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Update on Retinitis Pigmentosa

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Retinitis pigmentosa (RP) is a group of hereditary diseases in which progressive photoreceptor degeneration results in increasing visual dysfunction. Worldwide, the prevalence is approximately 1 in 4000. Inheritance patterns include: autosomal dominant (30%-40%), autosomal recessive (50%-60%), and X-linked (5%-15%). Patients may also present as isolated cases without known affected family members. Over 100 forms of RP with different genotypes and phenotypes have been identified; the disease course varies among the different subtypes, as well as among different members of the same family.[1] This issue of *Ophthalmology Rounds* reviews the clinical signs, etiology, diagnosis, current treatment options, and new research in the management of RP.

Clinical features

The onset and course of RP is highly variable. Visual compromise may be evident early in infancy or may not become apparent until adulthood. Involvement is usually bilateral with similar severity in each eye. In highly asymmetric cases, postinfectious or post-traumatic etiology should be considered.

In typical RP, clinical findings include impaired dark adaptation, progressive loss of peripheral vision beginning in the mid periphery, and, later, loss of central vision. Patients may report symptoms of nyctalopia, reduced peripheral and central acuity, poor colour vision, and photoaversion. Physiologically, the rods are usually the first photoreceptors to be affected, although, less frequently, the cones will become affected first.[2]

The onset of symptoms is not necessarily an accurate guide to the onset of the disease process, since many factors may confound and mask recognition of visual difficulties. Patients may have only 50° of visual field and 10% of cones left in the fovea, yet may still be unaware of any difficulties with daily activities. Visual acuity (VA) may be preserved even in advanced cases, if there is central retina function.[3,4] X-linked RP appears to be the most progressive form and is associated with a severe visual handicap early in life. Some X-linked RP female carriers also develop severe impairments of VA. Typical examination findings in RP include mid-peripheral "bone-spicule" intraneural retinal pigmentation, retinal pigment epithelial (RPE) thinning and atrophy in the mid and far peripheral retina, "waxy pallor" of the optic nerve head due to gliosis, and attenuation of the retinal arterioles (Figure 1). Later manifestations include posterior cortical and subcapsular cataract, and cystoid macular edema (CME).[1]

Syndromic RP

RP typically occurs in isolation; however, it presents as part of a syndrome in 20%-30% of cases and diagnosing associated systemic conditions may have major medical implications. The most common syndromic form is Usher syndrome, in which RP is associated with hearing impairment. Other important syndromic forms of RP include Bardet-Biedl syndrome (which may have associated obesity, cognitive impairment, polydactyly, hypogenitalism, and renal disease),[5] Kearns-Sayre syndrome (with cardiac abnormalities that may result in life-threatening arrhythmias), and neuronal ceroid lipofuscinosis (involving neurological problems, such as seizures and mental deterioration).

Genetic markers

Since the first gene responsible for dominant RP was identified in 1990, knowledge in this field has accumulated rapidly. Now >100 genes for retinal degeneration have been identified,

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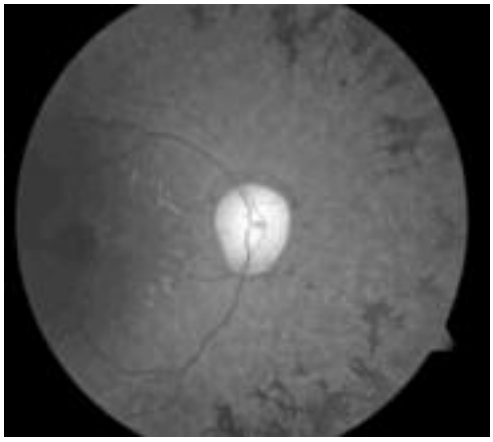
Figure 1: Fundus picture of right eye of a retinitis pigmentosis (RP) patient showing typical waxy pallor of disc, arteriolar narrowing and bone-spicule pigmentation.



