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Review and update: Current treatment trends for patients with retinitis pigmentosa

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Abstract

BACKGROUND: Retinitis pigmentosa (RP) is a heterogeneous group of inherited retinal disorders characterized by progressive photoreceptor apoptosis. It is the leading cause of inherited retinal degeneration–associated blindness. RP has a unique set of clinical characteristics that make it a complex disease associated with distinct inheritance patterns. An understanding of the pathogenesis is essential in the process of the differential diagnosis and the development of treatment options. Recent developments in research are likely to expand the various therapeutic modalities to include gene therapy, pharmacologic treatment, cell transplantation, and neuro-prosthetic devices.

METHODS: A literature search was performed to comprehensively review RP diagnosis, pathophysiology, and treatment.

CONCLUSION: Advances in the understanding of the pathophysiology of RP are creating new opportunities for the treatment of this often visually debilitating eye condition. Optometrists, as primary eye care practitioners, should be aware of the inheritance, pathophysiology, and current treatment options for RP as well as treatments in development so that they can best care for their patients with inherited retinal disorders.

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The family of diseases known as retinitis pigmentosa (RP) is the most common inherited retinal degeneration worldwide.[1-7] The word "retinitis" is a misnomer because retinal inflammation does not play a prominent role in the disease's pathophysiology.[2] RP is defined as a heterogeneous group of inherited retinal disorders characterized by progressive degeneration of the photoreceptors with subsequent degeneration of the retinal pigment epithelium (RPE).[1-10] Although the typical manifestations present between adolescence and early adulthood, the age of onset has been documented to range from infancy to adulthood.[1-6] The earliest visual symptoms typically manifest as night blindness with peripheral visual field loss. Although the rate of progression varies, the nature of the disease carries with it a high probability that devastating visual loss will ensue.[1,10]

Overview

RP is the most common of the retinal degenerations with a prevalence approximately 1 in 3,000 to 1 in 5,000 individuals,[2-6] affecting approximately 1.5 million people worldwide.[7,8] RP funduscopic findings were initially described by Donders in the 1800s.[9] Although clinical presentation

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may vary, diagnostic criteria for the disease have been established.[11] These are described as bilateral, progressive degeneration of the photoreceptors leading to nyctalopia and visual field defects.[12] Today the term RP includes a wide spectrum of disorders with diverse chromosomal, metabolic and morphologic findings, many being genetically predetermined and all associated with a progressive degeneration of the photoreceptors.[1,2,13]

Nomenclature, classification, and categorization

Historically, RP groupings have been broadly classified. For example, RP has been classified according to distribution of retinal involvement, using *central*, *pericentral*, *sector*, or *peripheral* to describe the subtypes.[1,2] It has also been categorized based on age of onset (Leber's congenital amaurosis, juvenile, and late onset). Among the most common classifications are modes of inheritance and predominant photoreceptors involved.[1,3] However, because a uniformly accepted classification system has yet to be established, many have chosen to divide RP into 2 main groups, *primary* and *syndromic*, with subclassifications involving inheritance patterns thereafter. *Primary cases* include those in which the disease process is confined to the eye alone. *Syndromic cases* include those in which the ocular degeneration is associated with abnormalities in 1 or more organ systems.[13] Syndromic RP may be multifactorial, involving the interaction of genes and the environment. Most syndromic cases are inherited via an autosomal recessive pattern. Early intervention is imperative because progression of some syndromes or even reversal of associated signs and symptoms can be accomplished with simple dietary changes.[14] Among the most common syndromic forms of RP are Usher syndrome, Refsum disease, Bassen-Kornzweig syndrome, Bardet-Biedl syndrome, and Batten disease (*see* Table 1).

Pathophysiology

Genetics

The pathogenesis of RP can be considered a continuum of metabolic disorders that initially cause rod photoreceptor degeneration with accompanying associated retinal pigment epithelium degeneration, eventually leading to complete cell death.[1,7,8] Rod degeneration may also promote secondary cone degeneration.[15] Studies evaluating the function of the bipolar cells have uncovered that the bipolar pathway remains intact after rod cell apoptosis.[16,17] However, John et al.[17] postulate that healthy bipolar cells attempt to reestablish communication with other nerve cells, such as the cones. Regrettably, these new connections relay inappropriate signals, leading to cone degeneration and eventually apoptosis.[17] Interestingly, although affected genes may be expressed in all retinal cells, studies have reported that mutations of these genes typically are associated with only degeneration of the photoreceptor neurons, highlighting the functional diversity of the genes implicated in this retinal degeneration.[18-20] Although it has been speculated that the inner retina is preserved during the course of RP, one study[21] found that bipolar and horizontal cells within the red mouse retina affected with RP undergo dramatic morphologic modifications after photoreceptor loss. This provides an example of how the second-order neuron pathway may be influenced by photoreceptor apoptosis.[21]

Currently, photoreceptor apoptosis is poorly understood and cryptic. Defects in particular genes encode for errant proteins involved in either photoreceptor structure, phototransduction cascades, or the visual cycle, to name a few, leading to photoreceptor cell death.[18] A widely accepted mode of cell death has been studied through the evaluation of gene mutations affecting the rhodopsin gene. Animal models have shown that structural abnormalities associated

Table 1 Most common RP syndromes

Syndrome	Associated characteristics	Additional information
Usher's syndrome	Congenital neurosensory hearing loss (partial or profound)	Most common RP syndrome Type I: profound deafness Type II: moderate/medium deafness Type III: deafness during first decade and progressively worsens
Bassen-Kornzweig (Abetalipoproteinemia)	Malformation of the red blood cells with associated neuromuscular disturbances	Decreases fat-soluble vitamin absorption (A, E, and K); leads to clotting abnormalities and retinal dysfunction
Refsum's disease (Heredopathia atactica polyneuritiformis)	Chronic polyneuritis, progressive paresis, ataxia, anosmia, and deafness	Both infantile and adult types associated with elevated phytanic acid
Bardet-Biedl syndrome (Laurence-Moon syndrome)	Mental retardation, cerebellar atrophy, congenital obesity, hypogenitalism, polydactyly, and renal dysfunction	Characterized by a cone-rod dystrophy with legal blindness usually by age 20
Batten disease (Neuronal Ceroid Lipofuscinosis)	Mental retardation, seizures, peripheral neurological degeneration, and ataxia	Associated with accumulation of lipopigment granules in neurons Unlike typical RP, starts with acular involvement

with the rhodopsin G protein are linked to rod cell dysfunction.[22] Structurally abnormal proteins may not be able to be transported to the rod's outer segment disc membranes. Buildup of these aberrant proteins leads to toxicity. Because this process takes time, the rods function for years before signs or symptoms develop. The knowledge of such events may aid in creating future novel therapeutic interventions.

