BMJ Best Practice

Retinitis pigmentosa

Straight to the point of care

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Summary

Primary symptoms of retinitis pigmentosa include impaired night vision, problems with dark adaptation, decreased peripheral vision, and eventually decreased visual acuity.

Electroretinograms help confirm the diagnosis by demonstrating attenuated rod and cone signals.

Onset and pattern of degeneration vary but most cases demonstrate atrophy of the retina and retinal pigment epithelium, bone spicule pigmentation, waxy pallor of the optic nerve, and retinal vascular attenuation.

There is no cure. Vitamin A (retinol) supplementation and docosahexaenoic acid (fish oils) are given in some centres with the aim of slowing retinal degeneration. Gene replacement therapy has demonstrated improved functional vision in patients with RPE65-mediated inherited retinal dystrophy.

Definition

Retinitis pigmentosa (RP) is a term that encompasses a broad category of hereditary conditions of retinal degeneration that share a common pathophysiology.[1] [2] Symmetrical retinal degeneration is caused by a genetic mutation in 1 of over 100 different genes, leading to loss of rod and cone photoreceptors in the retina. Inheritance can be autosomal dominant, autosomal recessive, X-linked, or, rarely, mitochondrial or digenic. It most commonly presents with night blindness and progressive loss of peripheral vision.[3] The timing, patterns, and course can be heterogeneous. Cone-rod and cone dystrophies are sometimes classified separately from RP, but increased genetic knowledge is revealing that these disorders are part of the RP spectrum.

Epidemiology

Worldwide, the estimated prevalence of all forms of retinitis pigmentosa (RP) is 1 in 4000.[6][7] Population-based studies report a relatively higher prevalence of 1 in 750 in India (1 in 372 in the rural setting and 1 in 930 in urban areas).[8] [9] A presumed period prevalence of 1 in 6500 has been reported in South Korea; incidence of RP was found to be 1.64 cases per 100,000 person-years.[10]

The rates of autosomal dominant (ADRP), autosomal recessive (ARRP), and X-linked (XLRP) RP vary considerably from region to region. A study of medical and social service sources in Maine reported rates of 19% ADRP, 65% ARRP, and 8% XLRP.[11] Mass screening in China revealed rates of 5.2% ADRP, 3.0% XLRP, and 91.8% ARRP.[12] In a series from the UK, rates were 39% ADRP, 25% XLRP, and 36% ARRP.[13] The age of onset is variable and depends on the mutation involved.[6]

X-linked RP primarily affects males and is associated with early onset and severe disease.[14] Female carriers may exhibit a wide range of atypical and/or asymmetric disease due to random x-inactivation.[15] While some female carriers may have subclinical disease and be asymptomatic, others may exhibit severe disease with classic features of RP.[15][16]

Aetiology

RP is caused by mutations in genes that code for proteins important in the function and survival of photoreceptors and the retinal pigment epithelium. Mutations in more than 100 individual genes have been found to cause RP. The function of these different genes is diverse, including phototransduction, the retinoid cycle, photoreceptor structural integrity, phagocytosis of outer segment tips, structure and function of the cilium, metabolic homeostasis, mRNA splicing, and transcription of proteins. A family history of RP can help to reveal the pattern of inheritance.

RP is most frequently an isolated eye finding. However, there are some rare forms of syndromic RP, which present with systemic findings in addition to a typical pigmentary retinal degeneration. The most common forms of syndromic RP are Usher's syndrome and Bardet-Biedl syndrome.[17] In syndromic forms of RP, the affected genes have an impact on photoreceptor function but additionally play an important role in other organ systems such as the ear or kidneys.

Syndromes associated with RP

- Usher's syndrome: this affects hearing and vision due to RP and a defective inner ear. Many patients also have balance problems, and children with this condition may be slow to walk.
- Bardet-Biedl syndrome: there is usually both growth and intellectual impairment, with features including polydactyly or syndactyly, dilated cardiomyopathy, renal failure, and hepatic fibrosis. The degree of mental impairment can range from mild cognitive impairment to severe intellectual disability.
- Alstrom's syndrome: a rare autosomal recessive condition. Features include RP (cone-rod dystrophy), sensori-neural hearing loss, infantile cardiomyopathy, and obesity. Without cardiomyopathy, the condition may not be diagnosed until the later development of diabetes mellitus.
- Joubert's syndrome: a rare condition usually inherited in an autosomal recessive manner that results in malformation of the cerebellar vermis (which connects the 2 halves of the cerebellum). Ataxia is a key feature, and others include learning difficulties, decreased muscle tone, renal cysts, sleep apnoea, and extra fingers or toes.
- Senior-Loken syndrome: a rare autosomal recessive disorder caused by a mutation in a gene involved in protein formation in the cilia. RP is accompanied by progressive kidney disease caused by defective

nephron function and the formation of medullary cysts. Renal disease typically presents in the first year of life.

- Neuronal ceroid-lipofuscinosis: a family of rare genetic neurodegenerative liposomal storage disorders. There is gradual motor and neurological degeneration, seizures, and visual loss due to RP. Visual loss can be an early feature.
- Kearns-Sayre syndrome: a mitochondrial disease that typically presents <20 years of age with visual loss due to RP. Other features may include ophthalmoplegia, hearing loss, ataxia, and dysphagia.
- Bassen-Kornzweig disease (abetalipoproteinaemia): a rare autosomal recessive condition that results in the poor absorption of fats, fat-soluble vitamins (A, D, E, K), and cholesterol. Symptoms usually present within the first few months of life and include failure to thrive, poor growth, and fat and blood in the stool. RP and ataxia may develop during later childhood.
- Infantile Refsum's disease: a metabolic disorder due to a defect in peroxisomal biogenesis. It usually presents in early childhood with visual and hearing impairment, poor muscle tone and co-ordination, intellectual impairment, and abnormal facial development.
- Adult Refsum's disease: this may be suspected in children presenting in late childhood with RP and combinations of anosmia, hearing loss, ataxia, cardiac arrhythmias, and short metacarpals and metatarsals. Some have a sensory or motor neuropathy.