with >45 genes attributed to RP. These account for approximately 60% of the genes responsible for RP, but the remaining 40% are unknown. Three genes are collectively responsible for approximately 30% of all cases. The rhodopsin gene (RHO) was the first major RP gene identified and RHO is responsible for about 25% of dominant RP. The Usher 2A gene (USH2A) causes ~20% of recessive disease, and the RP guanosine triphosphatase (GTPase) regulator gene (RPGR) accounts for roughly 70% of X-linked RP. Most of the other identified genes cause only a small proportion of cases. The Retinal Information Network (RetNet) and the Online Mendelian Inheritance in Man (OMIM) are excellent sources for updated lists of genes.[1]

The majority of RP genes affect components of the phototransduction cascade within the rod photoreceptor. In RHO alone, approximately 70 different mutations have been found that alter the function of its protein in different ways. Another set of genes code for structural proteins in rod cells and include retinal degeneration slow (RDS)/peripherin and rod outer segment protein 1 (ROM1). Developmental genes are also implicated (eg, the cone-rod homeobox gene, CRX) in the development of cone-rod degeneration.

The molecular mechanisms whereby these mutations cause rod-cell death are unclear, but the final common pathway appears to be apoptosis. Although multiple pathways have been implicated, the resulting calcium level reduction has been proposed as a trigger for apoptosis. Why cones then die is still unclear, but one hypothesis suggests that rod-cell death causes high oxygen levels and, subsequently, oxidative damage to cones. This represents a potential target for therapeutic research because, if cones could be salvaged, then useful vision might be preserved.[6-8]

Subjective investigations

Colour vision: Colour-vision testing provides useful information about cone function. The Farnsworth D-15 panel is a sensitive index that can detect early foveal-cone involvement. The commonly used Ishihara plates are less helpful in RP because they detect congenital red-green defects rather than the blue cone deficiency (acquired tritanopia) that can develop in patients with RP.

Contrast sensitivity: A decline in contrast sensitivity is also seen in RP patients and may be measured with a contrast chart (Pelli-Robson chart).

Visual fields: Patients with RP typically demonstrate abnormal visual fields, with mid-peripheral scotomas that enlarge with progressive photoreceptor loss. In advanced disease, patients are left with a small central island of vision and isolated small islands of visual field in the far periphery. Goldmann perimetry is the field test of choice in RP, since it tends to produce the most reliable and reproducible results. Central fields may be followed with Humphrey 24-2 or 10-2 programs, but results are not as precise in determining the degrees of remaining central visual field.[1]

Objective investigations

Electrophysiology: Electrophysiological testing is the key objective measure of retinal function. It is also useful for accurate diagnosis and subtyping, assessment of severity, monitoring the rate of progression and the effects of treatment, and detecting carrier status. The full field electroretinogram (ffERG) reflects the total retinal response. The relative degree to which the scotopic and photopic ERGs are affected helps differentiate rod-cone from cone-rod disease. This is a useful prognostic indicator. Rod-cone disease tends to be more severe, with more marked eventual visual loss, whereas cone-rod disease affects central vision early and peripheral vision late and tends to have a better visual prognosis.

In patients with RP, the ERG shows reduced amplitudes of a and b waves, and a delay in peak implicit times (time interval between stimulus flash onset and peak response). The ERG is sensitive to mild photoreceptor impairment; rod b-wave amplitudes are reduced even in the earliest stages of disease. Prolonged implicit time is useful in distinguishing these patients from those with self-limited or stationary diseases, who have normal implicit times.[9]

In advanced cases, ffERG may lack adequate sensitivity to detect the minimal response from a residual functioning central retina. Multifocal ERG (mfERG) and multifocal visual evoked potential (mfVEP) allow localized retinal stimulation, and localized measurement and mapping of the retinal response. mfVEP measures the cortical responses from the stimulation of localized parts of the retina and allows retinal function to be distinguished from visual pathway dysfunction. Both appear useful in evaluating and monitoring residual central retinal function and residual central visual fields.[10,11] X-linked RP-carrier status can be detected in approximately 80% of examined carriers with ffERG and clinical eye examination. Female carriers often have a delayed cone b-wave implicit time in response to a 30-Hz flicker. mfERGs are also useful in X-linked carriers, who often have patchy areas of retinal dysfunction, and function in these small, localized areas of the retina can be evaluated by mfERG. In children suspected to have RP, or other associated systemic conditions, electrophysiology

allows earlier diagnosis and identification of visual problems, which may suggest the need for systemic evaluation.[10]

