Recent Trends and Update on Treatment of Retinitis Pigmentosa and Stargardts Disease

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Retinal degenerations are a leading cause of blindness in many parts of the world[1,2]. The notion that "nothing can be done" for patients with retinal dystrophies is no longer true. Electrophysiological testing and autofluorescence imaging help to diagnose and predict the patient's course of disease. Better phenotyping can contribute to better-directed, cost-efficient genotyping. Combining fundoscopy, autofluorescent imaging, and electrophysiological testing is essential in approaching patients with retinal dystrophies. With increased life expectancy, the problem posed by these conditions is magnified, as affected individuals will have to endure more years of visual loss unless new treatments are found New gene-based treatments for these devastating conditions are emerging which shows lot of promise in the management of these conditions.

RETINITIS PIGMENTOSA

Retinitis pigmentosa (RP), also known as rod-cone dystrophy, has both genetic and allelic heterogeneity[3]. RP inheritance can be autosomal dominant, autosomal recessive, or X-linked recessive, and there is genetic heterogeneity even within each group. Retinal degeneration slow (RDS) protein and retinal-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCA4) are examples of allelic heterogeneity in that they can cause macular dystrophy in some patients and cone-rod dystrophy in others. Approximately 50% of patients have no family history of RP or evidence of parental consanguinity, and likely, many of such cases are autosomal recessive. However, some may be males who have X-linked disease from female carriers, and other cases may be new autosomal-dominant mutations or manifestations of autosomal-dominant disease with reduced penetrance. Accurate genetic counseling depends on identifying the causative mutation and mode of inheritance.

The age of onset of RP is variable and patients do not always present with the classic triad of intraretinal pigment migration, optic nerve pallor, and attenuated vessels. In general, patients who develop symptoms at younger ages have worse prognosis, and dominant disease has a less severe natural history with later onset when compared to X-linked and recessive variants. In RP, patients with normal VA and smaller, higher-density autofluorescent rings correlate with worse-pattern ERGs. This represents a shrinking area of photoreceptor function as disease progresses[4,5]. In time, VA declines, visual fields coalesce to give the classical peripheral ring scotoma, and posterior subcapsular cataracts or cystoid macular edema (CME) may develop.

Enhanced S-cone, also known as Goldmann-Favre syndrome, is a subtype of autosomal-recessive RP featuring larger photopic single-flash ERG a-wave than 30-Hz b-wave amplitudes. Patients also have supernormal S-cone function, which is due to an increased number of S-cones, low numbers of L- and M cones, and a lack of rods.

Goldmann-Favre is one of the most frequently described hereditary vitreoretinal disorders[6,7]. Although the fundus appearance is variable, patients may have deep, nummular-shaped RPE clumping in the mid-periphery.

Common clinical findings of RP (Figure 1) are:

- Usually bilateral and symmetric.
- Bone spicule pigmentation or pigment clumping.
- Retinal arteriolar narrowing.
- Waxy pallor of optic nerve.
- Epiretinal membrane.
- Atrophy of retinal pigment epithelium (RPE) and choriocapillaris starting in the mid peripheral retina and extending with time.
- Preservation of RPE in the macula until late in the disease
- Posterior subcapsular cataract.
- Cystoid macular edema (CME)
- Carriers will have a normal retina, isolated geographic patches of RPE atrophy and pigment clumping, or diffuse retinal changes.
- Rarely symptomatic patients with absent retina findings (retinitis pigmentosa sine pigmento).

Diagnostic findings

- An electroretinogram (ERG) is useful in patients with early disease and minimal clinical findings. Early in the disease state, the rod ERG amplitude is affected more than that

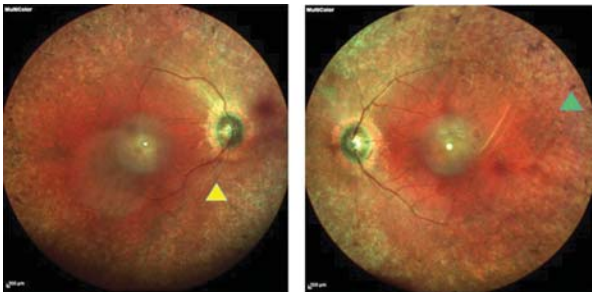

Figure 1: *Multicolour photos of Retinitis pigmentosa showing generalized arteriolar attenuation ▲ and bony spicules ▲*