Degeneration of photoreceptors associated with RP, although stimulated by various processes, is primarily genetically programmed.[1-8] To date, the field of molecular genetics has identified numerous genes responsible for about half of the nonsyndromic forms of RP.[23,24] The inheritance modes of RP include autosomal dominant (adRP), autosomal recessive (arRP), X-linked (XLRP), digenic RP, and mitochondrial RP. The terms *simplex* and *multiplex* are also used to describe pedigrees. *Simplex* refers to an isolated case with an absence of any family history, whereas the term *multiplex* describes 2 or more affected family members (typically siblings) who have no pre-existing family history.[23,24] Because of the variation in both the nature of the penetrance and expressivity genes coding for RP, ocular manifestations vary among the inherited modes and even among members within the same family.[25-30] The mode of inheritance is believed to play an important role in determining the prognosis of the disease. Unfortunately, in many cases, determining the exact genetic mode of inheritance is not possible. More than 40% of RP cases in the United States have no family history of the degeneration.[23]

Autosomal recessive RP (arRP) is the most frequently inherited type of RP, accounting for approximately 20% to 30% of cases[27] with 18 arRP genes identified to date.[27] Autosomal recessive RP affects men and women equally.[29,31] For the recessive trait to be phenotypically apparent, both parents must contribute an abnormal gene. Children born of parents who are each a carrier of the same arRP gene will have a 25% chance of receiving 2 normal genes (therefore, be neither a carrier nor affected), a 25% chance of receiving 2 recessive RP genes "homozygous" (being affected), and a 50% chance of receiving 1 normal gene and 1 RP gene (making the offspring an asymptomatic carrier of the abnormal gene "heterozygous").[29,30] Consanguinity strengthens the likelihood that a recessive trait will be manifested. Parents and offspring of an affected individual typically do not show signs of the disease. Common mutations include the PDE6 gene and the gene encoding for myosin VIIa.[27,31] The PDE6 gene has been linked to 2% to 5% of arRP.[27] Of current interest, the PDE6 gene has similar structure to the PDE5 gene. PDE5's expression is inhibited by sildenafil,[32,33] a commonly used medication for erectile dysfunction. PDE5 and PDE6 have similar structures, and the use of sildenafil has been linked to the decline in electroretinogram (ERG) amplitude measurements among arRP-exposed mice.[33] Because patients are not typically aware of their particular genetic RP subtype, and sildenafil may have the potential to propagate complications, patients with RP should be appropriately counseled and those experiencing problems tested.

Autosomal dominant RP (adRP) is the second most frequently inherited type of RP, accounting for approximately 15% to 20% of cases.[27] Sixteen adRP genes have been identified to date.[27] Among the most prevalent are rhodopsin and peripherin/RDS.[27,34] The rhodopsin gene was the first gene linked to RP. Its mutations are responsible for 20% to 25% of the autosomal dominant cases.[27] More than 100 mutations have been identified in the rhodopsin gene, causing variation within the clinical presentations.[27] Another common cause of adRP is attributed to the peripherin/RDS gene mutation, which accounts for 5% of adRP.[27] An affected individual usually has a parent who is also affected. There is a 50% chance of passing the defective gene to the offspring, with males and females having equal chances of being affected. The disease generally is present in successive generations. In a definitive autosomal dominant pedigree, the disease is present in at least 3 generation pedigrees with male-to-male transmission observed. Most pedigrees show complete penetrance, and yet, adRP can vary greatly from individual to individual even within the same pedigree.[35] Although it is believed that adRP has the slowest progression,[35] controversy exists regarding the authenticity behind this statement.[36]

X-linked RP (XLRP) is the least frequently inherited type of RP, accounting for only 6% to 10% of cases.[27] Six genes to date have been identified.[27] The RPGR and RP2 genes are among the most commonly found in X-linked RP cases, estimated to account for 70% to 90% and 10% to 20% of XLRP, respectively.[27] The phenotypical expression of the gene is related to gender, with the abnormal recessive gene residing on the X chromosome. Because males have 1 X chromosome and 1 Y chromosome, they typically manifest the disease. Females typically do not manifest the trait because, having 2 X chromosomes, the normal gene on 1 X chromosome compensates for the abnormal gene on the other X chromosome. Therefore, the transmission of the abnormal gene to an affected male is passed on from a female carrier. A female carrier has a 50% chance of passing along the abnormal gene, thus all male offspring will have a 50% chance of being affected, and all female offspring will have a 50% chance of being a carrier.[37] There is no male-to-male transmission of the abnormal gene (because male offspring will receive the normal Y chromosome from an affected male). A male with X-linked RP can only pass on the defective gene to his daughters, making all daughters carriers. The affected males tend to have a severe form of RP. Severe visual impairment with visual acuity of less than 20/200 is typically observed by age 30 to 40.[1,2,37]

Less common modes of inheritance include digenic and mitochondrial DNA. Digenic RP occurs when altered genes for RP occur on 2 different chromosomes in the same individual. The interaction of the 2 genes causes RP. Cases have been associated with simultaneous heterozygous mutations in the ROM1 in addition to the heterozygous mutations in the Peripherin/RDS gene.[27] Mitochondria have their own DNA, and it is inherited from the mother. Defects in mitochondrial DNA lead to a variety of

disorders. Yet, because of the complexity of mitochondrial genetics, the presentation is variable. Kearns-Sayre and an Usher-like syndrome are believed to be inherited as mitochondrial genes.[38]

Investigative theories

Aside from genetics, other features responsible for the degeneration of the photoreceptors include free-radical formation, neurochemical changes, and deterioration of retinal oxygenation.[39-43] During the normal process of photoreceptor metabolism, disk membranes are shed with the RPE mediating their disposal. Free radical formation has been linked to chronic disturbances in the disk membrane renewal process within the outer segments of the photoreceptor cells (both the rods and cones),[1,8] resulting in debris accumulation. This causes alteration of the photoreceptors' and RPE's architecture, structure, and function and eventually results in retinal degeneration.[36]

In recent years, there has been accumulating evidence implicating neurochemical changes in the loss of photoreceptors.[40] This evidence suggests that the metabolic pathways involved in neurotransmission may also be abnormal in patients with RP. An additional mechanism associated with RP is the deterioration of retinal oxygenation.[41,42] This is represented by marked attenuation of the retinal blood vessels as well as atrophy of the choriocapillaris.[41,42] It is believed that the retinal vasculature and choroidal capillaries become poorly perfused secondary to low oxygen pressure within the tissues. However, this condition is generally thought to be an effect rather than a cause of the disease. Because poor oxygenation seems to trigger apoptosis in cases of stroke and myocardial infarction, researchers theorize that decreased oxygenation of the retina similarly contributes to photoreceptor cell death.[42,43]

Grouping via the predominant photoreceptor

The predominant photoreceptor subtype is the most common method of categorizing RP. It also can help determine the prognosis of the disease.[1,44] Rod-cone dystrophies have been recognized as having a better overall long-term prognosis and are associated with a slower progression. A rod-cone dystrophy is categorized by the diffuse loss of rod sensitivity followed by a loss of cone sensitivity in the later stages.[45] Patients typically present with a history of night blindness followed by mid-peripheral visual field loss. In the later stages of the disease, cone degeneration becomes more apparent with progression of the disease associated with a loss of central vision acuity and color vision defects.[46]

Cone-rod dystrophy (inverse RP), which is more regional, is associated with a simultaneous loss of cone and rod function.[47] Visual acuity and color vision are both reduced early in the course of the disease. Because of the loss of normal cone function, patients typically complain of photophobia. The cones loose their ability to adapt to brightness and become light sensitive. Patients also present with the complaint of nyctalopia along with central scotoma or partial/complete pericentral ring scotomata.[47,48] Unlike typical RP, the retinal signs typically are seen adjacent to the macular area rather than in the periphery, sometimes mimicking bull's eye maculopathy. The ERG shows a loss of cone function in the early stages of the disease. However, unlike cone dystrophy, cone-rod dystrophy shows a simultaneous reduction of photopic ERG in addition to the scotopic ERG.[45,47] The prognosis is poor because of the early involvement of central vision. Syndromes associated with cone-rod dystrophies include Bardet-Biedl syndrome and Batten disease.[49]

The clinical features of retinitis pigmentosa (rod-cone retinitis pigmentosa)

Because rod function is primarily affected, the most common initial symptoms of rod-cone RP include nyctalopia followed by visual field defects with preservation of central visual acuity until the late stages of the disease.[1-6]

Nyctalopia

Nyctalopia is a hallmark of rod-cone RP, usually observed by the second decade of life.[50,51] Patients may report feeling "lost" while outdoors on dimly lit evenings. More severe clinical RP presentations are associated with earlier onset of nyctalopia. The etiology of nyctalopia is mid-peripheral retinal degeneration, where the rods are more abundant.