Optical coherence tomography (OCT): OCT has become an important tool for evaluating *in vivo* retinal architecture in a number of different retinal diseases. In RP, photoreceptor loss produces a thinning of the retina that can be demonstrated using standard resolution OCT. More recently, ultra-high-resolution OCT has allowed the visualization and measurement of the RPE and photoreceptor layer in greater detail; as well, foveal photoreceptor thickness correlates with VA. OCT is also helpful in the management and monitoring of patients with CME, and is more sensitive than fluorescein angiography in assessing change.[12]

Genetic testing: Most cases of RP can be diagnosed based on clinical evaluation, but many of the phenotypes are very similar. Genetic testing can confirm the diagnosis at the molecular level and provide a visual prognosis, identify carriers, and support prenatal diagnosis. Currently, comprehensive genetic testing is expensive, time consuming, and labour intensive. Furthermore, genetic testing on a clinical basis is available for only a small number of inherited eye diseases and, worldwide, is only accessible through a few laboratories. Rather than screen for all possible mutations, one approach is to start with the most commonly mutated RP genes: RHO, RPGR, and USH2A. Recently, microarray or "disease chips" with known mutations have become available to identify known mutations in patients with autosomal dominant, autosomal recessive, and X-linked RP, as well as Stargardt macular dystrophy, cone-rod dystrophy, and Leber congenital amaurosis. Screening by these chips is faster (~4 hours per patient), more affordable (approximately $150-200 US), and can be updated as "chips" with new genes and mutations become available.[13]

Management of RP

Currently there is no cure for RP. Management includes monitoring for progression, managing associated pathologies (eg, cataract and CME), and providing low-vision support. However, 3 syndromic forms are particularly important because, potentially, they can be treated with specific dietary modifications and nutritional supplements. Abetalipoproteinemia (Bassen-Kornzweig syndrome) requires high oral doses of vitamin A. Phytanic acid oxidase deficiency (Refsum disease) requires the restriction of phytanic acid intake. Familial isolated vitamin E deficiency (alpha-tocopherol transport protein deficiency) requires treatment with vitamin E.[14]

Cataracts typically develop at an earlier age in patients with RP, compared with the general population. They present as posterior cortical and subcapsular opacities, and can be disproportionately disabling in advanced RP when only a small central island of visual field remains. Aside from the general risks of cataract surgery, additional factors must be considered in these patients, including: increased risk for phototoxic retinal damage during surgery, a 10%-15% higher risk of postoperative macular edema, and the risk of more aggressive posterior capsular opacification and anterior capsular contraction. In a retrospective study of 89 RP patients with central visual fields of <10° undergoing cataract surgery, VA improved in approximately 75%, and 96% of patients reported a functional improvement in visual symptoms, including glare reduction.[15]

CME is another recognised complication of RP leading to reduced VA. This is thought to be due to either RPE dysfunction, or slow retinal vascular leakage. The most effective therapy has been oral carbonic anhydrase inhibitors (eg, acetazolamide). However, this medication is often limited by significant systemic side effects and some eyes appear refractory to treatment. Studies using the topical carbonic anhydrase inhibitor, dorzolamide, 3 times/day, demonstrated efficacy in significantly reducing CME in most patients. Nevertheless, a rebound phenomenon or a worsening with continued treatment was observed in ~30% of patients.[16] Other proposed therapies have included laser photo-coagulation, systemic corticosteroids, pars plana vitrectomy and posterior hyaloid dissection, removal of the posterior internal limiting membrane (ILM), and gas tamponade. Recently, studies have examined the use of intravitreal steroids and intravitreal anti-vascular endothelial growth factors (anti-VEGFs). Results have been variable; similar to carbonic anhydrase inhibitors, anatomic improvement does not necessarily correlate with an improvement in VA and the effect may be temporary.[17-19]

