

Pediatric retina: Lessons from the past and goals for the future

Over the past 20 years, pediatric retina has developed into a subspecialty of the retina that incorporates traditional medical approaches as well as evolving therapies, such as drug and gene therapy, and exciting new regenerative medical therapies. This editorial will outline where we have come from, where we are today, and where we hope to be in the future. Although pediatric retinal diseases have been recognized early as retinal drawings of congenital X-linked retinoschisis in 1881,^[1] just after the development of the ophthalmoscope, it really was not until retinopathy of prematurity was described that a more organized approach to understanding the pathogenesis, and then pathogenetically driven treatments followed.^[2,3] People such as Arnall Patz, Everett Kinsey, Tatsuo Hirose, and William Tasman have all made great contributions to pediatric retina especially with regard to retinopathy of prematurity and other pediatric retinal diseases. Schepens and Criswick described familial exudative vitreoretinopathy, and Paul Sieving has spent many years describing the disease congenital X-linked retinoschisis.^[4,5] Interestingly, ophthalmology provided the first randomized prospective clinical trial to try and determine the treatment for diabetic retinopathy.^[6] This was actually the first randomized clinical trial in medicine. It showed us that to be able to perform such a trial, the classification of the disease needed to be understood by the physicians around the world and be consistent at each location. It was not until that was done that testing of different treatment modalities could be performed. Following the lead of the diabetic retinopathy study, a standard classification system for retinopathy of prematurity was developed largely driven by John Flynn and other people interested in retinopathy of prematurity. The international classification of retinopathy of prematurity or ICROP led to an understanding of the progression of the disease process, and that understanding allowed us to test a treatment that had been initially tried in Japan for peripheral ablation of the avascular retina. This early treatment was performed with cryotherapy and was referred to as the CRYO-ROP study.^[7] This showed us that peripheral destruction of the retina was able to reduce severe blinding retinopathy of prematurity disease. The classification system allowed us to understand the progression of the disease and change the name from retrolental fibroplasia to retinopathy of prematurity, which includes all the stages of retinopathy of prematurity from Stages 1 to 5.

The ICROP classification system has now been modified several times. Most recently, the third ICROP classification system deals with some of the issues of treatment with anti-vascular endothelial growth factor (anti-VEGF) drugs versus laser therapy for the early stages of retinopathy of prematurity.^[8] In addition, there have been recent drug versus laser therapy studies for retinopathy of prematurity such as the RAINBOW trial, which used ranibizumab versus laser to treat retinopathy of prematurity, and more recently the BUTTERFLY trial, which used Eylea to treat retinopathy of prematurity versus laser.^[9,10] Both of these trials were trying to demonstrate the benefit of one versus the other.

However, the RAINBOW trial did not actually reach statistical significance but did show that there was some potential effect of drug therapy. The biggest flaw of the RAINBOW trial, in my opinion, was the absence of photographic documentation of either the entry criteria or adequate treatment, whereas the BUTTERFLY trial, the results of which will be released toward the end of this year, had photographic documentation of both entry criteria and the treatment itself. This type of documentation is very important in laser treatment, as inadequate laser treatment is like giving an inadequate dose of the drug. Unless both treatments are done properly, the results cannot be fairly compared.

Although retinopathy of prematurity is perhaps the most common pediatric retinal disease, many other pediatric retinal diseases, all of which tend to be rare diseases, have been studied over the past several years, first using clinical observations as tools to establish a classification system, and then using these findings to direct management. In the rest of this editorial, we will address a few of these diseases – familial exudative vitreoretinopathy, Norrie's disease, congenital X-linked retinoschisis, and persistent fetal vasculature syndrome.

Familial Exudative Vitreoretinopathy

Familial exudative vitreoretinopathy is an inherited retinal disease that prevents proper retinal vascular formation, especially the absence of some or all of the peripheral retinal vasculature. The disease has been classified into five stages, ranging from Stage 1 with incomplete vasculature alone to Stage 5 with total retinal detachment and blindness.^[11] The disease is genetically determined and originally described by Criswick and Schepens.^[4] They noticed that the disease was primarily autosomal dominant or autosomal recessive. Later Plager *et al.*^[12] described the X-linked form of inheritance. Currently, six genetic mutations have been described related to familial exudative vitreoretinopathy; however, nearly half of the patients diagnosed with familial exudative vitreoretinopathy do not have a known mutation.^[13] There is, however, approximately a new mutation found every few years. In the future, as new mutations are found, we may be able to confirm the diagnosis and not rely solely on clinical diagnosis.

Familial exudative vitreoretinopathy, as the name implies, occurs in families and requires screening of family members with wide-field fluorescein angiography to accurately determine the clinical findings.^[14] The treatments currently involve peripheral retinal ablation, usually with laser or the use of anti-VEGF drug, or if retinal detachment ensues, vitrectomy and scleral buckling may be helpful, especially if there is a rhegmatogenous retinal detachment component. The treatment of familial exudative vitreoretinopathy hopefully will involve future therapies, which we will discuss later in this editorial.