Pathophysiology

While RP can be caused by mutations in an array of functionally different proteins, the underlying common pathophysiological feature is apoptosis of the rod and cone photoreceptors. The cones are centrally arranged in the retina, and loss of cone photoreceptors will impair visual fields under light-adapted (photopic) conditions and can result in light sensitivity, decreased visual acuity, and loss of colour vision. Loss of rod photoreceptors leads to impaired vision and constricted visual fields under dim (scotopic) conditions, as a well as problems with dark adaptation. Most commonly, the rod photoreceptors degenerate first, followed by the cones (rod-cone dystrophy), but certain genes can cause a cone-rod dystrophy, where the cones degenerate first followed by the rods. Finally, some mutations cause an isolated cone dystrophy.

As retinal photoreceptors degenerate, the retinal pigment epithelium migrates into the neural retinal layer to form bone spicules surrounding retinal vessels.[18] Secondary disorganisation of the inner retinal layer is also seen.

Classification

Classification by inheritance

- Autosomal dominant
- X-linked
- Autosomal recessive
    - Simplex: no family history, presumed to be recessive, but could be de novo dominant mutation as well
    - Multiplex: autosomal recessive with other affected siblings.
- Mitochondrial (rare)
- Digenic (rare)

THEORY

Classification by functional loss

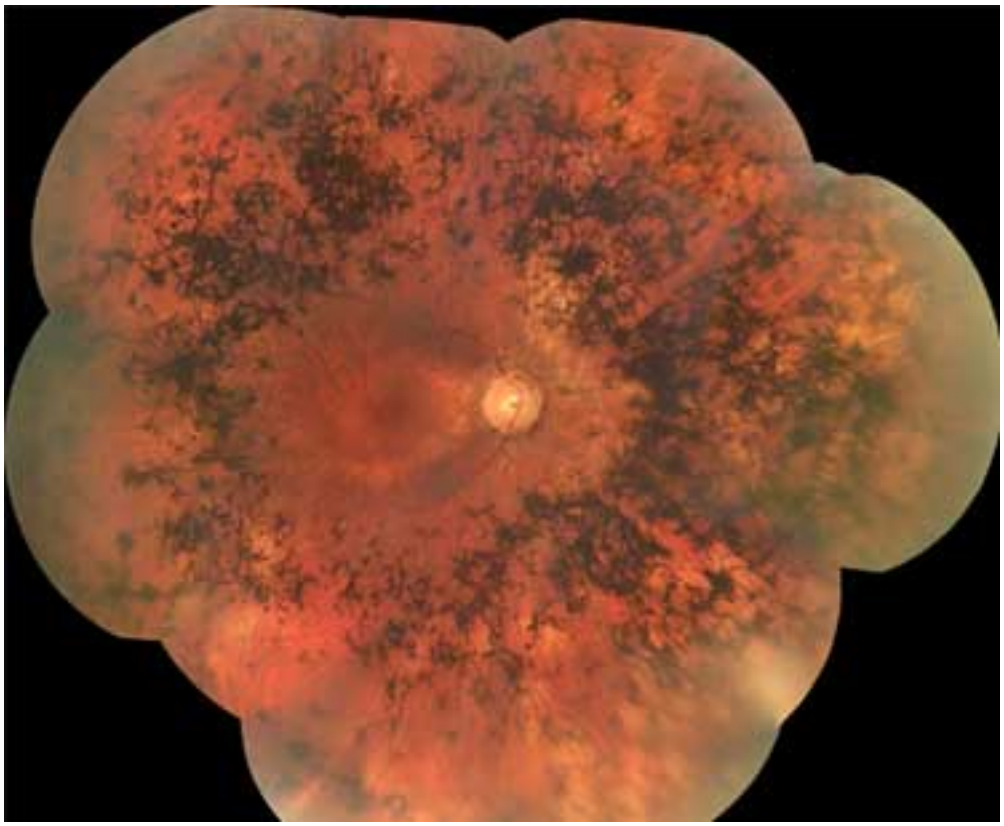
- Rod-cone dystrophy
- Cone-rod dystrophy
- Cone dystrophy

Classification by age of onset

- Leber's congenital amaurosis: mutations in genes that cause severe disease with onset at <1 year of age
- Juvenile RP: mutations in genes that cause severe disease with onset between 1 and 5 years of age
- Typical RP: variable onset >5 years of age