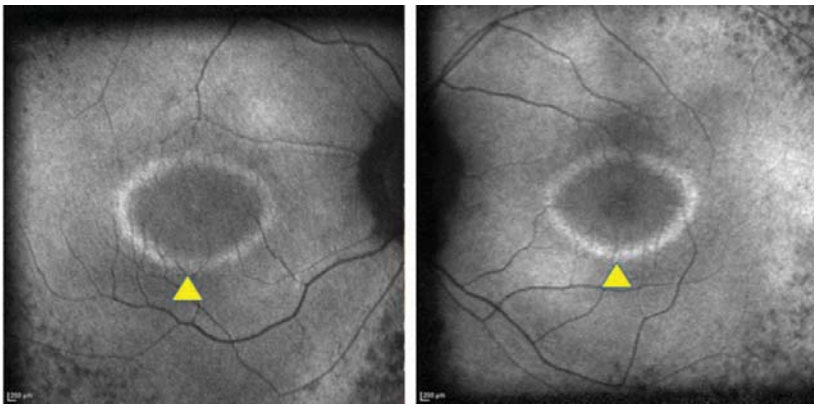

Figure 2: *Fundus autoflourenscence images often reveal a ▲ paracentral ring or arc of locally elevated AF relative to background levels in the image.*

of the cones. With progression of disease, both rod and cone responses are extinguished.

- The electro-oculogram (EOG) correlates with the ERG and is reduced. An EOG is unnecessary if the ERG is diagnostic.
- Visual field initially shows a midperipheral ring scotoma, which enlarges peripherally and centrally with disease progression.
- Fluorescein angiography (FA) shows areas of choriocapillaris loss. Petaloid leakage occurs in CME.
- In general, FA is not required to make the diagnosis of retinitis pigmentosa.
- Optical coherence tomography (OCT) evaluates the presence of epiretinal membrane and CME.
- Fundus autofluorescence (Figure 2) images often reveal a paracentral ring or arc of locally elevated AF relative to background levels in the image
- Ultra high-resolution OCT can document photoreceptor loss
- Medical evaluation should be performed if an associated systemic condition is present

TREATMENT OF RETINITIS PIGMENTOSA

Beyond refractive correction, most other medical interventions are of questionable value for this degenerative condition. It is important to recognize gyrate atrophy, Refsum syndrome, and abetalipoproteinemia because they are 3 types of retinal dystrophies that dietary treatment can help. The main clinical manifestations of Refsum syndrome are RP, cataracts, chronic polyneuropathy, cerebellar ataxia, and cardiac arrhythmias[8,9]. Elevated serum phytanic acid levels are diagnostic. Avoiding foods high in phytanic acid (eg, fat and butter) and plasmaphoresis help to improve all neurologic signs. Bassen-Kornzweig syndrome (abetalipoproteinemia) is due to malabsorption of cholesterol, fats, and fat soluble vitamins from the small intestine. Deficiencies of vitamin A and vitamin E cause failure to thrive, peripheral neuropathy with muscle weakness, spinocerebellar ataxia, and RP. Vitamin A (300 IU/kg/day) and vitamin E (100 IU/kg/day) restore function and slow the progression of retinal degeneration.

A randomized controlled study sponsored by the National Institutes of Health (NIH) looking at vitamin therapy for RP in adults showed that vitamin A (15 000 IU) delays the progression of cone ERG loss. The same study showed that vitamin E (400 IU) may have a deleterious effect on RP patients[10]. These results have not been universally accepted in ophthalmic centers. Subgroup analysis revealed that patients who started taking docosahexaenoic acid (1200 mg/day) at the same time as vitamin A may have a modest additional benefit of slowing RP[11]. A safety study did not find substantial side effects of high-dose vitamin A

Table 1: Few syndromic RP associations are summarised below

Syndrome	Retinal abnormalities	Systemic abnormalities
Alagille syndrome	Diffuse pigment deposition	Pulmonary valve stenosis, biliary atresia, jaundice, dysmorphic craniofacial features, axial skeletal anomalies
Alstrom disease	Juvenile-onset pigmentary retinopathy severe vision loss extinguished ERG	Bardet–Biedl-like with diabetes and acanthosis nigricans, deafness, obesity
Bassen Kornzweig (abetalipoproteinemia)	Retinitis pigmentosa sine pigmento, night blindness	Vitamin A and E de ciency, absent serum betalipoprotein, neuropathy, celiac syndrome, ataxia, acanthocytosis
Cockayne syndrome	Usher-like juvenile-onset retinitis pigmentosa	Deafness, dementia, precocious aging, developmental delay dwar sm
Flynn–Aird syndrome	Pigmentary retinopathy	Deafness, dental cavities, seizures, cystic bone changes, elevated CSF protein, joint stiffness, peripheral neuritis, dementia, ataxia, baldness
Jeune syndrome	Leber-like congenital pigmentary retinopathy	Dwar sm, digital anomalies, nephrophthisis
Senior-Loken syndrome	Juvenile polycystic kidney disease, tapetoretinal degeneration	Wide spread systemic anomalies
Mucopolysaccharidoses	Pigmentary retinopathy associated with cornea clouding	Craniofacial dysmorphism, hepatomegaly