Visual field loss

Another hallmark feature of rod-cone RP is the insidious, progressive loss of the visual field, owing to photoreceptor degeneration.[2] Visual field defects are typically present by the teenage years.[1-3] The visual field defects associated with the earliest stages of RP may present as small scotomas, unnoticed by the patient. However, as the disease advances, the field progresses to form a "tunnel" configuration.[52] In general, there is a strong tendency for the visual field loss to be symmetric, with a direct correlation to fundoscopic alterations.[2] For example, altitudinal visual field defects often are observed in association with sectoral RP. Characteristically, multiple relative mid-peripheral scotomas enlarge, deepen, and coalesce to form confluent ring scotomata between 20° and 50° from fixation.[52,53] Peripheral islands of field are lost before the central field is affected. The visual field constriction expands more rapidly outward with a slower progression inward toward the central field.[52]

Although the rate of progression of visual field loss is slow, it is relentless. In one study, it was estimated that the visual field deteriorated on average by 4.6% per year.[36] Often patients do not notice what may be a significant interval loss of peripheral visual field because sizable regions of

nonaffected central seeing areas remain. It is only after the disease enters the advanced stages that patients become aware of the cumulative effect.[54] This sudden discovery of visual field loss often leads patients to the false conclusion that the rate of degeneration is accelerating. (Visual field loss may be so severe that the patient is rendered legally blind and thus disabled according to the definition under Social Security Act.[55])

Central vision loss

Typical rod-cone RP is associated with the preservation of central vision until the later stages of the disease, once cone degeneration begins. Variability exists with regard to how long the central visual acuity will be preserved. Patients with adRP are more likely to retain good acuity beyond 60 years of age, whereas patients with XLRP are usually legally blind (20/200 or worse) by age 40.[56,57] In addition, atypical RP, such as inverse RP, may be associated with an earlier onset of central visual impairment.[47,58] Associated factors, such as cystoid macular edema and cataracts, can also contribute to the earlier onset of decreased central vision.[57]

Photophobia

In addition to nyctalopia, complaints of photophobia are common in patients with cone-rod RP. This seems to be especially true in the later course of the disease. This is caused primarily by hypersensitivity to glare and light scatter, which occurs when an RP patient suddenly experiences a higher level of light than that to which the retina is adapted. As the rods and cones degenerate, RP patients have difficulty adapting to even small changes in light levels, taking more than twice as long to recover from any photopic stress.[24,52]

Photopsia

Many patients with cone-rod RP experience photopsia in their mid-peripheral field of vision, adjacent to areas of scotoma. These phenomena are presumably from aberrant signals sent from degenerating retina photoreceptors.[2] Photopsias are described as tiny blinking or shimmering lights by some and as coarse sparkling grains by others (similar to those reported by patients with ophthalmic migraine). RP-related photopsias are generally stationary within the field and may be continuous rather than episodic. As scotomas become denser over the years, the photopsias decrease.[2]

Color vision defects

Color vision in patients with typical rod-cone RP remains good until the central vision is affected at a level of 20/40 or worse.[59] A tritan defect is the most common color anomaly [2,59] with variability observed in many cases. Color vision defects may be noted early in some syndromic RP cases, such as juvenile Batten disease and Bardet-Biedl[49] syndrome, in which central cones appear to be abnormal earlier on during the progression of the disease.

Fundus findings

When ophthalmoscopically detectable abnormalities are present, there is typically a high degree of symmetry between the 2 eyes.[2] Asymmetric presentations or strictly unilateral presentations have also been reported.[60] (Although, as mentioned previously, established diagnostic criteria[11] require bilateral presentation to be termed RP.) The common ophthalmic triad includes bone spicules, attenuated vessels, and waxy pallor of the optic nerve (*see* Figure 1). These findings are consistent with long-standing retinal and RPE degeneration. Fundus signs will depend on the stage of retinal deterioration.[2,60] All of these signs need not be present to confirm the diagnosis. In fact, in the initial stages, there may be an absence of any visible funduscopic changes with the only diagnostic sign being an abnormal ERG response.[61]

RP sine pigmento is a term used to describe RP with no or minimal RPE pigmentary changes and a reduced ERG.[61] Although RP sine pigmento has been regarded as a distinct entity, it is most likely a representation of an early-stage RP in which the alterations are so subtle that they are clinically unrecognizable.[1] The earliest fundus changes observed in most RP patients include a pigmentary mottling ("moth-eaten" pattern) and dustlike granularity of the RPE (*see* Figure 2) with normal associated vasculature. The retinal/RPE degeneration often presents as a grayish fundus appearance with greater visibility of the underlying choroidal vessels through the more transparent pigment epithelium.[62] The middle stage shows a more patchy loss of the RPE and the beginnings of retinal vessel attenuation.[1] With time, regional or diffuse pigmentary mottling and atrophy of the RPE are observed.[63] The associated pigmentary changes are variable and may include hypopigmentation.

Retinitis punctata albescens (RPA) is characterized by numerous whitish-yellow punctate spots that radiate outward

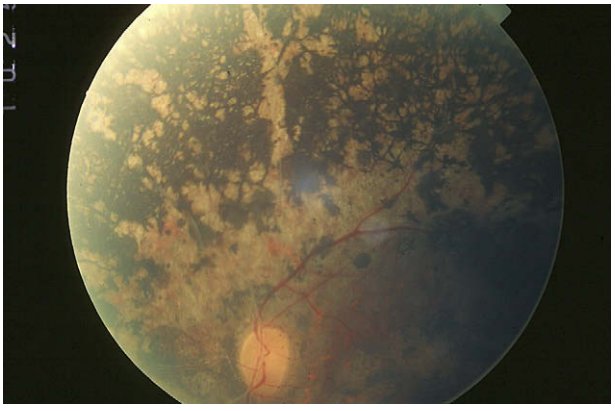

Figure 1 Typical fundus findings of an RP patient: RPE bone spiculing, attenuated vessels, and waxy pallor of the optic nerve.

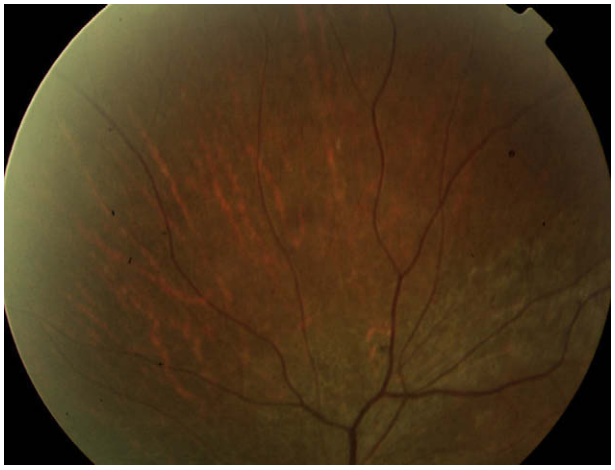

Figure 2 Early pigmentation mottling observed in an RP patient (courtesy of Mark Dunbar, O.D.).