Low-vision assessment plays an integral role in the management of patients with RP. Low-vision aids can optimize remaining vision and improve quality of life. Telescopes, hand and stand magnifiers, electronic devices, and illumination control have been beneficial. In RP patients with <10° degrees of visual field, spectacle-mounted base-in prisms can provide visual-field expansion and noticeable spatial orientation benefits.[20] Patients with significant night blindness experience impaired orientation and mobility under reduced lighting conditions. Studies have indicated that these patients may benefit from night-vision goggles (NVG). NVG are head-mounted devices with a built-in camera that records images of the surrounding environment. Images are light enhanced and presented in real-time on 2 black-and-white displays located in front of the eyes. Most patients using NVG report an improvement in mobility and orientation, as well as an increase in independence, both after a short period of use (5 weeks) and when questioned again after 2 years.[21]

Ongoing research

Ongoing research is directed towards slowing disease progression and restoring sight. Strategies include vitamin and antioxidant supplementation, gene therapy, and the use of retinal prostheses.

Vitamin and antioxidant supplementation: Vitamin A is essential for the formation of light-sensitive rhodopsin in the photoreceptor outer segment. Routine use of vitamin A in RP patients remains controversial. Patients do not notice any short-term benefit in vision, but consumption of high-dose vitamin A palmitate may add additional years of vision over a lifetime. A

randomized clinical trial of 601 RP patients compared daily high-dose vitamin A, daily high-dose vitamin E, a combination of the two, or trace amounts of the two, for 4-6 years.[22] The study found that the group taking high-dose vitamin A palmitate (15,000 IU) revealed a significantly slower decline in vision loss than the other groups. A significant negative effect from vitamin E alone was also found. Vitamin A palmitate is not recommended for pregnant women or those planning to conceive due to an associated higher risk of birth defects. Children under age 18 and patients with less common forms of RP were not included in the study, therefore, study findings cannot be applied to them. Patients taking high-dose vitamin A require regular testing for serum liver enzymes and vitamin A levels. Older patients also require monitoring for osteoporosis risk, due to a slight increased risk of hip fractures in post-menopausal women and men >49 years old.

Docosahexaenoic acid (DHA) is an omega-3 fatty acid; it is a major lipid component of membranes containing rhodopsin and cone opsins in photoreceptor cells. Lower concentration levels of DHA are found in patients with RP. Two independent studies examining oral DHA supplements demonstrated no clear benefits, even though patients with the highest levels of DHA had the slowest rates of retinal degeneration.[23,24]

Antioxidants have also been proposed as potential treatments for RP. This is based on the hypothesis noted previously that rods are a major source of oxygen utilization in the retina and after widespread rod loss, the oxygen levels in the outer retina are increased, possibly causing oxidative damage to cones. Studies in mouse models of RP indicate that after rod-cell death, gradual cone-cell death due to oxidative damage does occur; as a result, antioxidant therapy may be of benefit in slowing degeneration. Various antioxidants have been studied including lutein, zeaxanthin, alpha-lipoic acid, reduced L-glutathione, alpha-tocopherol, ascorbic acid, and manganese (Mn) (III) tetrakis porphyrin (MnTBAP). Further work is still required to determine whether antioxidants are effective and, if so, what doses, combinations, and delivery systems would be beneficial in humans.[25,26]

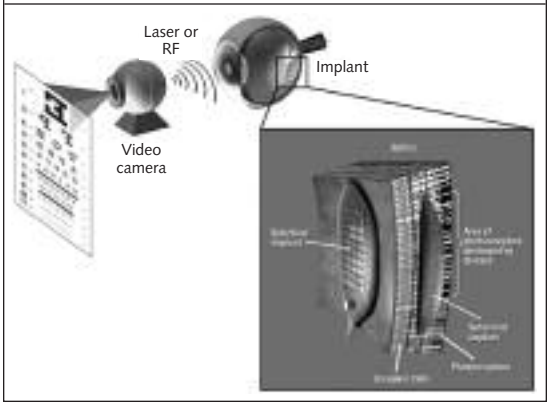
Gene therapy: A gene therapy approach depends on the type of mutation. Recessively inherited diseases usually arise from gene mutations that eliminate the encoded protein and may be amenable to gene-replacement therapy. One of these genes is RPE65, which encodes an isomerase in the RPE critical for the production of 11-cis-retinal. Without this enzyme, photoreceptors seem to survive a long time after severe visual loss and can become functional again if provided with 11-cis-retinal or a related photopigment. Studies of subretinal injection of adeno-associated virus vectors containing the RPE65 gene have demonstrated some success in mice and dogs, and other gene replacements have been successful in a variety of animal models of genetically identified forms.