Classification by pattern on fundus examination

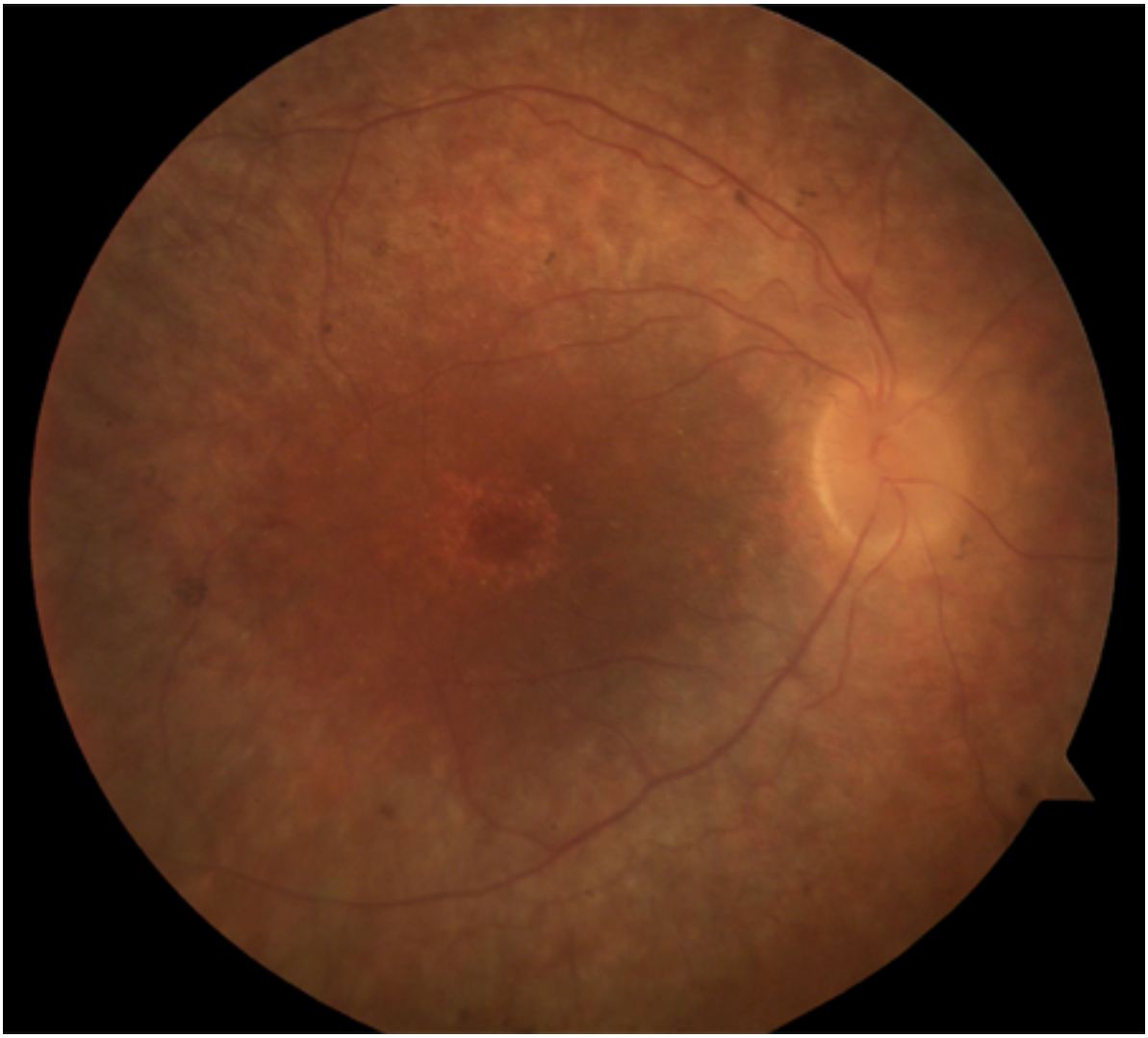
- Classic pattern: starts in mid-periphery and extends to the periphery and then centrally



Retinitis pigmentosa

From the Oregon Retinal Degeneration Center collection

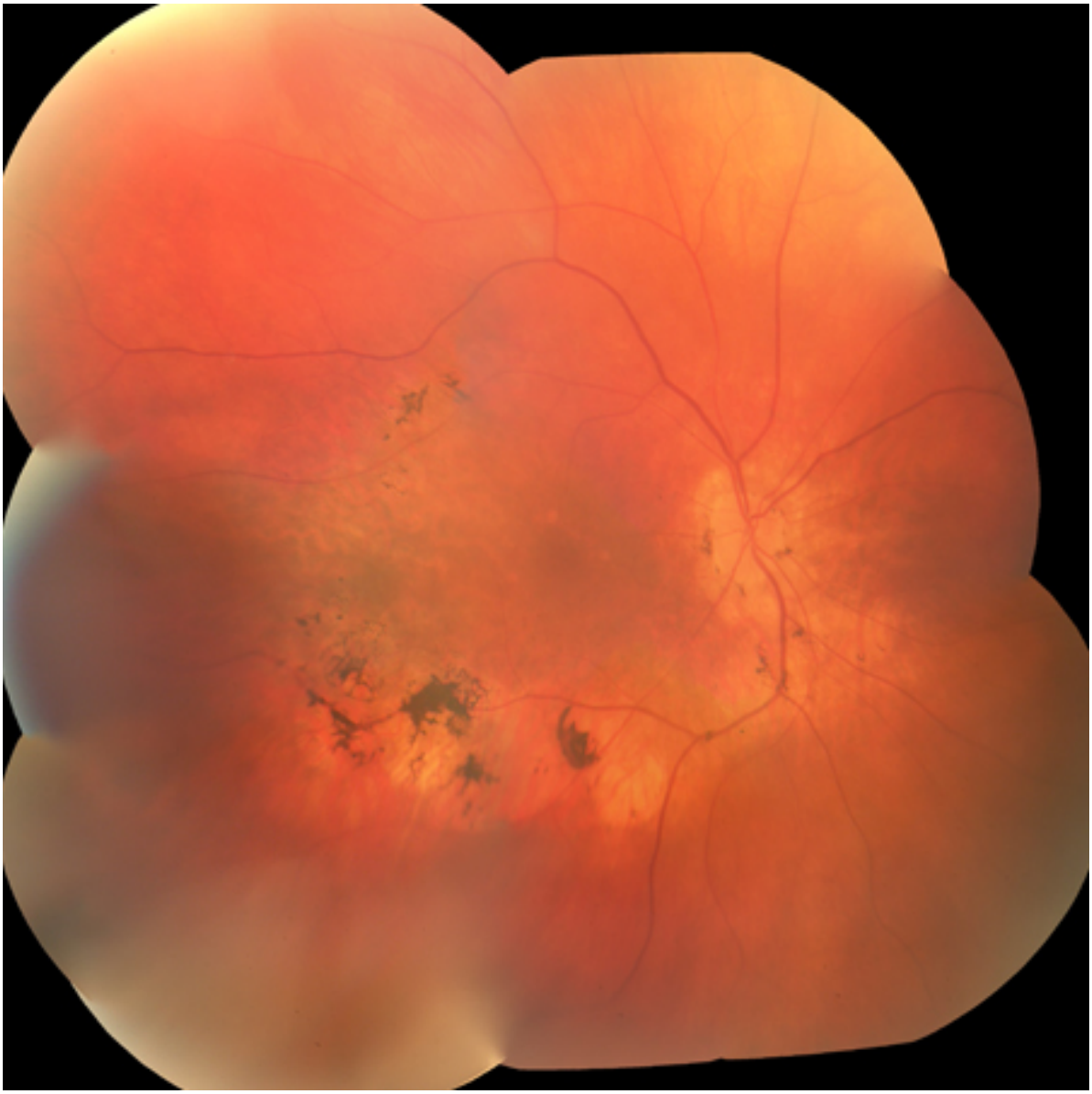
- Bull's-eye maculopathy: seen in cone-rod and cone dystrophies (rare in typical RP)



