“There is No Cure for Stargardt’s”: The Prognosis and Rehabilitation of a Patient with Genetically Confirmed ABCA4 Mutations
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ABSTRACT
Background
Stargardt’s macular dystrophy is an autosomal recessive inherited retinal dystrophy associated with mutation in the ABCA4 gene. Although there are no current FDA approved treatments or cures for patients with Stargardt’s macular dystrophy, current research avenues include nutritional supplementation, drug therapies, and gene therapy.


Case Report
A 58 year old African American female presents with suspected Stargardt’s with visual reports for comprehensive rehabilitation, including magnification assessment and genetic counseling of a patient with Stargardt’s macular dystrophy.

Conclusion
Genetic testing provides insight to the phenotype and magnification determination provides significant rehabilitation to these individuals.

INTRODUCTION
Stargardt’s disease is an inherited retinal dystrophy that is commonly referred to as a juvenile form of macular degeneration. Autosomal recessive mutations in the ATP-binding cassette transporter ABCA4 are the most common cause of Stargardt’s disease. Pathogenic variants in ABCA4 gene lead to the accumulation of toxic retinoid compounds within the outer segments of the photoreceptors [PR] and in the phagolysosomes of the retinal pigment epithelial [RPE] cells. The buildup of toxic A2E retionoid within RPE cells leads to oxidative damage to RPE cells and eventual RPE and PR degeneration. ABCA4 mutations leave toxic byproducts in the retina, eventually killing off the photoreceptor cells of the retina.

Funduscopically, Stargardt’s disease progresses through different stages throughout the disease process. Fishman described 4 stages of Stargardt’s disease. Stage 1 appears with yellowish “fleck” in the parafoveal area. Stage 2 presents with these flecks throughout the posterior pole. Stage 3 is defined as extensive flecking that have resorbed.

Stage 4 shows retinal pigment epithelium [RPE] atrophy. There are no FDA approved treatments or cures for patients with Stargardt’s macular dystrophy. Current research avenues include nutritional supplementation, drug therapies, and gene therapy. So, without sound FDA approved treatments, patients

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with Stargardt’s disease management focuses on low vision rehabilitation.

Rehabilitation success rates are high within Stargardt’s patients because of the relative stability of visual acuity at 20/200 and the ability of these patients to use both preferential retinal locus [PRL] in combination with magnification to aid in viewing tasks.\textsuperscript{4,5} Patients who have Stargardt’s disease generally maintain a stable Visual Acuity [VA] between 20/200 and 20/400. In a study done at University of Illinois at Chicago, 97.5% of Stargardt’s patients maintained a VA of 20/200 or better.\textsuperscript{3} This case will look at the comprehensive rehabilitation, including magnification assessment and genetic counseling of a patient with Stargardt’s macular dystrophy.

**CASE PRESENTATION**

RA, a 58 year old African American woman, presents for a second opinion and ocular health examination. She was clinically diagnosed with Stargardt’s and was told by several eye doctors she would “never see 20/20”. She first noticed vision changes when she was nine years old. Her ocular history is also positive for primary open angle glaucoma in both eyes (OU), and takes two medications for this: dorzolamide dosed three times a day, and latanoprost at night OU. She denies any family history of glaucoma or Stargardt’s disease. Systemically, she has both hypothyroidism, hypercholesterolemia and takes levothyroxine 112 mg tab daily.

**Figure 1:** Funduscopic view of patient RA. Figure 1A: Heavy pigmentation over macula with surrounding RPE dropout, pisciform flecks throughout the periphery, R eye. Figure 1B: Heavy pigmentation over macula with surrounding RPE dropout, pisciform flecks throughout the periphery, L eye. Figure 1C: Macular hypo-reflectivity with pisciform hyper/hypo fluorescence throughout the periphery, R eye. Figure 1D: Macular hyporeflectivity with pisciform hyper/hypo fluorescence throughout the periphery, L eye.
Ocular Health Examination

Upon ocular health exam, her entering acuities were: right eye (OD) 20/200 PHNI and left eye (OS) 20/150 PHNI. Preliminary testing and anterior slit lamp exam was within normal limits. Posteriorly, each optic nerve head was labeled with a cup-to-disc ratio of 0.7 vertical/0.7 horizontal with mild pallor OU. Fundus photos were taken (see Figure 1). The maculae in both eyes had pigmented scars, lacked a foveal light reflex, and had extensive flecking throughout the posterior pole and periphery. Fundus autofluorescence showed dense hyperintense and hypointense pigment clumping in the macula with white-hyperintense flecks throughout the periphery.

Functional Vision Evaluation

RA received a low vision examination with ultimate goals to see bus numbers, navigate transportation independently, spot people from across the room, read medication labels, and be comfortable in outdoor, sunny, conditions. A Visual Functioning Questionnaire [VFQ] was completed and she reported that reading mail, menus, and small labels were most challenging for her. Other difficulties included reading street signs and bus numbers at distance. RA had a moderate contrast impairment, log 1.05 reduction in both left and right eyes. A 120 point visual field was peripherally full, with central five degrees of absolute loss as seen in Figure 2. Amsler grid revealed central scotomas in both left and right eyes with rivalry present; RA preferred her left eye.

