in Stargardt disease.

One pharmaceutical currently under investigation, emuxistat hydrochloride, is a direct inhibitor of the visual cycle component retinol isomerohydrolase (RPE65), which converts all-trans retinyl ester into 11-cis retinol. This leads to a decrease in the production of retinaldehyde and sequesters all-trans-retinal and A2E, which would otherwise encourage the accumulation of lipofuscin in RPE.[21] In a ABCA4 knock-out mouse model, treating young mice with emuxistat for three months reduced A2E accumulation and lipofuscin autofluoresence.[22] One trial showed a reduction in rod-B wave amplitude recovery after photobleaching on electroretinography (ERG) after various doses of emuxistat in humans with Stargardt disease.[23] Rod-B-wave amplitude on ERG has been regarded as a reliable measure of rhodopsin, and thus 11-cis-retinal regeneration, and thus a reduction in amplitude would confirm the mechanism of action of emuxistat.[24]

Physicians often recommend avoiding excessive vitamin A intake because it has been shown to accelerate the accumulation of lipofuscin in ABCA4 knock out (KO) mice,[25] and theorized to limit the production of all-trans-retinal since vitamin A is the immediate precursor molecule to retinal. The evidence that reduction of dietary vitamin A provides benefits in the setting of Stargardt disease is mixed. Although a cross-sectional study showed higher visual acuity in Stargardt disease patients with low vitamin A intake compared with patients in high vitamin A intake,[26] a larger prospective cohort study found no association with vitamin A intake and visual acuity either at baseline or over a year.[27]

Moreover, non-functional ABCA4 may lead to a buildup of bis-retinoid fusion products such as A2E.[28] As a result, A1120, a non-retinoid retinol binding protein antagonist, is being studied as a potential therapeutic.[29] This drug may decrease the levels of vitamin A and subsequently A2E, thereby decreasing the accumulation of lipofuscin.[29] Additionally, there are clinical trials underway to investigate the effect of metformin on the course of Stargardt disease. Previously, metformin use has been shown to be associated with reduced odds of developing age-related macular degeneration (AMD), a disease characterized similarly to Stargardt disease, in patients matched based on mortality risk.[30] Metformin has been shown to stimulate glucose metabolism in the retina and protect retinal photoreceptors from mutations and oxidative stress in mouse models through activation of 5' adenosine monophosphate-activated protein kinase (AMPK) in the retina.[31] AMPK is an cellular energy censor responsible for detecting increases in the ADP:ATP ratio, a sign of cellular energy stress, and reprogramming those cells in a protective fashion against said stress.[32] Given this role in protecting against stress-induced photoreceptor damage in AMD, it is possible that protection could play a role in Stargardt disease as well.

Due to the genetic etiology of the disease, gene supplementation strategies would be an optimal form of treatment and the preferred vector in this therapy, adeno-associated virus (AAV), has been shown to have a minimal side effect profile.[33] But the large sequence of the ABCA4 gene makes the use of AAV difficult.[34] A recent study has tested the dual-vector AAV technology in mice, which delivers the sizable gene in two halves to produce a fully functional ABCA4 gene in vitro.[35] The outcome of the study revealed this method to be safe and effective, as treated retinas only showed minor photoreceptor loss and minor thinning of the outer nuclear layer and significantly decreased A2E accumulation in mice treated with the dual vector platform compared to ABCA4^{-} mice.[35] Additionally, researchers at Case Western have developed a method for performing non-viral gene therapy using a multifunctional pH sensitive amino lipid for intracellular delivery of nucleic acids.[36] This technology was used to induce specific gene expression of ABCA4 plasmid in photoreceptors in ABCA4^{-} mice.[36] They found that the treated mice maintained ABCA4 expression for at least 8 months, had a 35% decrease in A2E accumulation, and a 6 month delay in Stargardt disease progression.

Since Stargardt disease involves the death of RPE and photoreceptor cells, the only treatment method that can encourage improvement of vision, rather than prevent progression, is stem cell therapy. A study has revealed that in rats with a defect in RPE by a mutation leading to impaired phagocytosis of shed photoreceptor outer segments causing degeneration of photoreceptors, there was an improvement in visual acuity when treated with human embryonic stem cells (hESC) derived RPE compared to those untreated.[37] The best performers improved to 90% of normal acuity, compared to no improvement in the control group, who remained around 25% of normal. These findings led to clinical trials in which patients with late-stage Stargardt disease received hESC-RPE transplants, where they identified a trend of no serious adverse effects and increased corrected visual acuity in the transplanted eyes.[38,39] Though each of the three prospective methods of treating Stargardt disease have proven potential, more research is necessary to translate to clinical practice and offer patients a safe and effective method to slow or reverse the progression of vision loss.

Conclusion

Stargardt disease is the most common inherited macular dystrophy.[40] Though significant advances have been made in identifying presentations on imaging and understanding clinical features, with a highly heterogeneous phenotype and genotypic presentation, early diagnosis has proven difficult. Better understanding of the pathogenesis of the disease and enhanced technology in treating heritable conditions have allowed for increased clinical trials and potential pharmaceuticals to be investigated. Current treatments, which include avoiding direct sunlight, smoking cigarettes, and excessive intake of vitamin A uses theoretical thought to slow the progression rather than reverse vision loss. Thus, more research is required in potential pharmacotherapy, gene

therapy, and stem cell therapy to discover safe and clinically validated effective treatments for Stargardt disease and offer patients improved prognostication and genetic counseling.

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Conflict of interest

None of the authors have identified a conflict of interest.

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