## Commentary: An eye on the genes

"*The eyes cannot see what the mind does not know*." Genetic eye disorders are a diverse group that may stare us in the face with an obvious structural defect or they may be subtle, hiding behind a normal looking fundus. They may be restricted to the eye or they may involve other organ systems. At times, the pieces of the puzzle fit into a well-established syndrome, while at other times, they do not. Not only does one need to be aware of the red flags in ocular examination but also the systemic associations that indicate a possible genetic etiology, in keeping with the ideology of viewing the patient as a whole. The easiest clue to a possible genetic etiology comes from a positive family history. While many common eye conditions like refractive errors, glaucoma, and cataract to name a few may also have a genetic predisposition, it is the rare disorder that requires the treating ophthalmologist to give more thought to the genes orchestrating the phenotype.

Caring for children provides a unique opportunity to not just witness the changing signs of an evolving disease but also to catch them at an early stage where gene therapy may be more successful as fewer working cells have been lost. This puts greater responsibility on the shoulders of pediatric ophthalmologists. While it may take time for the widespread availability of approved gene therapies, the groundwork has to be started and an essential component of that is genetic testing.

Whole globe anomalies like microphthalmos and anophthalmos attributable to genetic abnormalities are now a leading cause for childhood blindness as documented by many studies conducted at blind schools.[1,2] Retinal disorders mainly dystrophies also add significantly to this burden. Traditionally, management of these patients was limited to nutritional supplements, counselling, and rehabilitation with no hope for curative therapy. Advances in gene therapy literally provide a ray of hope to those living in darkness. In 2017, the USFDA approved gene replacement therapy under the trade name Luxturna for patients of leber congenital amaurosis type 2 with biallelic RPE65 mutation and trials are also underway for LHON and choroideremia.[3] There are more than 250 genes associated with inherited retinal disorders, and the road ahead is long but full of promise.

The utility of genetic testing is in finding the exact etiology so that one may know if the patient can be given information and hope about any potential treatment with appropriate care taken to keep their expectations realistic. It helps in prognosticating and also deciding on surveillance for other known ocular or systemic manifestations of the particular genetic defect. Genetic testing has implications not just for the patient one is caring for but the family members as well. A carefully elicited pedigree provides valuable information and genetic testing can further reveal the actual carrier status and risk of involvement of other members. Preconception and antenatal testing can help parents take decisions about family planning.[4]

Despite widespread interest in this field, recent surveys have shown a disturbing gap in knowledge. A 16 question survey in 2019 answered by 264 AAPOS members showed that 48% had no understanding of any genetic testing modalities.[5] According to the 2019 EURETINA Clinical Trends Survey, 74% of delegates had only moderate to little understanding of gene therapy. An innovative and interesting Indian study published in this issue titled, "Cross-sectional observational analysis of the genetic referral practices across pediatric ophthalmology outpatient departments in an urban setting" has analyzed the genetic testing referral practices of pediatric ophthalmologists in an urban setting and highlighted the discrepancy between referral by a pediatric ophthalmologist and a geneticist. The findings of the aforementioned study revealed 49 of 126 patients (38.3%) were referred for genetic evaluation, of which 3 (6.1%), 31 (63.26%), and 15 (30.6%) cases were referred by the ophthalmologist alone, geneticist alone, and by both the specialists, respectively. In the second limb of the study, they also went on to contact the families referred for testing, but only one of the 49 referred had complied.[6]

The very limited number of specialists to refer to in the field of ocular genetics is a major hindrance for practitioners. Other reasons for low referral may be failure to suspect genetic disorders in certain conditions and the presumption that testing may not be fruitful for patients suffering from incurable diseases, especially those with limited financial resources.

The American Academy of Ophthalmology Task Force for Genetic Testing has published its recommendations.[7] The enigma of genetics makes the idea of testing and therapy exciting, but caution is essential because of the significant psychological and financial impact of a genetic diagnosis. One must also acknowledge the limitations of testing. There are a large number of nonpathogenic genetic variants that can be uncovered in nonspecific testing, which may only add to the stress. Pre- and posttest counselling is imperative as is interpretation of the genetic test by an expert.

The way forward to make genetic testing and counselling a regular part of our practice is education and collaboration.

The boom in telemedicine is the silver lining of this COVID-19 pandemic and can facilitate collaboration with a geneticist or an ophthalmologist with genetic expertise. A recent patient survey even demonstrated the acceptability of remote genetic consultations by families of children with inherited eye disorders both new consultations and follow-ups.[8] Private practitioners and smaller hospitals can overcome the major hurdle of availability of genetic services if they can get an opportunity to liaison with government and private institutes that have a Department of Ocular Genetics. Gene therapy holds much promise especially for children as many can harbor hope for possible treatment of hitherto untreatable disorders. The fast paced development in this field, however, provides a challenge to the pediatric ophthalmologist who justifiably struggles to understand the nuances of this unfamiliar subject and will benefit greatly from well-planned webinars and courses.

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