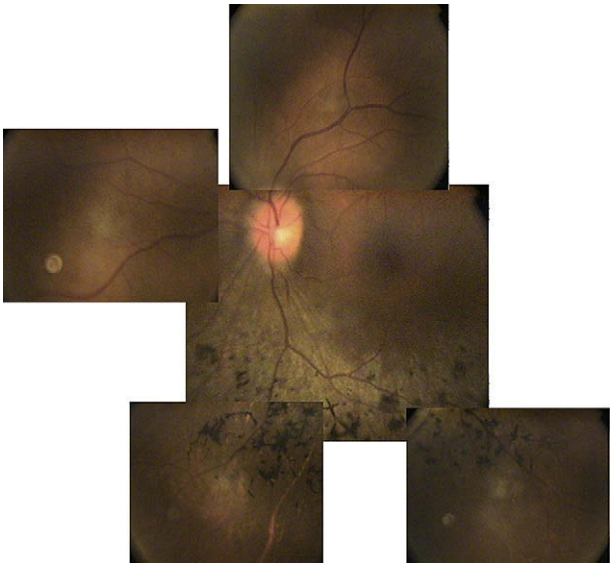

Figure 3 Focal inferior distribution of RPE hyperplasia and retinal degeneration in a sectoral RP.

from the posterior pole. RPA is described as a retinal dystrophy associated with visual field loss and nyctalopia. The course of RPA is relatively slow with preservation of good vision beyond the fifth decade.[1] An advanced case may show some pigmentary clumping in the equatorial retina with associated disc pallor and vessel attenuation. It has been suggested that RPA may be a descriptive term, like *sine pigmento*, rather than a diagnostic entity.[53]

In RP, the classic fundus hyperpigmentation is noted as a result of retinal remodeling. Migration of pigment from disrupted RPE typically begins to form clumps or mottling in the mid-peripheral retina. In the late stage, the hyperpigmented accumulations in the interstitial spaces surround retinal vessels, producing a perivascular pigmentary cuffing (bone-spicule formation). Pigment distribution is variable.

Sector RP is characterized by pigmentary changes limited to 1 or 2 quadrants.[64,65] The fundus changes observed in sectoral RP (*see* Figure 3) typically involve the inferior quadrants, more often the inferior nasal quadrant. Although the rest of the retina appears normal, there are RPE changes throughout the entire tissue, as demonstrated by fluorescein angiography.[66] Progression of sector RP is slow, with visual function preserved until the ages of 50 to 60 years. Some patients actually remain stable throughout life. Because of the focal nature of the RP, patients typically are asymptomatic with a diagnosis suspected after a routine examination.

With increased progression, there is loss of outer retina and RPE. This process leads to decreased retinal oxygen demand, which is believed to contribute to the attenuation of the retinal vessels seen in RP patients.[1] Abnormalities of the optic nerve are also more common in the advanced stages of the disease where associated waxy pallor of the optic nerve becomes apparent. Whereas optic nerve pallor probably results in part from ganglion cell atrophy, it has been shown that the peculiar appearance of the disc is associated with gliosis overlying the disc.[2] Other associated optic neuropathies include open-angle glaucoma[67] and optic nerve head drusen.[68-70] Histologic studies support the concept that drusen occur as a manifestation of aberrant axoplasmic transport.[68-70] Characteristically, they are often located near the edge of the disc and have a tendency to migrate out underneath the sensory retina.

Another associated finding is an abnormality of the vitreous, such as the presence of fine dustlike, pigmented cells released from degeneration of the RPE. These particles are observed before early fundus changes. Other reported vitreous anomalies include posterior vitreous detachment, cotton ball–like opacities, interwoven filaments in the retro-cortical space, spindle-shaped vitreous condensations, and asteroid hyalosis.[71]

Because of continued retinal degeneration, many RP patients have macular compromise caused by widespread RPE changes. Alterations to the blood–retinal barrier lead to leakage and macular edema.[72] Cystoid macular edema (CME) contributes to decreased central vision. CME is observed in as high as 70% of all RP patients.[72,73] Other variable maculopathies observed in RP patients include cellophane maculopathy and focal RPE atrophy.[74] Wrinkling of the macula is caused initially by either a change in the vascular permeability about the region or atrophy of the area's retinal elements. Fluorescein angiography or optical coherence tomography may help confirm a suspected diagnosis.

Anterior segment abnormalities

Cataracts are the most common anterior segment complication of RP with an increased prevalence of posterior subcapsular cataracts.[75] The prevalence of cataract varies among the distinct inherited patterns with 50% observed in adRP, 40% in arRP, and 70% in XLRP.[75,76] Although they are typically observed between 20 and 39 years of age, the severity and incidence increases with age. Although RP patients are at greater risk for keratoconus than the general population, the occurrence of keratoconus is actually rare.[77]

Refractive status

Myopia varies among distinct subtypes of RP, with increased prevalence in XLRP.[78] In addition, XLRP patients typically have a more significant myopic refractive error.[74] High hyperopia has been associated with Leber's congenital amaurosis.[79]

Current management options

A key element to initial management is information gathering. Patients should be asked to provide a history of the age of onset of dark adaptation problems or night blindness, visual field loss, and loss of visual acuity, using as much detail as possible. Symptoms of night blindness often reflect problems under dimly lit conditions, such as night driving. Progressive visual field loss often is correlated to complaints of increased clumsiness. A full review of systems should include history of cardiac dysfunction, deafness, intestinal disease, renal problems, or liver disease. This can be valuable toward evaluation of the likelihood of syndromic RP. A detailed family history provides information with regard to modes of inheritance. Determination of consanguinity in the pedigree is important because it increases the likelihood of an autosomal recessive condition.

The role of electrophysiology in retinitis pigmentosa

Although the diagnosis of RP can be made based on clinical presentation, the ERG can confirm the diagnosis and may be helpful in monitoring the disease process. The ERG is a technique that measures the summation of the electrical activity in the retina as it responds to light stimuli.[80-83] An electrogram is placed either on the eye or on the eyelid skin. Patients are fully dark adapted before testing. A dim blue flash is used to isolate rod function, a brighter single white flash records a combined rod/cone response, and a 30-Hz flicker stimulus isolates cone function. Testing is also done under photopic conditions after light adaptation. An initial A wave shows hyperpolarization of photoreceptors followed by a B wave resulting from depolarization of cells in the inner nuclear layer.

In typical RP, the disease manifests as an initial reduction of response related to rod function; an abnormal ERG finding may be seen even in the absence of fundus findings.[80-83] Patients with early stages of RP have scotopic ERG measurements that show a reduction in amplitude with a prolonged implicit time.[82,83] Scotopic ERG amplitudes show an average loss of 16% to 18% per year.[35] Because the ERG measures a widespread area, 30% retinal dysfunction is required before detecting abnormalities.[80-83] For example, patients with sectoral RP may have a normal ERG result using the standard testing procedure because the affected region does not produce a sufficiently detectable disseminated retinal defect. The ERG is especially useful in early stages of the disease, during which the patient may be asymptomatic and have a normal fundus appearance. An ERG can help with differential diagnosis of conditions such as syphilitic chorioretinitis or other entities that funduscopically may mimic the classic clinical picture of RP (*see* Table 2). Common differential diagnoses include retinal inflammatory/infectious diseases (rubella and syphilis), retinal trauma, and congenital stationary night blindness. Serial standard ERG testing has been valuable as an objective means of monitoring therapeutic intervention such as vitamin A and other supplementary therapy. The ERG often is used at the initial presentation. As a monitoring tool, it is less effective because its value decreases when response levels drop below 4 to 5 microvolts.[84]

The photopic ERG and 30-Hz flicker test results often are interpreted as normal in the early stages of the disease, although atypical forms of RP, such as cone-rod dystrophy, may show early reductions. The 30-Hz flicker has been useful in monitoring more advanced stages of the disease, when the rod function is extinguished. As the disease progresses, affecting the cones, the 30-Hz flicker response shows reduced amplitudes with associated delayed responses.[85,86]

New technology, such as pattern ERG (PERG) and multifocal ERG (mfERG), may help to better monitor late stages.[87-90] PERG is an established technique for objective assessment of central retinal function.[88] PERG uses an alternating checkerboard stimulus on a pattern screen to test retinal function. The responses are smaller in amplitude to those observed in flash ERG. The normal PERG consists of 2 main components: P50 and N95. The inner retinal response (P50) is driven by macular photoreceptors and therefore may play a role in detecting early macular involvement or associated maculopathy.[88] Curiously, studies have found that the PERG P50 may be reduced in patients with RP, even if visual acuity is normal.[88] The mfERG component uses topographical measurements to depict retinal function within various