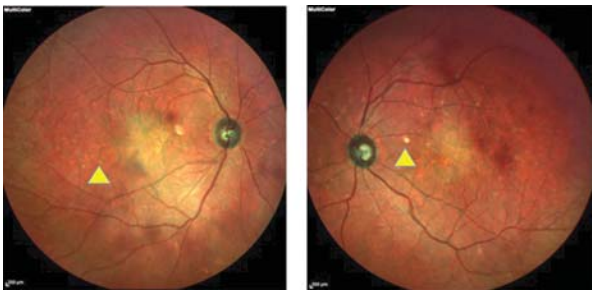

Figure 3: *Multicolour photos of Stargardts disease showing bilateral white yellowish deep retinal lesions (flecks) ▲ seen in the posterior pole which can extend to the mid-periphery with progression to a loss of the foveal reflex.*

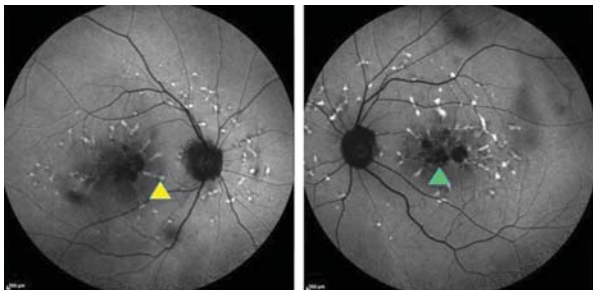

Figure 4: *Fundus autoflourenscent shows hyper- autoflourenscence flecks ▲ with around the hypo- autoflourenscent central macula ▲.*

therapy. Currently, the NIH recommends that adult RP patients take a supplement of 15 000 IU of vitamin A daily under the supervision of an ophthalmologist and avoid use of high-dose vitamin E supplements.

Physicians should follow RP patients at infrequent but regular intervals to detect treatable complications such as posterior subcapsular cataract, macular edema, and the rare autoimmune reaction. Cataract extraction can improve visual perception and brightness. CME can be treated with oral acetazolamide or topical carbonic anhydrase inhibitors. RP patients with a rapid progression of visual symptoms and ERG progression should have a Western blot analysis for antiretinal antibody. If this serum test is positive, patients presumably have developed autoimmunoretinopathy or a CAR (cancer-associated retinopathy) like syndrome and should undergo evaluation for an occult malignancy. There is a Coats'-type variant of RP thought to occur in as many as 3% of all RP patients. These fundi have typical bone spicules of RP with Coats-type changes in the inferotemporal quadrants. Retinal telangiectasia and exudative retinal detachments are treated with photocoagulation or cryosurgery as indicated.

In gene therapy, harmless virus is introduced to deliver a healthy version of gene consisting of the corrected DNA into patient's eye. There are several genes which can cause RP when mutated. Among them, Retinitis Pigmentosa GTPase Regulator (RPGR), which is responsible for maintaining the photoreceptors, is very prone to mutation. The California Institute for Regenerative Medicine is funding a number of projects to create a therapy for RP using ES cell-derived retinal progenitor cells, although FDA approval awaits the results of preclinical safety and efficacy studies.

For patients who have end-stage retinal disease, an electronic retina implant offers limited restoration of visual perception. Produced by Second Sight Medical Products Inc (Sylmar, CA), the 60-electrode Argus II retinal prosthesis was shown to improve the ability of more than half of the 28 subjects in one study to identify the direction of motion of an object on a screen[12]. The device consists of a camera worn attached to a pair of glasses, along with an electrode array placed epiretinally that transmits wireless signals from the camera to the retinal neural circuitry, as well as an electronics case on the sclera that connects with a ribbon to the electrode array.