Dominantly inherited mutations tend to alter the transcribed amino acid sequence and result in abnormal variants of the encoded protein. One therapeutic approach is gene-inactivation therapy. Current experiments include ribozyme-based or interference ribonucleic acid (RNA)-based gene therapy to inactivate or reduce expression of specific dominant alleles.[27,28]

Neuroprotective treatments: Neuroprotective treatments that affect secondary biochemical pathways have been explored using neurotrophic factors as potential therapeutic agents. One of these, ciliary neurotrophic factor (CNTF), has demonstrated effectiveness in slowing retinal degeneration in at least 13 animal models. As a result, a human phase I trial in patients with severe RP was conducted.[29] The study surgically implanted, intravitreally, a slow-release biological device consisting of encapsulated cells transfected with the human CNTF gene. Three of 7 patients had a 2- to 3-line improvement on standard Snellen acuity charts over 6 months. Although this trial was not powered to allow any conclusions about clinical efficacy, it raised 2 points of interest. First, CNTF not only slows retinal degeneration, but could possibly improve VA by stimulating enough metabolic activity in damaged cone photoreceptors to allow them to resume action and contribute to visual function. Second, encapsulated cell implants represent a safe, effective, sustained delivery system. An advantage to this delivery system over conventional methods of administration is the ability to freshly synthesize and release protein *in situ*; the protein is more potent than purified recombinant factors and, therefore, reduces dose requirements. In addition, adequate concentrations can be achieved at the appropriate target site and, with the barrier properties of the brain and eye, the potential for systemic toxicity is minimized. Finally, the implants can also be retrieved, adding to their safety.[30] Other groups have designed implantable devices based on retinal stimulation with the neurotransmitter, glutamate. The reuptake of glutamate must be well regulated because of its excitotoxic effect in excess.[31,32]

Retinal transplants: Various groups have been studying retinal transplantation with photoreceptors, RPE, and stem cells for nearly 2 decades. A significant advancement in retinal transplant research was the development of the rhodopsin transgenic pig model for RP, which involved the rhodopsin mutation, Pro347Leu, first described in 1997.[33] Transplants with neonatal and, recently, fetal neuroretina donor tissue have been found to survive and maintain morphologically normal photoreceptors for up to 6 months when placed in the subretinal space with correct polarity.[34] Transplantation of RPE in one patient resulted in a slight increase in VA and a phase II study is ongoing.

Figure 2: Schematic diagram showing an epiretinal implant and a subretinal implant.[31]



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Although it has been demonstrated that stem cells can differentiate into cells that express retina-specific markers, previous attempts at transplanting brain- and retina-derived stem cells into an adult retina have been unsuccessful. Last year, MacLaren et al[35] reported on the use of a mouse model. If donor cells are taken from the developing retina at a time coincident with the peak of rod genesis, ie, immature postmitotic rod precursors, then these transplanted cells were able to integrate, differentiate into rods, form functional synaptic connections, and improve visual function. This suggests that rod photoreceptor transplantation might be successful, if the optimal ontogenetic stage of donor cells is used.[34]