Table 2 Differential diagnoses of RP

Based on fundus findings
- Acquired retinal degenerations (peripheral reticular pigmentary degeneration)
- Cancer-associated retinopathy
- Drug toxicity retinopathy (phenothiazine, chlorpromazine, chloroquine, deferoxamine)
- Grouped pigmentation of the retina (bear-track)
- Infectious/inflammatory retinopathy (rubella/syphillitic retinopathy)
- Choroidal melanoma
- Pigmented paravenous retinochoroidal atrophy
- Retinal detachment resolution
- Traumatic retinopathy

Based on associated nyctalopia
- Congenital stationary night blindness
- Dystrophies of the choroid and retina (Gyrate atrophy, choroideremia)
- Vitamin A deficiency

locations of the central retina,[87] providing a measurement of independent cone function within these areas.[89] The mfERG is an objective method for studying patients with extinguished full-field ERG.[87] The test is particularly useful in monitoring the progression of small remaining regional cone responses in advancing disease.[90]

Ancillary tests

Visual field testing is the most commonly used clinical tool for evaluating and monitoring the functional status of RP patients.[91-100] Visual field testing can be used to monitor the progression of the disease as well as evaluate the severity of the condition in newly diagnosed patients.[94] Furthermore, individuals with RP may qualify as legally blind by visual field criteria before central visual acuity drops to established legal blindness levels (i.e., 20/200).[55] Even though most RP patients show a decline of the visual field over time, findings[35,36,98,99] continue to show inconsistencies regarding the rate of degradation per year.[99,101] It is unclear if this disparity is secondary to the variability of the disease or the studies themselves.

Typical visual field defects include an enlarged blind spot, mid-equatorial visual field defect, and generalized constriction.[102] Subtypes of RP may be associated with distinct visual field defect patterns. For example, sectoral RP is typically associated with arcuate or altitudinal visual field defects. Therefore, Goldmann kinetic perimetry is recommended because of its sensitivity, its ability to test the far periphery, and its reproducibility. In addition, patients' responses to standard automated perimetry may be poor and variable.[103]

Fluorescein angiography (FA), although not a diagnostic test, may be helpful in evaluating patients with RP. In RP, FA reveals diffuse hyperfluorescent mottling during the choroidal phase in association with RPE changes.[66] In advanced cases, there may be irregular areas of nonfilling of the choriocapillaris, often occurring in regions corresponding to the abnormal accumulation of retinal pigment. Historically, the most useful aspect of the test with respect to RP patients is the ability to help in the diagnosis of associated maculopathies, such as CME. A hyperfluorescent pellatoid pattern within the macula is characteristic of CME.

Optical coherence tomography (OCT) has been used as both a diagnostic tool and a way to evaluate the effects of therapy[104,105] for macular pathology in patients with RP. The OCT provides a high-resolution cross-sectional image of the retina with quantitative indices of retinal thickness (*see* Figure 4). Hirakawa et al.[104] noted that the OCT aided in the diagnosis of associated maculopathies such as CME, especially in cases of indiscernible macular fundoscopic findings associated with minimal hyperfluorescence in angiography. Apushkin et al.[105] used the OCT as a therapeutic monitoring tool, showing notable improvement in retinal thickness and cystic lesions in patients with RP after proper treatment for related CME.[105] The use of the OCT has further helped document progressive central retinal thinning

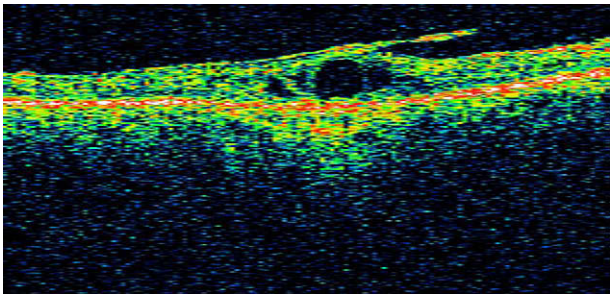

Figure 4 OCT shows CME and associated ERM in a patient with RP.

associated with cone degeneration.[58] Sandberg et al.[58] determined that significant decreases in visual acuity were related to the decreased retinal thickness, correlating well to photoreceptor cell loss.

The role of counseling

Education and counseling is imperative in the management of RP. Counseling modalities include genetic counseling, psychological counseling, and low vision rehabilitation counseling.

Genetic counseling. The aim of genetic counseling in optometry is to educate patients about the hereditary nature of their eye disease and the likely mode of inheritance based on pedigree analysis and genotype (if known) as well as the likelihood of the trait expressing itself in other family members or future generations. Counseling enables affected individuals to become prepared to make informed decisions regarding future plans, such as pregnancy, vocational choices, and medical intervention. Because risks are based on the mode of inheritance,[106] a complete detailed pedigree (*see* Figure 5) with evaluation of affected and nonaffected family members is essential.[23] Examination of nonaffected family members may assist with the establishment of the correct diagnosis and prognosis.

Genetic subtyping[107] has been used primarily as a research tool, but advances in the area of molecular genetics have undoubtedly facilitated genetic counseling. Although 50% of RP cases still have no known genetic cause,[23,24] the potential does exist to detect asymptomatic affected patients and alert them to the potential risks of carrying the defective gene. (The burden of recognizing the probability of carrying the defective gene can become a psychological encumbrance to a patient, especially because no cure exists at this time. Thus, genetic testing should be approached with sensitivity.)

Psychological counseling. Patients identified with progressive retinal degenerations (for which there are no curative treatments) might need psychological counseling. Any eye care practitioner should make referrals for counseling when appropriate. Patients and their family members also frequently benefit from support groups, such as those available online through The foundation Fighting Blindness

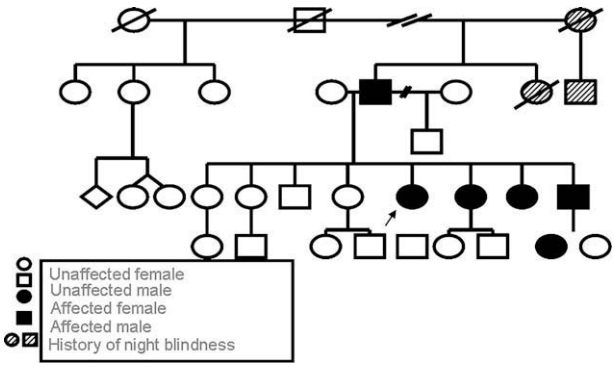

Figure 5 Three-generation pedigree analysis of an adRP family.

(Hunt Valley, Maryland), in which they can talk to others who have similar problems. The foundation's aim is to raise funds for future research and increase public awareness associated with this devastating disease. Chat rooms and message boards are available (*www.blindness.org*),[108] providing patients with advice, support groups, and encouragement. The education and support provided through counseling can help patients come to terms with their disease. Treatment modalities, such as low vision rehabilitation, are more successful once the patient is properly motivated to succeed.

