Common Inherited Retinal Diseases: Presentation, Diagnosis, Treatment

— Experts review approaches to retinitis pigmentosa, Stargardt disease, and choroideremia

by Kate Kneisel, Contributing Writer, MedPage Today
June 6, 2022

Vision accounts for more than 80% of the information humans obtain from the outside world. The ability of the eyeballs to capture and process visual information sent onward to the brain relies primarily on the health of the retina.

Three relatively common inherited retinal diseases challenge that process, though: retinitis pigmentosa (RP), choroideremia, and Stargardt disease (STGD).

Retinitis pigmentosa affects about 1 in 4,000 people, and collectively encompasses the largest group of inherited retinal diseases. With over 100 known mutations associated with RP, symptoms and age of onset can vary widely across different genotypes, Christina Y. Weng, MD, MBA, of the Cullen Eye Institute in Houston, told *MedPage Today* in an interview.

The earliest symptoms of RP are similar to those associated with choroideremia, including night vision loss, followed by progressive loss of peripheral vision, with eventual photosensitivity and loss of central vision, Jacque Duncan, MD, interim chair of clinical ophthalmology and academic director of the retina service at the University of California, San Francisco, told *MedPage Today*. In addition to these symptoms, RP patients may complain of light flashes or headaches, Weng noted.

Stargardt disease is the most common form of juvenile-onset macular degeneration, affecting one in 8,000 to 10,000 people. "Because the central macula is usually affected earlier than in RP, patients often complain of blurry vision, wavy vision, or central blindspots at an earlier age, with less impact on peripheral vision," Weng said. Other

symptoms include difficulty adapting to dim lighting, impaired color vision, and sensitivity to glare. "Many patients with Stargardt disease will progress to legal blindness, although patients with late-onset disease can maintain excellent visual acuity for a long time," noted Weng.

Choroideremia presents in childhood with night blindness, and progresses in adolescence to cause peripheral vision loss without affecting central vision or visual acuity until middle age, Weng explained. In their 40s to 60s, "patients will often develop a sudden deterioration of central vision along with loss of color vision," she added.

"Because choroideremia is X-linked, female carriers may be asymptomatic or may have mild night vision issues," she noted. "Even amongst affected males, the variation in phenotype and symptomatology can be drastic."

Diagnosis

All of these inherited retinal diseases require a careful dilated fundus examination, Weng said. "With RP, one can see bone spicules in the mid-periphery, a waxy pale optic nerve, and attenuated retinal vessels. In Stargardt disease, yellow pisciform flecks can be observed along with a bullseye maculopathy or pigmentary mottling in the macula. In choroideremia, there are well-delineated regions of atrophy with visible underlying sclera and large choroidal vessels."

In addition to a complete eye examination, patients should usually have some measurement of their side vision with visual field testing, Duncan said:

"I prefer Goldmann kinetic visual field testing to capture the earliest midperipheral, annular patterns of visual field loss in patients with rod-cone degenerations."

"OCT [optical coherence tomography] scans are helpful in examining the outer retinal layers in the macula; electroretinography testing is very important to measure the extent of disease involvement of both the rod photoreceptors (night vision), and cone photoreceptors (daytime, color and fine detail vision)," Duncan continued.

Depending on the disease in question, photographs of the back of the eye are also helpful, especially when they image autofluorescence from the retinal pigment epithelium cells under the retina, Duncan said.

However, genetic testing is "perhaps one of the most important tests nowadays," Weng noted. "I highly encourage all eye care specialists to test any patient in whom they suspect an inherited retinal disease." She pointed to at least two programs offering no-cost testing using a blood or saliva sample: Invitae (sponsored by Spark Therapeutics) and Blueprint Genetics.

Treatment

Currently there is only one FDA-approved treatment, voretigene neparvovec (Spark Therapeutics' Luxturna), for patients with inherited retinal degeneration associated with bi-allelic disease-causing variants in the gene *RPE65* that cause early onset retinal degeneration, or Leber congenital amaurosis, Duncan said.

However, more than 30 clinical trials of inherited retinal diseases are currently in the works, and all three of the disorders discussed here are being targeted for genetic therapy.

Generally, inherited retinal disease (IRD) patients tend to lose photoreceptors over time, with progression showing an inferior perimacular distribution with relative retention in the foveal and superotemporal macula. Artur Cideciyan, PhD, of Scheie Eye Institute at the University of Pennsylvania in Philadelphia, was quoted in *Retina Today* as saying that for improving vision, molecular intervention will be most effective in "IRDs in which patients have lots of photoreceptors and relatively little visual function... But if the goal of the treatment is to arrest photoreceptor degeneration and stop the loss of vision, then IRDs with a steady but slow progression have the greatest promise, such as the RP class of diseases."

Stargardt disease differs etiologically from choroideremia and X-linked retinitis pigmentosa, which "has led to a spectrum of treatment strategies that approach the problem from different aspects...from small molecules and anti-sense oligonucleotides to

viral gene supplementation and cell replacement," and CRISPR-based approaches are also likely to contribute to future therapies, noted one recent review.

When a patient's genetic mutation is not known, "treatments are being developed that may be effective independent of mutation, such as antioxidants, neurotrophic factors, and stem cells delivery to prolong the survival of photo-receptors and improve vision," Duncan said. And trials of optogenetics, prosthetics, and stem cells are underway for patients with advanced vision loss, Duncan added. "There's a lot in development, and there will be even more in the future."

Kate Kneisel is a freelance medical journalist based in Belleville, Ontario.

Disclosures

Duncan reported relationships with Acucela, AGTC, Allergan/Abbvie, Biogen/NightstaRx, ConeSight, DTx Therapeutics, Editas, Eloxx, Eyevensys, Gyroscope, Helios, Nacuity, ProQR, PYC Therapeutics, Replay Therapeutics, Spark, SparingVision, and Vedere Bio. Duncan's spouse has a relationship with RxSight.
Weng reported relationships with Alcon, Alimera Sciences, Allergan/AbbVie, the Dutch Ophthalmic Research Center, Genentech, Novartis, Regeneron, and Regenxbio.