Retinal prostheses: RP causes blindness through progressive degeneration of the outer retina. Postmortem analyses of patients with RP have revealed that, while up to 95% of the photoreceptor layer in the outer retina may be lost, 80% of the inner nuclear layer and 30% of the ganglion cell layer may be spared.[31,36] In the last decade, a major field of research has been the development of prosthetic devices that electrically stimulate the retina, optic nerve, or visual cortex. Electrical stimulation to the retinal nerve fibre layer and outer retina has produced phosphenes in humans and VEPs in animal models of retinal degeneration. Based on these observations, several groups have developed prostheses that bypass the photoreceptors and stimulate the remaining intact neurons to restore vision. The two approaches under development are subretinal implants and epiretinal implants (Figure 2).[36,37]

Subretinal implants: Subretinal implants are placed between the pigment epithelial layer and the outer retinal layer, either via an intraocular approach through an incision in the retina (*ab interno*) or an incision through the sclera, choriocapillaris, and RPE (*ab externo*). This implant consists of multiple small photodiodes or electrodes that act as artificial photoreceptors absorbing light and converting it to a graded electrical response, which then stimulates adjacent nerve cells (eg, bipolar or horizontal cells).[31,38-40]

In a phase II study, Chow et al[37] implanted passive subretinal prostheses into patients with RP. They reported on safety and visual function of 6 eyes in 6 patients with their implanted ASR (artificial silicon retina) microchip over a 6-18 month follow-up period. The ASR was a 2-mm diameter, 25-µm thick, semiconductor, microphotodiode, array chip consisting of approximately 5,000 microelectrode-tipped microphotodiodes, powered by incident light. The microchips were well tolerated with no safety issues and subjective visual improvement was reported in all patients, including perception of brightness, contrast, colour, movement, shape, resolution, and visual-field size. Interestingly, some subjects also reported increased visual fields distant from the implant site within 1 week to 2 months after implantation, suggesting that the implant alone or coupled with the low-level electrical stimulation, induced an indirect, generalized, neurotrophic effect, which improved retina health and visual function.

Epiretinal implants: Epiretinal implants are typically more complex because they generally require external imaging devices and power sources. The external unit converts ambient light or images to an electrical signal that is transmitted to a microchip receiver inside the eye. The receiver distributes the signal to a microcontact electrode array implanted on the inner retinal surface that releases electrical impulses stimulating retinal ganglion cells. Each electrode maps to a specific location in the visual field.[31,38-40]

The first functional, permanent, epiretinal prosthesis was implanted by Humayun et al[41] and reported in 2003. In the first 10 weeks after implantation, the completely blind subject was able to see phosphenes after stimulation of an electrode array (4×4 pixels) interfaced with the retina and, therefore, was able to detect the presence or absence of ambient light or motion and recognize simple shapes.

Additional patients have had these devices implanted. In a study in the United States (US), 3 blind test patients with severe RP (1 with no perception of light, 2 with perception of light only) were permanently implanted with prototype epiretinal stimulators for between 7 and 18 months. The prototype was implanted in the eye with the least light sensitivity. The prosthesis has an intraocular stimulating array that consists of 16 platinum electrodes arranged 4×4, which is tacked to the epiretinal surface and connected by a 16-wire cable to a camera system or computer interface within an electronic case surgically implanted into the temporal bone. These subjects performed better than chance in 83% of the tests conducted in a controlled environment. These tests involved locating and counting objects, differentiating

3 objects, determining the orientation of a capital letter L, and differentiating 4 directions of a moving object.[42]

Research concerning prostheses still faces major challenges that have yet to be resolved. Prostheses must be tolerated in the eye for decades without inciting rejection, infection, inflammation, neovascularisation, retinal detachment, migration, or erosion.[38] With an increased number of electrodes, it is hoped that future implants will allow more resolution and increasingly complex stimulation patterns. Prostheses with 32, 60, and 100 electrodes have already been developed. There is now US Food and Drug Administration (FDA) approval to conduct a clinical study on a second-generation implant with 60 electrodes. The current goal is to implant a high-resolution retinal prosthesis with 1,000 electrodes in a 5×5 mm package and with the potential to provide visual function at a level of face recognition and reading.[31]

Visual scientists are directing their research through both technological and genetic vectors for the treatment of RP. Both disciplines provide extremely promising and exciting approaches in their quest to slow progression and restore vision loss in this devastating disease.

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