Bull's-eye appearance in RP

From the Oregon Retinal Degeneration Center collection

- Sector RP: involving 1 or more regions of the retina in both eyes



Sector RP

From the Oregon Retinal Degeneration Center collection

- Mosaic pattern: can be seen in female carriers of X-linked mutations
- Pericentral RP: starts pericentrally within the arcades and extends centrally
- Concentric: starts in the far periphery and progresses centrally
- Unilateral: most likely not RP, but a disease that mimics RP
- RP sine pigmento: lacks characteristic bone spicule pigmentation; may be seen in early disease
- RP with preserved peri-arteriolar retinal pigment epithelium: classic pattern, but preserved retina near arterioles
- Pigmented paravenous retinochoroidal atrophy: bone spicules limited to area around retinal veins.

Case history

Case history #1

A 30-year-old woman presents with difficulty driving at night and problems seeing when entering a darkened movie theatre. There is no family history of eye disease. Her visual acuity is 20/20 in both eyes. A dilated examination reveals mild posterior subcapsular cataracts, a pale and waxy optic nerve head, widespread attenuation of retinal vessels, and bone spicule pigmentary changes in the mid-peripheral fundus. A visual field test reveals a ring scotoma in the mid-periphery of both eyes. A diagnosis of simplex RP is made.

Case history #2

A 7-year-old boy presents with problems seeing the board in class. He already wears glasses for myopia, but his parents note that the glasses do not seem to be working as well as they used to. They also note that he has been bumping into furniture at home and is afraid to be left in the dark. Family history reveals a maternal grandparent with a history of RP. The patient's best corrected visual is 20/70 in each eye. Slit-lamp examination is unremarkable, but a dilated fundus examination reveals a waxy optic disc with a cup-to-disc ratio of 0.1. The retinal blood vessels are attenuated. In the mid-periphery, the retinal pigment epithelial is atrophic and bone spicule pigmentation is prominent. Visual fields are symmetrically constricted. A diagnosis of X-linked recessive RP is made.

Other presentations

Sight loss is gradual and progressive. Reduced peripheral vision and difficulty seeing in poor light are typical symptoms. X-linked forms of the disease usually present in childhood, while autosomal recessive and dominant forms tend to present later in life.[4] A severe subtype of RP, known as Leber's congenital amaurosis, can present in infancy with decreased vision, sluggish pupils, and nystagmus.[5] RP tends to be symmetrical, but asymmetrical presentation can be seen, especially in female carriers of an X-linked mutation. Glare from bright lights might be a problem in advanced disease.

Approach

RP is a lifelong incurable disease that leads to progressive loss of vision. Due to the implications of such a diagnosis, it is important that patients with suspected RP be seen by a consultant. If RP is confirmed then syndromic associations should be considered.

History

Visual loss is gradual and progressive. Visual acuity varies from perfect 20/20 vision to merely light detection. It is unusual, however, to have total visual loss, and some degree of sight is usually maintained into old age. Central acuity can be decreased in advanced forms of the more common rod-cone dystrophy form of the disease or at an earlier time if cystoid macular oedema (CMO) develops.

Symptoms depend on which types of photoreceptors are affected. Most commonly, the rods are affected first, and some of the earliest symptoms include difficulty driving at night due to poor vision and impaired adaptation when entering a dark room. Loss of peripheral vision is another feature, and the patient may report bumping into furniture or the edge of doors or having difficulty playing racket sports. Visual field loss often goes unnoticed until it reaches a moderate stage due to the overlapping visual fields of each eye.

In cone-rod-type RP, where the cones are predominantly affected first, symptoms may include difficulty in reading or seeing detail (due to central visual loss) or impaired colour vision. Patients may report seeing flashes of light or luminous rays, although these may also be seen with migrainous aura or retinal detachment. However, with RP, the flashes are continual rather than episodic. Glare from bright lights may be a problem in advanced disease.