LEBER'S CONGENITAL AMAUROSIS

LCA accounts for 5% of all retinal degeneration world-wide. LCA is the counterpart of adult-onset retinitis pigmentosa and represents a number of genetically distinct disorders manifesting with blindness during infancy. The entity was first described by Leber in 1869 as a retinitis pigmentosa associated with congenital blindness, nystagmus, poor pupillary reactivity, and autosomal inheritance. Following the development of the ERG, an extinguished or near absent ERG with relatively normal fundus findings was added to its characterization.

GENETICS

The most commonly encountered mode of inheritance is the autosomal recessive pattern. Like other inherited retinopathies, the genetic basis is heterogeneous and overlaps with a variety of other retinal dystrophies. Fourteen genes and over 400 mutations have been identified, approximating 70% of causative mutations for LCA. The most common mutations include CEP290 (15%), GUCY2D (12%), CRB1 (10%) and RPE65 (6%). An estimated 30% of mutations causing LCA have yet to be identified[13].

DIAGNOSTIC TESTING

The key to diagnosis of LCA is the absence of scotopic and photopic signals in the ERG of an infant with relatively subtle fundus changes.

GENE THERAPY FOR LEBER'S CONGENITAL AMAUROSIS

Voretigene neparvovec (Luxturna) is a novel gene therapy for the treatment of Leber's congenital amaurosis[13,14,15]. Married researchers Jean Bennett and Albert Maguire, among others, worked for decades on studies of congenital blindness, culminating in approval of a novel therapy, Luxturna. It was developed by Spark Therapeutics and Children's Hospital of Philadelphia. It is the first in vivo gene therapy approved by the FDA. Voretigene neparvovec is an AAV2 vector containing human RPE65 cDNA with a modified Kozak sequence. The virus is grown in HEK 293 cells and purified for administration.

The first post-approval administration of Luxturna was performed on March 20, 2018 at Massachusetts Eye & Ear in Boston, Massachusetts. The patient was Jack Hogan of Fair Haven, New Jersey, and the surgeon was Jason Comander M.D., Ph.D. This marked the first time an FDA-approved gene therapy was used for an inherited disease and the first FDA-approved in vivo gene therapy.

The full effect of this treatment on quality of life and patient-reported outcome measures needs to be assessed for quality-adjusted life-year calculations. This assessment will then enable health-care economists to decide how cost-effective the therapy is, which will be crucial for its widespread implementation.

STARGARDT'S DISEASE

Stargardt's disease (STGD) was first described in 1909 by Karl Stargardt is by far the most common form of juvenile macular degeneration[16]. STGD is characterized by discrete yellowish irregular deposits within the posterior pole due to mutation in ABCA4 gene. One variant of STGD, fundus flavimaculatus (FF)[17], describes patients with yellow–white pisciform flecks throughout the fundus, who typically retain good visual acuity until later in life. STGD and FF appear to represent a spectrum of disease presentation. Stargardt disease has an onset in first or second decade, with macular atrophy predominating and few flecks .Fundus flavimaculatus presents in third and fourth decades, with prominent subretinal flecks throughout the retina and less macular atrophy. In advanced stages, the clinical picture of the two entities overlaps. Common clinical findings are:

- Decreased visual acuity.
- Yellow-white subretinal flecks that are round, linear, or pisciform (fish-like) and fluctuate in number over time (Figure 3).
- Flecks reabsorb over time and are replaced by atrophy.
- Subtle retinal pigment epithelium (RPE) changes with loss of foveal reflex in early stages of disease.
- Beaten bronze appearance to macula
- Macular atrophy in advanced chronic disease.
- Peripheral degenerative changes.
- Vascular attenuation.
- Optic disc pallor.

Diagnostic findings

- Hypofluorescence of the choroid (known as a dark choroid) visualized on fluorescein angiography in about 85% of eyes, due to accumulation of lipofuscin- like material in RPE.
- Lack of a dark choroid does not rule out Stargardt disease.
- Yellow flecks block fluorescence from lipofuscin accumulation and are hypofluorescent.
- Areas of atrophy transmit fluorescence and are hyperfluorescent.
- Fundus autofluorescence (Figure4) shows hyper - autofluorescent flecks with around the hypo-autofluorescent central macula
- In advanced atrophy with destruction of the choriocapillaris, window defect is absent with visualization of the choroidal circulation.
- Photopic and scotopic responses on electroretinogram are normal early in the disease process but deteriorate depending on the extent of retinal damage.
- Delayed dark adaptation.
- Electro-oculogram results (Arden ratio) may show mild abnormalities with advanced disease.
- Visual fields show central scotoma correlating to macular atrophy. Peripheral fields normal unless peripheral atrophy present.