Low vision rehabilitation

Low vision rehabilitation for RP patients has progressed from an optical/medical model to a functional disability model.[52] A careful history (which may include the Activities of Daily Vision Scale[109] or the National Eye Institute Visual Function Questionnaire[110]) can help identify specific functional problems that patients may experience during daily activities.[52] Eye care providers can provide or recommend appropriate low vision services, vocational guidance, mobility training, and techniques to help RP patients lead a more autonomous life style.[111-118]

Optometrists can prescribe optical devices that have the potential to improve the patient's quality of life. Optical devices used by patients with RP include visual field awareness devices, high-intensity lamps, filters, and magnifiers (such as closed circuit televisions).[111-114] Visual field awareness includes scanning training, minus lenses, reverse telescopes, and prisms. All these devices have been used to compensate for a restricted visual field.[52,111,113] Scanning is a key part of functional adaptation and involves eye movements, which can increase a restricted (static) visual field to an awareness of a larger visual field.[52] Fresnel prisms can be used to promote peripheral visual field awareness in RP patients with a visual field loss but are typically for patients with good central vision and small visual fields (10° or less) making success guarded.[52,111,113] Devices such as minus lenses or reverse telescopes are for tunnel vision and increase the field of view by minification.[111] Unfortunately, the trade-off for increased visual field awareness is reduced resolution within the remaining central field.[111]

Wide-field, high-intensity lamps have been used to compensate for poor scotopic vision by illuminating the surroundings.[111] The use of lens filters have also been used for patients with RP.[116] Tinted glasses help in brightly lit environments by providing better contrast and comfort.[115] Short wavelength photochromatic filters (e.g., CPF 550 and NoIR) decrease glare by decreasing surrounding luminance as well as aid in the reduction of photophobia symptomology.[115] These filters have enjoyed a long record of successfully providing subjective improvement in patients with abnormal dark adaptation.[114] Yet, their ability to improve visual function is controversial and anecdotal.[116,117] Nonetheless, diminishing short wavelength exposure may help minimize photoreceptor damage.[117-119] Short wavelength light has been linked as a triggering factor associated with photoreceptor apoptosis.[52] Blue (short wavelength light) has been shown to be drastically more damaging to photoreceptors compared with the long wavelength lights.[118] Thus, the use of lens filters may be indicated for RP patients.

Optometrists can also provide magnifiers to help with near vision tasks in the later stages of the disease during which central visual acuity is compromised; however, because visual fields are so severely compromised by then, magnifiers must be prescribed *carefully* to achieve the right balance between resolution and visual field.[111]

Current treatment modalities

Vitamin therapy

Currently, there are no established standard treatment modalities for patients with RP. Recent research has focused on the effects of nutritional and drug supplements and their ability to potentially preserve photoreceptor function.[120-134] Lutein, vitamin A palmitate, docosohexanoic acid (DHA), calcium-channel blockers, and ascorbic acid are among the various supplements that have been evaluated for their possible supportive role in retinal degenerations.[120-134] Unfortunately, although some studies have found benefits, others have reported no detectable changes.[122-125] The main objectives of nutritional supplements are: (1) to protect retinal cells against oxidative damage, (2) to optimize key elements of rod/cone structure, and (3) to ensure effective oxygenation of rods and cones by maintaining the integrity of the choroidal and retinal capillary systems.[119-134]

The most widely recognized nutritional supplement for RP patients is vitamin A palmitate.[84] Although there is no effective cure for retinitis pigmentosa, vitamin A palmitate has been shown to slow the rate of retinal degeneration. The precise mechanism is not clear.[84,120,126,131] (Vitamin A plays a role in the formation of rhodopsin, a protein that has a critical function in rod photoreceptors.) Studies by Berson et al.[84,126] using vitamin A palmitate therapy have found a decreased rate of ERG reduction in common forms of RP and Usher syndrome.[126] Their results indicate that the average patient taking 15,000 IU/d of vitamin A

palmitate could experience a slower progression of the disease.[126,127]

Interestingly, Berson et al.[126] also noted that vitamin E appeared to be associated with an increase in the deterioration rate of the ERG in RP patients. It is believed that an increase in vitamin E may be associated with a reduction of availability of other vitamins in the retina.[126] Currently, adult patients (over the age of 18) with common forms of RP (see above), who are in good general health, are recommended to take 15,000 IU/day (palmitate form) of a vitamin A supplement under medical supervision and to avoid high doses of vitamin E.[120,126] This is far beyond the daily recommendation (about 5,000 IU)[128] of vitamin A. In the context of this treatment, a beta carotene supplement is not a suitable substitute for vitamin A in the palmitate form. However, this therapy is not without controversy.

The November 1993 issue of *Archives of Ophthalmology* had an extensive editorial section with criticisms of the initial study. The authors of the editorials strongly criticized the use of the ERG measurements as the clinical trial endpoint, suggesting that it may not have relevance to functional measures of vision. Additionally, the safety of high-dose vitamin A was questioned. However, in 1999 Sibulesky et al.[127] reported that 15,000 IU vitamin A palmitate taken daily over a 12-year period was safe in a large cohort (n = 146) of people with retinitis pigmentosa. The National Eye Institute reaffirmed its recommendation for vitamin A supplementation for adult patients with common forms of retinitis pigmentosa in July 2008.

More recently, studies have investigated the role of docosahexaenoic acid (DHA) in the treatment of RP.[129-131] DHA is a long-chain omega-3 fatty acid, which is commonly found in fish. Studies have shown that patients with RP had mean decreased values of red blood cell DHA concentrations.[129,131] Serum levels seem to correlate with retinal levels. Rod membranes are composed of fatty acids, and these fatty acids play an integral role in maintaining rod structure related to disc membrane fluidity and rhodopsin function.[129] Patients who had recently begun vitamin A palmitate therapy showed further reduction in the rate of retinal degeneration when placed on concurrent DHA (1200 mg/d) supplements. This was functionally apparent in both the measurement of visual field sensitivity and ERG amplitudes. Unfortunately, benefits did not extend beyond 2 years; thus, it was recommended to cease the use of DHA after a 2-year course.[131] For patients who had previously taken vitamin A palmitate therapy, the addition of DHA did not offer any added benefits.[131] Of note, excluded from both vitamin A palmitate and DHA treatment trials were patients under the age of 18 years and pregnant women. Thus, no statement can be made with respect to the treatment of these subgroups.[126,128,130,131]

Patients should be aware of the expectations associated with vitamin therapy in addition to the risks. Although vitamin A palmitate therapy is associated with a reduction in progression of the disease, it has not been shown to have any beneficial effect on functional vision (such as visual acuity or visual field). In addition, even though the studies did not report toxicity associated with the longstanding use of these high doses of vitamin therapy, continuous monitoring by primary care doctors is still recommended because high doses of vitamin A may be teratogenic and can potentially cause liver damage. Laboratory workup of patients who are planning to start vitamin A palmitate and DHA therapy should include serum retinol levels, serum cholesterol levels, RBC DHA levels, and a liver enzyme panel. Patients should be monitored every 6 months while on therapy to watch for potential signs of toxicity. Female patients should be advised to cease therapy if they are planning to or become pregnant. Patients should also be advised of the importance of a well-balanced diet including leafy green vegetables and omega-3 fatty acids for further benefits.

Other research

Other ongoing research includes the evaluation of the role of oxygen and light in influencing photoreceptor death.[42-43,135,136] It is suggested that normal retinal photoreceptors have an increased oxidative metabolism. It has been hypothesized that transient hyperoxygenation may rescue retinal photoreceptors by helping them to complete their metabolic requirements. Hyperbaric oxygen delivery, inducing hyperoxia, has demonstrated an ability to bring about the rescue of retinal photoreceptors by helping them with their metabolic requirements. It seems that adjusting hyperbaric oxygen levels can be associated with modifications in the ERG measurement.[135]

Treating associated ocular manifestations

Although modification of the primary disorder may not be feasible, ophthalmic management includes treating the collateral consequences of the dystrophy, such as the development of cataracts and CME. Cystoid macular edema may cause significant additional loss of visual function in patients with RP. A small number of patients have been shown to respond to oral carbonic anhydrase inhibitors (CAI), such as Diamox™ (Duramed Pharmaceutical Inc., Cincinnati, Ohio).[137-140] The pharmacologic effects of oral CAIs decrease vascular permeability and "stimulate active transport across the blood-retina-barrier."[140] In recalcitrant cases, a retinologist can be consulted to consider other approaches, which might include intravitreal steroid injection or laser photocoagulation.

Cataract is another common ocular manifestation observed in RP patients. Patients with severe restriction of the visual field (less than 10°) seem to show the greatest benefits from cataract extraction.[141] The use of a potential acuity meter (PAM) or laser interferometer can aid in determining the prognosis. Surgical approaches to both retinal and cataract complications do not show any capacity to worsen the disease or its prognosis.