A severe subtype of RP, known as Leber's congenital amaurosis, can present in infancy with decreased vision, sluggish pupils, and nystagmus.[5]

Many patients with X-linked or dominant RP have a family history of the disease. Autosomal recessive inheritance may or may not reveal a family history. As X-linked forms only affect male offspring (although females can be carriers), this may not be obvious if there were no male children within a generation. X-linked forms of the disease usually present in childhood, while autosomal recessive and dominant forms tend to present later in life.[4]

Syndromic RP

RP is most often found in isolation but also can exist as part of a syndrome. To exclude the presence of syndromic disease, it is important to look for other symptoms and signs: in particular, hearing or balance problems (Usher's, Alstrom's), obesity (Bardet-Biedl), renal failure (Bardet-Biedl, Alstrom's, Senior-Loken), extra digits on the hands or toes (Bardet-Biedl, Joubert's), ataxia (Joubert's, Bardet-Biedl), seizures (neuronal ceroid-lipofuscinosis), and diabetes (Alstrom's disease). Hearing loss, ataxia, ophthalmoplegia, cardiac conduction defects, and dysphagia may be seen in Kearns-Sayre syndrome. Abetalipoproteinuria is a potentially reversible cause of RP, as many of the features are due to lack of absorption of fat-soluble vitamins. If diagnosed early, retinal problems can be prevented or slowed by supplementation with vitamins A and E. Infantile Refsum's disease usually presents in early childhood with accompanying hearing impairment, co-ordination problems, and poor muscle tone. In adult Refsum disease, features may include anosmia, ataxia, and cardiac arrhythmias. Referral to a geneticist may be required for syndromic diagnosis.

Eye examination

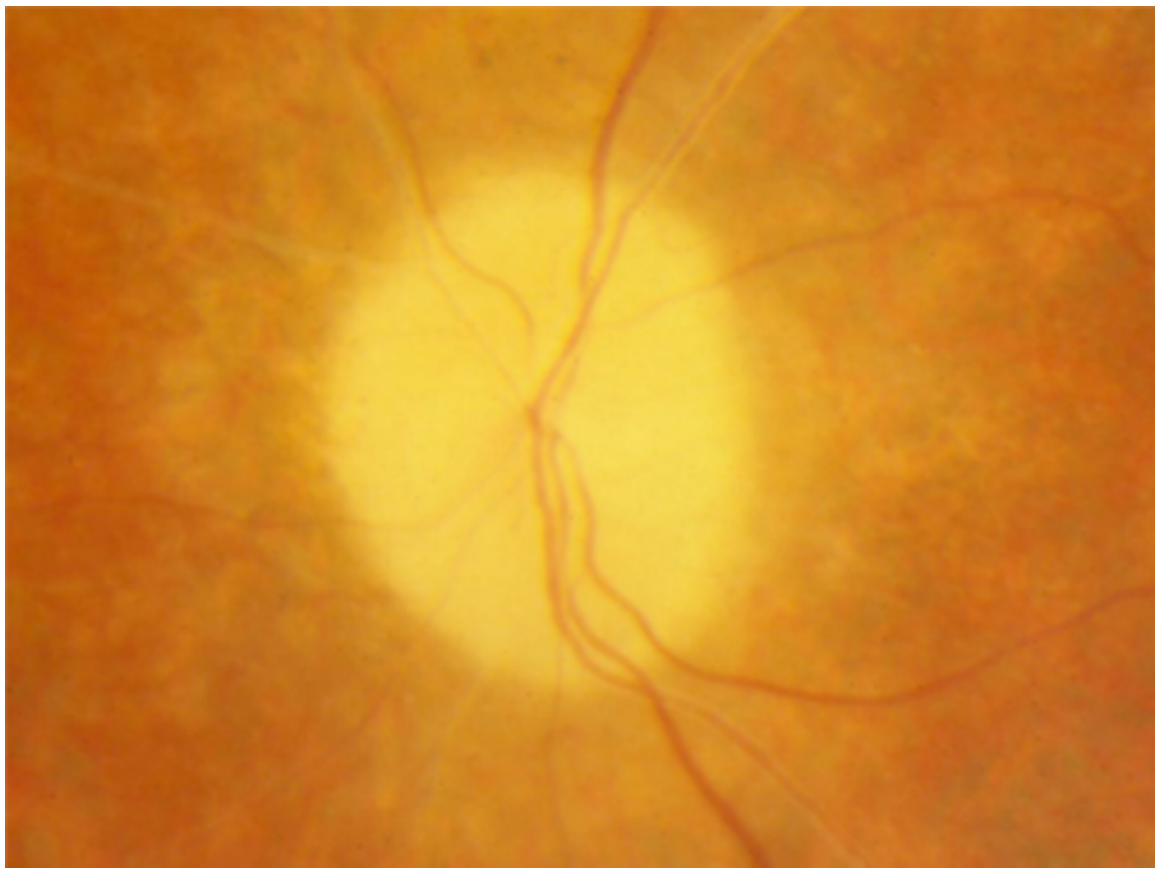
The American Academy of Ophthalmology Preferred Practice Pattern Committee reported on recommendations for the frequency for adult comprehensive medical eye examinations for asymptomatic patients, patients with, or without risk factors for eye disease.[22]

Visual acuity

- This may be measured using a Snellen chart and can be varied depending on the type and severity of RP. It is essential to record visual acuity for both functional and legal implications and to track progress. Refractive errors may be noted and sight may be improved by glasses if this is corrected, although underlying RP remains. In early severe forms of RP, such as Leber's congenital amaurosis, hyperopia predominates. In later-onset forms of RP, myopia and astigmatism are common. About half of patients with RP will develop cataracts, and removal may improve vision if underlying RP has not progressed too far.