Norrie's Disease

Norrie's disease is a very severe disease that affects the eyes, ears, and central nervous system.^[15] It is generally felt that, left alone, 100% of children would be blind in both eyes, and approximately 40% would have hearing loss and 40% central nervous system problems. Both familial exudative vitreoretinopathy and Norrie's disease have defects in the Norrin-driven Wnt signaling

system. Familial exudative vitreoretinopathy and Norrie's disease both show changes in the ability to produce Norrin. In Norrie's disease, Norrin cannot be produced. In familial exudative vitreoretinopathy, a mutation involves alteration in the production of Norrin or in its cell surface receptor composition. Treatment for Norrie's disease can be very difficult, especially in the more extreme forms of retinal detachment involving vitrectomy. Rarely, very low levels of vision can be achieved following surgical therapy.^[16] There is no treatment for hearing loss in Norrie's disease or the central nervous system changes.

Congenital X-Linked Retinoschisis

Congenital X-linked retinoschisis has undergone a classification system pointing out that, actually, unlike the classic teaching, that there are only two areas of retinoschisis: foveal and peripheral.^[17] Optical coherence tomography has revealed that there are actually three types of retinoschisis: foveal, lamellar, and peripheral schisis. These areas of retinoschisis allow a classification system to be formed.^[18] The classification system divides the diagnosis based on areas of involved retinoschisis into four types. These four types represent areas of the retina that are splitting due to the absence of appropriate retinoschisin. Retinoschisin is an adhesive and neuroconductive protein that holds the layers of the retina together.^[19] This absence of retinoschisin allows splitting, and the splitting prevents that area of the retina from functioning normally. There has been a great deal of work done relative to the potential of gene therapy in congenital X-linked retinoschisis.^[20]

Although the *Rs-1* gene is a small gene, there have been more than 175 different mutations reported. Paul Sieving has spent many years working on gene therapy for congenital X-linked retinoschisis in the hopes of regenerating healthy retinoschisin. As this retinoschisin is both an adhesive and neuroconductive protein, it is possible that if the schisis cavities can be closed, visual function can return to these areas.

Persistent Fetal Vascular Syndrome

Persistent fetal vascular syndrome is a process in which the primary vitreous or hyaloid system, as well as the tunica vasculosa lentis, does not involute as is genetically determined in the average human eye.^[21] This disease is an interesting disease because it involves areas of peripheral avascular retina that produces VEGF, and VEGF causes suppression of the genetically programmed involution of the hyaloid system and the tunica vasculosa lentis. In addition, not only is there disruption of this pathway, the cellular elements of the retina can also be disrupted, leading to visual reduction from retinal dysplasia. Posterior tractional retinal detachments can also be seen causing the fovea to be dragged toward the optic nerve. These patients, with what is called an eccentric stalk, often present with strabismus, unlike the classic persistent fetal vasculature child that presents at birth with leukocoria. The treatment for persistent fetal vascular syndrome is based on the anatomy of the eye at presentation.^[22] The visual results, however, depend on the amount of retinal dysplasia, and this retinal dysplasia can be minimal to clinical examination or very pronounced to clinical evaluation, but both of which can have effects on the patient's final visual results.

How Do These Diseases Cause Eyes to Be Blind?

Most of these diseases have a poorly developed retinal vasculature. Familial exudative vitreoretinopathy and Norrie's

disease show changes in the pattern of retinal vasculature and also the absence of peripheral vasculature. In addition to these changes, either secondarily or primarily, they are associated with neuroretinal degeneration. This combination is what causes these diseases to cause blindness. In congenital X-linked retinoschisis, a lack of adhesive protein that contributes to an anatomic change causes a reduction in vision. In persistent fetal vasculature syndrome also, a disruption of retinal anatomy leads to a reduction in vision. The major hope for these types of defects is what is called regenerative medicine. Our group has been working on Norrin-driven Wnt signaling, which is how normal retinal vasculature and retinal tissue are formed in the fetus and neonate. Norrie's disease is caused by the absence of the protein Norrin and causes 100% bilateral blindness, 40% hearing loss, and 40% central nervous system problems. The importance of Norrin protein is massive in terms of retinal neuro- and vasculature development. In hearing and central nervous system changes, only 40% are affected, because other molecules can trigger Wnt signaling, and they are able to pick up some of the jobs of the Norrin-driven signaling but not completely.

Regenerative medicine is being explored not only in ophthalmology but also in other forms of medicine.

Screening of Pediatric Retinal Diseases

Although the screening aspects of ophthalmic pediatric retinal disease are perhaps the least exciting activity, they are perhaps one of the most important. They also have undergone very significant changes in the recent past. Photographic screening for retinopathy of prematurity is something that has been used for many years.^[23] We have used and developed software programs that allow the doctor to read images from any location from around the world that has internet access. Certainly, in other areas of ophthalmology such as diabetes, we use not only photographic screening but also artificial intelligence to screen patients. This is genetically possible only in the areas with excellent internet connection. A company in India has developed a memory stick device that supplies artificial intelligence. This is something that is certainly usable for screening in countries with less reliable internet access.^[24] Another very large important area of screening is the screening of eyes of all new newborns. Darius Moshfeghi has been the champion of this type of approach in using photographic screening of newborns. This would allow us to pick up disease earlier.^[25] Children with pediatric retinal disease often may go for months or years without noticing a significant visual loss in one eye.

In the future, we think that we will see regenerative therapeutics. We believe that we will also see some medical devices that will help with visual function and hopefully screening, which will identify children at risk of developing more severe diseases at birth so that these diseases will be treated at an earlier stage so that hopefully significant recovery is possible for many of these diseases, which are now diagnosed only at the late stages.

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