At least 80% of Stargardt patients have a "silent choroid," which is a dark choroid on fluorescein angiogram. A2E (N-retinyl-N-retinylidene ethanolamine -a by-product of the visual cycle) accumulation in the RPE causes this phenomenon[18]. Stargardt patients' functional phenotypes may not be predictable from fundus exam, but ERG can help prognose peripheral vision of patients by dividing them into 3 groups[19]. Type 1 patients (have a normal full-field ERG; type 2 patients have more loss of photopic function; type 3 patients have both abnormal scotopic and photopic ERG with the worse prognosis. It is important to subtype Stargardt patients for better counseling regarding their prognoses. Fundus flavimaculatus frequently manifests as type 1 Stargardt disease. Macular autofluorescence is usually abnormally high in Stargardt patients, but normal levels of lipofuscin could also indicate late disease where the RPE cells have burnt out[20].

One commercially available method is a genotyping microarray (gene chip) for the ABCA4 gene. Allelic heterogeneity in the ABCA4 gene has been associated with 5 distinct phenotypes, including Stargardt disease/fundus flavimaculatus, cone-rod dystrophy, and AMD. This gene chip screens for more than 400 different ABCA4 variants with >98% efficacy of finding them.

TREATMENT OF STARGARDT'S DISEASE

Corrective glasses and low vision aids are the main modalities of treatment. However, Stargardt's patients should avoid a diet high in vitamin A because the defective gene (ABCA4) encodes for a transmembrane transporter of A2E intermediates, a toxic by-product of vitamin A. Emixustat (Acucela) is an inhibitor of the RPE-specific protein RPE65, which converts all-trans-retinyl to 11-cis-retinol visual pigment. As this reaction is rate-limiting in the visual cycle, targeting RPE65 may provide a way to control the visual cycle such that toxic by-product accumulation is reduced. In vitro and in vivo studies showed that emixustat inhibits RPE65 in a dose-dependent, reversible manner and reduces the accumulation of A2E in the RPE. Due to the exclusive expression oǫ RPE65 by RPE cells, Emixustat is highly selective[21]. In clinical trials, Emixustat suppressed rod photoreceptor sensitivity, consistent with the proposed mechanism of action[22]. However, results ǫrom the phase 2b/3 SEATTLE study did not show any significant difference in lesion growth rate or visual acuity changes between treatment groups.

FUTURE TREATMENTS FOR RETINAL DEGENERATIONS

With respect to the future for retinal degenerations, some imminent new therapies hold promise for different retinal degenerations. Light deprivation and pharmacologic interruption of the vitamin A cycle are possible treatments for Stargardt disease. Gene therapy is being considered for children with early stages of severe forms of retinitis pigmentosa, and Usher syndrome type IB, Stargardt disease. Studies in animal models and a phase I study in humans support the proposal that neuroprotective agents such as ciliary neurotrophic factor (CNTF) may stabilize retinitis pigmentosa[23]. Gene replacement for recessive mutations and RNAi-based therapy, sometimes referred to as "gene silencing", for dominant mutations are of current interest. Nutritional interventions should continue to be explored. Neurotrophic factors, small molecule therapies such as aminoglycosides, and stem cell therapy have precedent of success in treating animal models or human disease. Light deprivation and inhibitors of apoptosis also deserve further study in animal models with known gene abnormalities. Channel blockers such as D-cis-diltiazem have so far not been shown to be beneficial. Retina and/or retinal pigment epithelial cell transplantation are also of theoretical interest and therefore deserve research. Nanoparticle technology has been recently described as a non-viral approach for gene transfer to ocular tissues. Extending some of these studies to humans presents considerable challenges as any treatment modality proposed must not only be effective but must also be

safe. In the case of gene therapy, it may be difficult to introduce genes under the retina in retinitis pigmentosa because of adhesions of the retina to the pigment epithelium in more advanced stages of this condition; moreover this approach may not prove effective in patients who no longer have rod or cone photoreceptor cells to accept gene transfection.

Risk factor analyses combined with molecular genetic findings may reveal additional factors that could slow the course of these conditions with possible implications for therapy. Clearly much work remains to be done and the opportunities for rational investigations are enormous. Management of complications that arise in these retinal degenerations such as cataracts, leaking vessels, and macular edema and to provide genetic counseling and low vision aids are the main stay treatment . Looking to the horizon, we need to enrol patients in genetic registries so that they can contact patients when a specific genetic cure becomes available.

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