Device Evaluation

For the goal of spotting distance tasks, using a 4x Keplerian telescope held over RA’s left eye with her best correction spectacles on, she obtained a visual acuity of 20/40 (previously 20/140). RA was trained how to localize, focus, spot, track, and trace with device. An initial training session was completed and 8 weeks later a second training session was completed to ensure RA was comfortable, and competent with the telescope tasks. After successful training, RA was fit in a 4x Ocutech Sport bioptic over the left eye. The prescription in the carrier lens was OD: -3.00 -0.50 x080 and OS: -3.00 -0.75 x015. The pupillary distance was 65mm. She was trained how to spot in and out of the bioptic and could do so with

Figure 2: 120 dB visual field of patient RA. Figure 2A: Peripherally full field with central 14 degree loss horizontally and 12 degree loss vertically, R eye. Figure 2B: Peripherally full field with central 8 degree loss horizontally and 12 degree loss vertically, L eye.
been reported primarily in patients of African American ancestry. The third variant ABCA4 c.294C>G is another missense variant previously described in a compound heterozygous state with known pathogenic variants in patients with Stargardt’s disease. This genetic variant has been classified as “probably damaging”. The fourth ABCA4 variant c.1927G>A had been reported in heterozygosity in 452 individuals of predominantly African ancestry as well. Although, based on bioinformatics predictions, this amino acid change seemed to be deleterious, there is not enough clinical data to demonstrate the pathogenicity of this ABCA4 c.1927G>A missense variant and is classified as a variant of “uncertain significance” (VUS). RA was heterozygous for three pathogenic changes that cause the loss of functional ABCA4 protein and confirms the clinical findings. The patient did not have children or siblings and her parents were deceased. Family testing would have demonstrated the compound heterozygous state compatible with Stargardt’s disease.

**MANAGEMENT**

In our case, low vision rehabilitation was essential for keeping RA completing her activities of daily living [ADLs] with success. Patients with Stargardt’s have large central scotomas and decreased contrast due to their large foveal scars. They learn to use PRL’s that push the damaged area of the retina away, attempting to use intact retina to see. Magnification is then added so that the less sensitive peripheral retina detect larger stimulus and the brain can interpret the image. Our patient read 0.8M, (ie small newspaper headlines), with an equivalent viewing power of +6.00D.

Magnification was applied for distance using her 4x hand held telescope as well as her bioptic. With her 4x Sport Ocutech bioptic mounted over the left eye, she could read 20/40 on the Snellen acuity chart. With this device, she can see adequately at distance to see street signs, as well as bus numbers. In
fact, by the Texas state recommendations, she meets driving requirements with her bioptic as she is 20/40 in her better seeing eye through the bioptic and has 140 degrees of visual field. RA was referred to occupational therapy for intensive behind-the-wheel training using her bioptic before receiving a modified Texas state driver's license.

The prognosis of Stargardt's is relatively stable as visual acuity normally stabilizes between Snellen 20/200-20/400. With magnification, RA was able to accomplish her activities of daily living.

Although there are no current FDA approved treatments or cures for patients with Stargardt's macular dystrophy, current research avenues include nutritional supplementation, drug therapies, and gene therapy. One promising study done by Prokopiou et al, revealed that Omega-3 supplementation may be therapeutic in decreasing the oxidative stress in the photoreceptors in the retina in a mouse model. The hypothesis concludes that there may be a therapeutic effect on patients with Stargardt's disease and current clinical trials are undergoing.

Another promising clinical trial is through Acucela Inc. Currently a drug, Emixustat hydrochloride, is undergoing phase III clinical trials for individuals with genetically confirmed ABCA4 Stargardt's disease. This drug, taken 10mg orally each day, has been hypothesized to slow the progression of macular atrophy. The drug works to inhibit RPE65, a critical protein in the visual pathway, and reducing the availability of vitamin A derivatives in the visual cycle, limiting buildup of toxic A2E retinoid to prevent oxidative damage to RPE cells and photoreceptor degeneration. Current subjects enrolled in the study must have mutation in the ABCA4 gene. This solidifies the importance that patient inherited retinal conditions are genetically confirmed so participants can be properly selected.

Gene therapy studies have also been established. One study in clinical phase I/II was recruiting patients with two mutant ABAC4 alleles in the hopes of injecting a normal gene via a viral vector through subretinal injection, in hopes that transcriptional machinery of the host cell would re-integrate non-diseased gene into diseased RPE.

Genetic testing identified genes for classification, allowing further phenotypic expression of the disease to be classified genotypically. Plotting genetic abnormalities provides better insight to the genotype of the disease. A study by Schulz et al looked at 335 Stargardt's patients from a multicenter cohort to identify variant genes, giving researchers more data to determine gene variant and protein variants. Schulz's study revealed 48 novel pathogenic gene variations in the ABCA4 gene alone. It is therefore of critical importance that genetic testing is done. Genetic confirmation not only yields a diagnosis for patients, but also provides hope for future research toward the development of a cure.

CONCLUSION

Stargardt's is a genetic disease that affects an individual's retina at a measurable cellular level. Although diagnosing patients at a cellular level is not immediately life changing, science continues to press forward and the potential of future gene therapy is a possibility. Identifying pathogenic genes makes a database to help identify other patients, as well as qualify patients for future gene therapy. Patients with this disease, however, function at a very high level when provided with low vision rehabilitation.

Until an answer is found these patients need to be assisted with appropriate rehabilitation. Gene therapy does not help individuals complete ADLs, therefore, low vision (LV) referrals and rehabilitation are necessary. These patients respond well to magnification and eccentric viewing changing and maintain a high level of functionality, as seen in our case example.
REFERENCES


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Jackelyn Meyer, OD, completed her low vision residency at the University of Incarnate Word, Rosenberg School of Optometry. Among her special interests are considerations in driving with low vision, and the diagnosis and management of patients with Leber’s Hereditary Optic Neuropathy.