Funduscopy

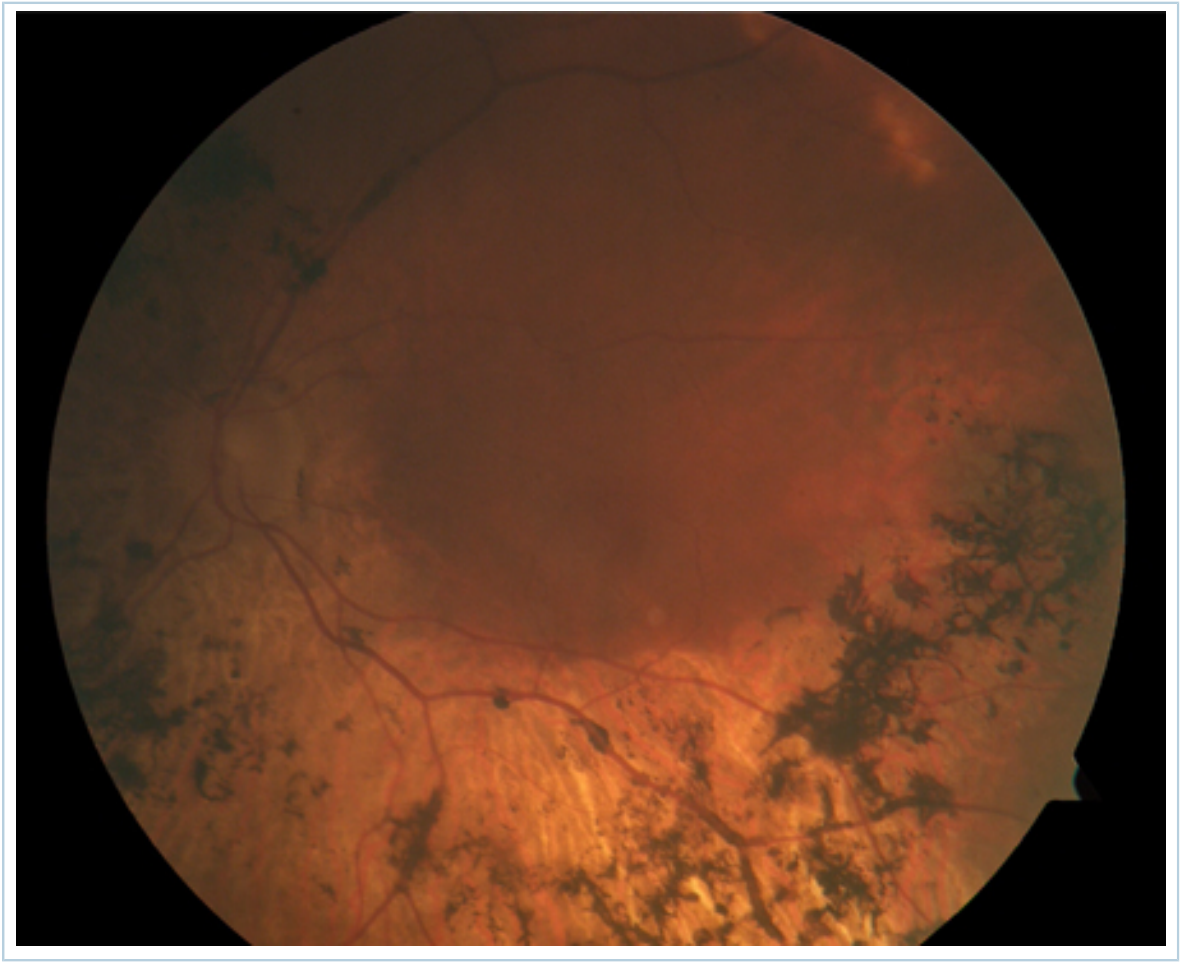
- Typically the optic disc is pale and the optic nerve has a waxy appearance, although it may appear normal in early disease.
- Vascular attenuation of retinal vessels helps to distinguish RP from choroideraemia (which demonstrates normal retinal vessels but atrophy of the choroidal vessels).