Investigational treatment modalities

New understanding of the pathogenic mechanisms continues to drive current research. Recent developments include therapeutic modalities associated with gene therapy aimed at correcting various specific mutations, cell transplantation to replace lost cells, pharmacologic options to help preserve photoreceptors, and the use of neuroprosthetic devices to generate visual perception.[142-202]

Gene therapy

Ten percent of human genetic diseases are associated with an inherited retinal dysfunction.[142] Gene therapy therefore will likely be a future vital therapeutic option. Gene therapy is a process that replaces or turns off the mutated disease-causing gene to restore some normal protein function.[143-150] In an inherited disease, like RP, there are a number of methods used to replace or correct "abnormal" genes: (1) insertion of a normal gene into the genome to replace nonviable or diseased genes using a carrier "vector," (2) ribozyme therapy, and (3) RNA interference.[142-149] Gene replacement is necessary in recessive conditions, whereas ribozyme therapy and RNA interference may be useful in autosomal dominant conditions. In dominant conditions, normal and abnormal gene products (proteins) are produced by the normal and mutant gene respectively. The aberrant gene product is detrimental to the photoreceptors and ultimately results in cell death. Ribozymes can be designed to cleave mutant mRNA molecules so that the detrimental protein is not produced, thereby rescuing the cells. Although ribozymes may not eliminate all mutant mRNA, this reduction was shown to be sufficient for the preservation of vision in an adRP canine model.[149] RNA interference works in a similar manner, causing destruction of the aberrant RNA by existing cell defense processes.

Advancements in gene replacement therapy have been successful in improving visual function. For arRP a corrective gene may be introduced into the cell through the use of a recombinant adeno-virus (or adeno-associated virus) vector, in hopes the virus may deliver the "normal" gene to the host's cell, replacing the "disease" gene.[142] These techniques have experimentally been shown to delay and even reverse the course of RP with associated improvement of photoreceptor function in various animal models.[142-146] ERG response recovery, as well as retinal structural improvement, has been documented in an animal model after gene replacement therapy at an early stage of the disease.[143]

Acland et al.[143] were able to show drastic improvement in ERG measurements in Briard dogs with Leber's congenital amaurosis after corrective gene implementation. Most recently, in one study,[203] 3 young patients with infantile rod-cone dystrophy (Leber congenital amaurosis) were given subretinal injections of recombinant adeno-associated virus vector 2/2 expressing RPE65 complementary DNA (cDNA) under the control of a human RPE65 promoter, with one of the 3 making positive changes both objectively and subjectively. Another study[204] reported that the same method of gene transfer of 3 subjects showed some improvement of retinal function. However, factors such as long-term efficacy, immune response, and tribulations associated with vectors used are some of the complicating factors associated with genetic therapy. Long-term safety and effectiveness still needs to be established.

Cell transplantation

It has been postulated that by replacing damaged photoreceptor cells, new connections can reform, thereby improving visual function. Future treatment options might someday include cell transplantation.[151-170] Cell transplantation is the re-infusing of cells into a patient in hopes of producing more healthy cells, which may replace nonfunctional cells. The 2 main sources of cells for transplantation in use today are retinal and stem cells.

Retinal cell transplantation is the introduction of healthy photoreceptor cells into the host. The advantages of retinal cell transplantation over stem cell transplantation is that retinal cells integrate well into the host retinal layers and express specific retinal cell markers.[156,158,171] Retinal transplantation before photoreceptor apoptosis is more likely to result in a decreased rate of progression. The use of retinal transplantation in small rodent models has been associated with restoration of photoreceptor function, as evidenced by normalization of the ERG responses.[154] Despite this apparent physical improvement, restoration of vision has not been well established. This shortcoming has been attributed to the failure of transplanted tissue to form functional connections with the host's neurons[156] as well as the loss of synaptic receptivity of the host's retinal neurons.[156,157] Another common disadvantage of retinal cell transplantation is an inflammatory response associated with immunologic rejection. Alternatives such as the use of donor cells from another region of the same eye have helped with some of the limitations related to retinal cell transplantation.

Stem cell transplantation is the process whereby a patient receives healthy stem cells, which may in turn begin producing normal retinal cells. One of the key advantages is that stem cells have the potential to differentiate into any type of cells, including retinal neural cells, which may replace lost photoreceptors.[161] Previous studies have indicated that stem cells integrate well into the retina and adopt the morphologies and positions of Muller, amacrine, bipolar, horizontal, photoreceptor, and glial cells in adult mice.[159] Stem cells commonly used in transplantation include adult neural (retinal or RPE) progenitor cells, bone marrow–derived stem cells, and fetal stem cells. Fetal stem cell transplantation involves transplanting photoreceptor cells and the underlying retinal pigment epithelial cells from the retinas of aborted fetuses.[162] Visual improvement (both subjective and objective) has been documented in a number of subjects following this cell transplantation form.[166-168] Radtke and Norman[166] demonstrated that fetal

retina transplanted into an adRP patient can survive 1 year without apparent clinical evidence of rejection and that continued improvement in visual acuity could be achieved. Gouras et al.[165] published histologic evidence of cellular reconnection after fetal retinal stem cell transplantation in adult rats. Their studies documented safe parameters associated with the procedure and apparent high tolerance for graft transplantation. Fetal stem cells have a greater immunologic tolerance, reducing the chance of rejection by the host and eliminating the need for immunosuppressive drugs. Fetal stem cells can easily overcome the trauma related to transplantation, unlike adult cells, which depend heavily on oxygen.[168] In addition, fetal stem cells have a high capacity to produce the trophic substances, enabling the retinal connections.[169]

There are still a number of disadvantages associated with fetal stem cell transplantation.[170] Cografting of fetal neural retina RPE cells has proven to be difficult. One problem is that fetal RPE cells can easily loosen from the retina during removal because the photoreceptor outer segments have not yet developed. Furthermore, storing partially dissected retinal RPE sheets over a long period of time is challenging because the tissue will eventually start to contract and roll up.

Currently, there are various ethical concerns regarding fetal cell transplantation.[170] Nonetheless, successful cotransplantation of photoreceptors and RPE cells has been reported with the hope that they will replace the old degenerated cells. Ongoing pilot studies of retinal transplantation in human patients with retinal degenerations are being conducted. Safe and efficient delivery of neural retinal cells was achieved, but results warrant further studies to quantify the benefits.

Pharmacologic options

It has been postulated that some of the success of retinal cell transplantation may be attributed to the release of diffusible factors that promote photoreceptor survival, known as neurotrophic factors.[171-174] Their role as a treatment modality for RP has recently been evaluated.[171-174] Neurotrophic factors are polypeptides that play a role in the general health and maintenance of cell function. They influence the growth of nerve cells and induce cell segregation. Removal of these neurotrophic factors has been associated with increased rod degeneration in RP patients.[172]

Pharmacologic possibilities using neurotrophic factors include basic fibroblast growth factors (bFGF) and ciliary neurotrophic factors (CNTF).[171-174] Injection of bFGF in RP rat models has resulted in delayed degeneration of photoreceptors across the retina for at least 2 months after a single injection.[172] Although the treatment did not eliminate the genetic defect, it did ameliorate the resulting condition. Ciliary neurotrophic factor injected into affected RP rats has also shown a reduction in photoreceptor loss as well as improvement in ERG response.[173] RPE cells genetically modified to produce CNTF can be implanted into the eyes of RP patients using Neurotech Encapsulated Cell Technology. Phase 1 testing showed high levels of CNTF in the vitreous.[174] Although the trial had a small patient population (n = 10), 7 patients showed visual acuity improvement.[172] There is a potential for these neurotrophic factors to provide benefits associated with decreased photoreceptor apoptosis; however, at this time, CNTF transplantation is only in the experimental phases. Currently, there is a multicenter human clinical trial using encapsulated cell technology underway.