Waxy pallor and vascular attenuation

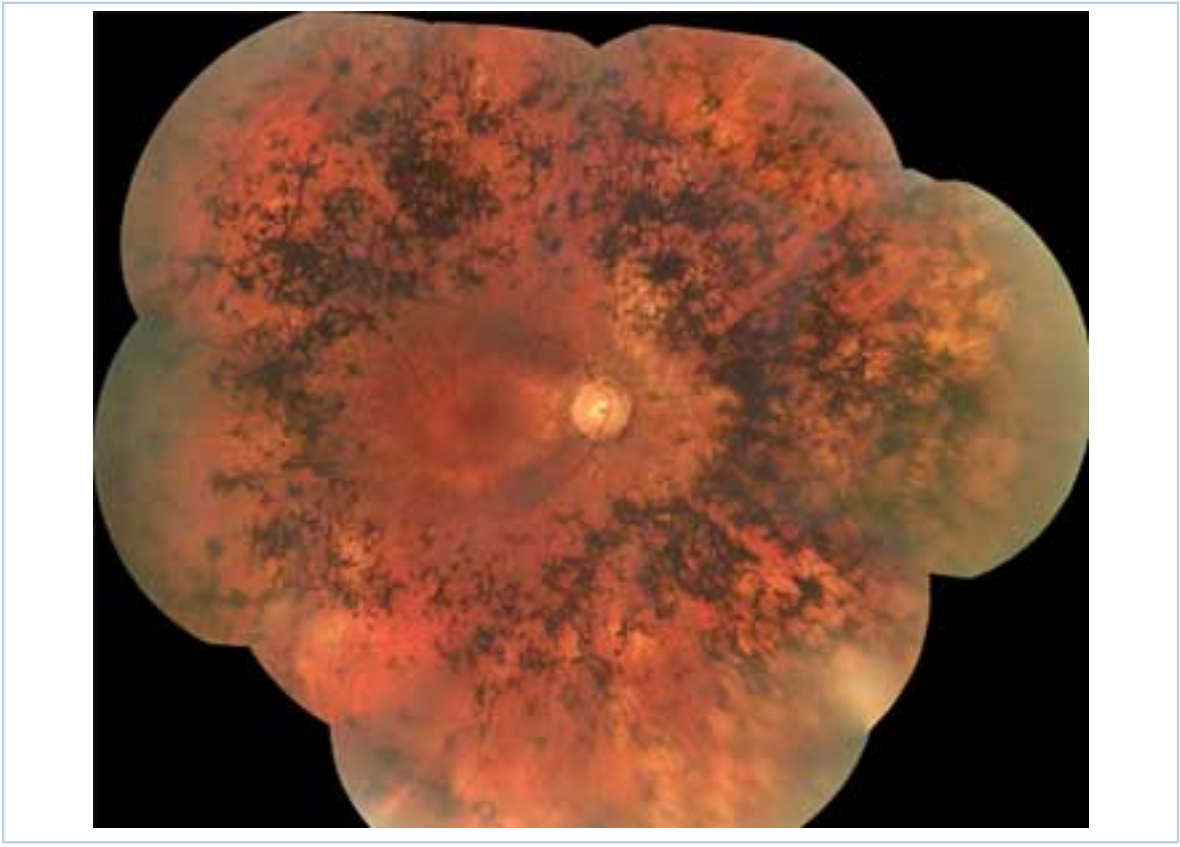
From the Oregon Retinal Degeneration Center collection

- Retinal pigment epithelium degeneration is a key feature. Bone spicule pigmentation results from migration of retinal pigment epithelial cells into the retina, often surrounding retinal vessels. The appearance is of black dots or clumps of dots on the retina.



Bone spicules

From the Oregon Retinal Degeneration Center collection



Retinitis pigmentosa

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- Optic nerve head drusen: optic disc drusen are congenital and developmental anomalies of the optic nerve head. They are formed by calcific degeneration in some of the axons of the optic nerve. They are often an incidental finding but are more common in patients with RP. With time they can grow and impinge on the retinal nerve fibre layer and cause visual field defects. A small cup-to-disc ratio may indicate buried optic drusen.
- CMO: this is a common complication of RP and it appears like a tiny cyst in the fovea when viewed on high magnification of the fundus using a slit lamp. These are unlikely to be visualised by the non-ophthalmologist.
- Mild vitreous cells: these may be observed when viewed by an expert on slit-lamp examination. More significant inflammation should prompt suspicion for other diseases that can mimic RP.
- Coats-like retinopathy: a rare sign seen in certain patients with RP. It is characterised by peripheral areas of retina with abnormal vascular telangiectasia, which can leak and cause retinal exudation.

Keratoconus and glaucoma

- More common in patients with RP than in the general population.
- Keratoconus is visual distortion due to structural changes in the cornea, which gives it a more conical appearance. This can affect visual acuity, and night vision is often particularly poor.
- Glaucoma is the result of either acute or chronic elevation of intraocular pressure causing damage to the optic nerve. It can be detected by measuring intraocular pressure.

Investigations

The number of tests varies between centres, but all patients with suspected RP should have visual fields tested and an electroretinogram (ERG).

- Examination of visual fields: can be performed in different ways, and tests depend on whether the stimulus is static or moving (kinetic). The Goldmann kinetic perimetry test has historically been the method for assessing a patient's full visual field. It provides essential information regarding function, such as ability to drive safely. However, Octopus 900 perimetry is now capable of performing both kinetic and static full field perimetry. Mid-peripheral visual field defects are one of the pathognomonic features of RP. Defects can start as islands in the mid-periphery, expand to form crescents, and finally result in a complete ring scotoma. In time, these ring scotomas can enlarge, ultimately leaving patients with a diminishing tunnel field of vision.
- Full field ERG: this measures the electrical response of cells in the retina, including photoreceptors. It involves placing electrodes on the cornea or skin around the eye and measuring the amplitude of responses to standard stimuli such as a flash of light. Abnormal ERGs are an essential feature of RP. A decrease in amplitude and an increase in latency can be seen in both the dark-adapted and light-adapted ERGs.

Further tests that may be carried out to confirm the diagnosis include elevated dark-adapted threshold and optical coherence tomography (OCT). These are not carried out routinely at all centres.