Other pharmacologic options used in patients with RP include anti-Parkinson's drugs.[175-177] The value of these pharmacologic options is based on their antiapoptotic properties. Anti-Parkinson's agents, such as Zelapar™ (Valeant Pharmaceuticals, Swindon, Wiltshire, United Kingdom) when used at very low concentrations, retard apoptosis by triggering a chemical reaction that enhances production of bcl-2 proteins.[176] Zelapar™ was tested on humans, evaluating its effect on cognitive functions in Parkinson's disease.

Neuroprosthetic devices

In 1929, it was documented that stimulation of the brain led to the perception of phosphenes, an entoptic phenomena, described as the perception of lights without "light" stimulation.[178] Currently, cortical stimulation, using surface or intracortical electrodes, has been successful in creating various phosphenes.[178-182] The aim of this new technology is to generate visual perception through the use of electrical stimulation along intact aspects of the visual pathway. Earlier studies on animal models have found an increase in visual-evoked potentials associated with stimulation of "extraocular electrical impulses."[180] The use of neuroprosthetic devices has been documented to evoke visual perception in otherwise blind patients.[184,185] Current neuroprosthetic devices use optic nerve, retinal, or cortical stimulation.[180-199] These approaches are being assessed in clinical trials, but so far no visual prosthesis has restored "normal" vision; patients have only a crude level of visual perception.

Optic nerve stimulation[188,189] involves electrodes placed around the optic nerve, resulting in colored phosphenes throughout the visual field. By changing the duration and amplitude of the electrical stimulus, an RP patient was able to perceive different levels of brightness of the generated phosphene.[189] This study provided a step toward the practical use of the optic nerve visual prosthesis. Direct stimulation of the optic nerve has several potential advantages:[188,189] (1) it does not require the surgical penetration of sensitive intraocular or intracranial tissues (optic nerve stimulation is less invasive than cortical-based visual neuroprosthesis), (2) the optic nerve is more stable than cortical-based visual neuroprosthesis and provides a larger field of spatial resolution, (3) the photosensitive component can be placed outside the body allowing the use of an external

power source, and (4) it allows greater selectivity of stimulation leading to less overlap between neighboring nerve fibers and more channels of stimulation leading to a better representation of the visual field. Of course, the main disadvantage of this approach is that a normal functioning optic nerve is required.

Retinal stimulation includes both subretinal and epiretinal prostheses.[178,183,198] The retinal implant is designed to take over the function of the lost photoreceptors. One subretinal device, known as Artificial Silicon Retina "ASR™ Microchip" by Optobionics (Naperville, Illinois), is powered entirely by the light entering the eye.[183] Electric current is generated by microphotodiodes. The subretinal approach involves the implantation of a microphotodiode array between the bipolar cell layer and the RPE. These microphotodiodes replace the function of degenerated photoreceptors. The main advantage of this procedure is that the information collected by the microphotodiodes is transmitted to functional bipolar and ganglion cells.[190] A subretinal microphotodiode implant could function similarly to a "solar cell," negating the need for a power or input source of any type. Chow et al.[183] using the ASR™ reported gains in visual function in all the tested patients as well as unexpected improvements in retinal areas distal to the implantation site. The advantages of subretinal stimulation include an increased number of electrodes, which provides higher resolution images. In addition, the smaller size implant reduces complications associated with surgery. Yet, not all studies have been encouraging. Because of some mixed and inconclusive results with the use of these devices, the ASR™ is no longer under development. Another subretinal device is currently being evaluated, which will use a microelectrode that must be externally powered (unlike the microphotodiode of the ASR™).[194]

The epi-retinal implant consists of an array of electrodes that are attached to the retina and are used in conjunction with an external camera and video processing system, providing a rudimentary form of vision (including light detection, object motion, object differentiation, and location). Like subretinal stimulation,[194] epiretinal stimulation has also been associated with phosphene perception. Yet, unlike subretinal devices, an epiretinal device is implanted on the surface of the intact retinal ganglions and thus is unable to use any remaining information from intact bipolar cells. Recently, Second Sight® Medical Products, Inc., (Sylmar, California) has developed a second-generation implant, the Argus II, which has a 60-electrode array. The Argus II is the only retinal prosthesis currently in clinical trials in the United States.[195]

Future research of such devices will aim toward the improvement of shape recognition in otherwise blind patients. It must be underscored that a retinal implant does not restore vision to normal. It has the potential to only give the patient more visual ability for increased mobility, confidence, and safety when traveling through the environment. Today, retinal prosthetics are still being studied in clinical trials and are not available commercially.

Cortical stimulation (surface or intracortical stimulation)[199] uses visual images captured by a camera, which are collected on a computer base stimulator mounted on a pair of glasses. The data captured by the device creates signals, which are carried by electrodes; these then pass over or within the cortex, leading to visual perception.[181] The cortical visual prosthesis is advantageous over other approaches because it bypasses the diseased retina and directly stimulates the primary visual cortex. A study[181] has shown the ability to evoke phosphenes and patterned perceptions through the use of electrical stimulation on the occipital cortex via chronically implanted electrodes.[181] Difficulties encountered in the past included controlling the number of phosphenes induced by each electrode and interactions between the phosphenes themselves. Other drawbacks of this system and similar systems include cost, low-resolution imaging provided within a small field of vision, increased risk of seizure activity, and the potential risks associated with craniotomy.[179] Among the most grave complications are seizures, which may be brought on by the use of high currents and large electrodes stimulating the brain.

Other devices

The knowledge that one sense may be augmented and used in exchange of another after disability has led to the discovery of other modalities of artificial human vision. Using this concept, Meijer[196] developed the vOICe technology™, which uses auditory information to substitute for visual sensory information. The vOICe technology uses an extraocular camera housed within sunglasses. Visual images from the camera are then mapped into sound, which the subject must decode into visual input. Unlike cortical simulation, this offers an option without the inherited risks of surgery. The company's Web site provides a number of testimonials from individuals who have used the product.[197] Yet, no large clinical trials have been conducted to truly assess its capabilities.

University of Florida researchers have invented speech recognition software, wearable computers, satellite positioning technology and other emerging technologies in a 21st century navigational aid for people who are blind (*The VoiceNote GPS™*).[200] Composed of a waist-worn computer and headset connected remotely to a map database server, the prototype delivers and responds to instructions verbally. It keeps track of the user's location while giving directions to a destination. *The VoiceNote GPS™* [200] has 2 main functions: receiving and recording pinpoint exact locations via a network of 24 GPS (global positioning system) satellites that continually orbit the earth and tracking of the exact route of the wearer. Since about 2001, people with vision impairment have had access to commercial GPS-based navigations systems.

Neurotransmitter implant systems combine fiber optics, microfluidics, and photo-trigger neurotransmitters. Using

an inactive pro-drug, such as glutamate, a tiny fiber optic creates a brief pulse of light, activating the glutamate pro-drug and causing a localized "chemical pixel" that would in turn cause visual perception. Iezzi[201] has been able to achieve 5- to 10-μm spatial resolution in vitro (cultured neurons).[191]

Conclusion

RP is the most common group of inherited retinal diseases worldwide. It is characterized by progressive photoreceptor degeneration. The progressive nature of the disease often ultimately leads to functional blindness. To date there is no effective treatment that can prevent or reverse the devastating vision loss. Continued research in pathogenesis of RP has significantly improved our understanding of the disease, although the exact mechanism is still not completely understood. The National Eye Institute has established a program (eyeGENE™) to collect DNA samples from patients to determine their genotype and phenotype. Patients benefit from genetic testing at no cost (except samples collection and shipping). In addition, scientists may benefit from a well-characterized repository of DNA samples with inherited eye disease.[202] The eyeGENE program, along with advancements in the human genome project, and current experimental research projects, may provide new treatment options, improving the prognosis of this disease and minimizing the functional burden to those patients who must endure it.

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