- Elevated final dark-adapted threshold involves placing a patient in a completely dark room and determining the dimmest light that can be perceived. It replicates symptomatic reports of difficulty adapting to darkened environments.
- OCT of the retina is a non-invasive imaging system using the detection of optical light reflection to build up a 3-dimensional picture. It is non-contact and does not involve any radiation exposure. It can reveal retinal atrophy and is the preferred method for determining the presence of CMO. This should be considered in any patient with decreased central visual acuity suggestive of CMO.
- Adaptive optics imaging is new technology that allows for high-resolution imaging of the photoreceptor mosaic by compensating for corneal and lenticular aberrations during imaging. Custom-built systems are capable of resolving individual cones and rods in some individuals.
- Genetic testing for RP involves drawing blood from the patient and sending it to a laboratory that tests for specific mutations for this disease. Genetic testing is available for only a subset of the total genes in RP, and even testing of known genes is not always completely sensitive. It is most effective when a particular gene is suspected. This is only performed in certain people after consultation with a clinical geneticist when the probability of identifying the responsible gene is good. This would confirm the diagnosis. Newer technologies using whole exome sequencing are now becoming available and allow testing of many genes at one time. Additionally, these technologies offer the hope of finding new genes for RP.
- Wide-field fundus autofluorescence (FAF), an imaging modality, identifies areas of the fundus with irregular distribution of lipofuscin and other fluorophores in the retinal pigment epithelium (RPE) cell monolayer. Patterns of irregular FAF in the posterior pole and peripheral retina are associated with specific hereditary retinal degenerations, and may be useful in monitoring disease progression and response to novel therapies. Guidelines from the American Academy of Ophthalmology give recommendations for the clinical assessment of patients with inherited retinal degenerations.[23]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Many patients with X-linked or dominant RP will have FHx of RP. Autosomal recessive inheritance may or may not reveal FHx of retinal degeneration. RP is usually an isolated finding but can be a feature of some rare genetic disorders in combination with other symptoms such as balance problems, hearing loss, and renal disease.

decreased peripheral vision (common)

- Key feature of the more common rod-cone form of RP. Visual field loss often goes unnoticed until it reaches a moderate stage due to the overlapping visual fields of each eye.

night blindness (common)

- Usually one of the earliest symptoms. Many patients report giving up driving at night due to difficulty seeing.

impaired dark adaptation (common)

- Patients often report difficulty entering movie theatres or, conversely, problems when going outside into a brightly lit environment.

decreased central acuity (common)

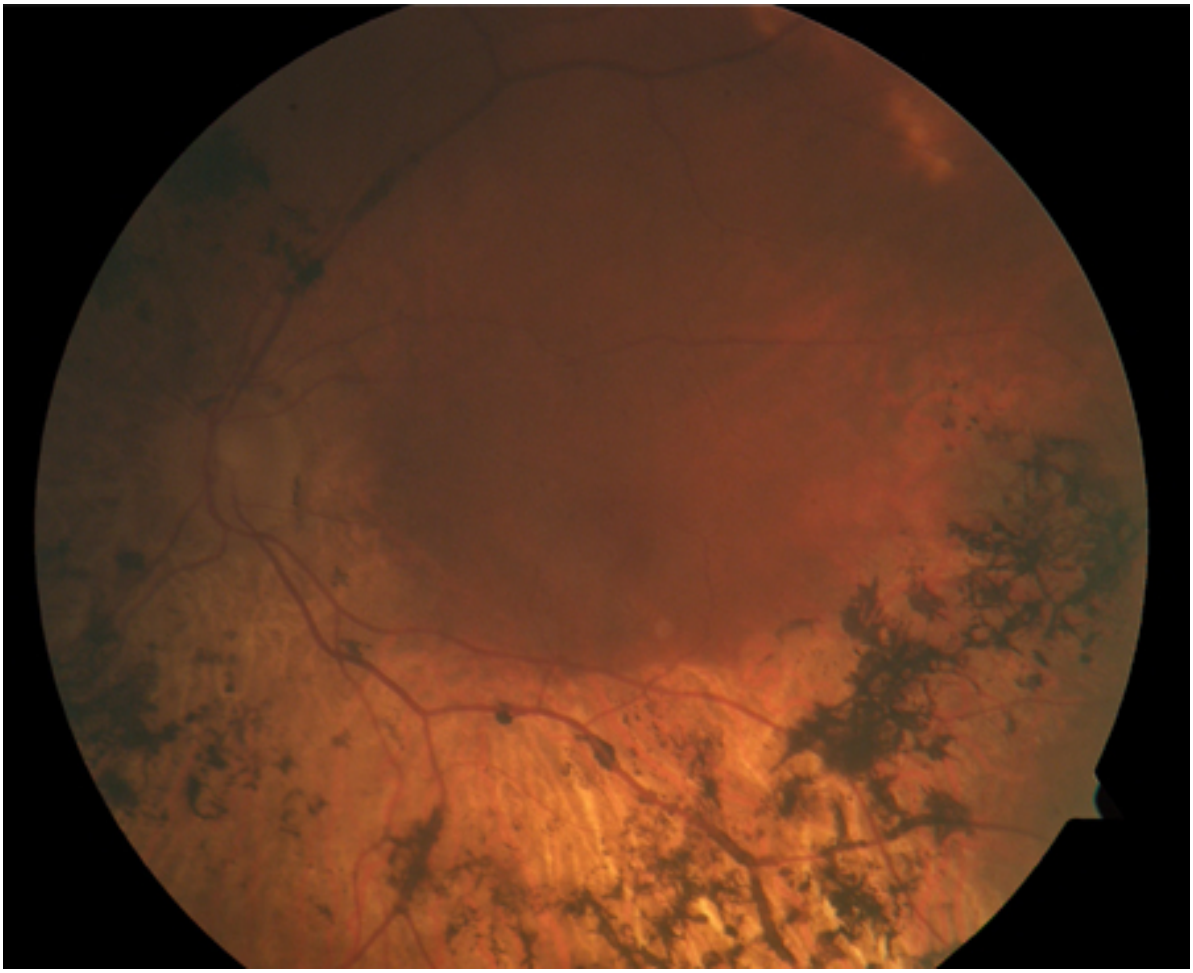
- Can be seen in advanced forms of the more common rod-cone dystrophy form or earlier if cystoid macular oedema develops. Cone-rod forms of RP can present with early decrease in central acuity.

atrophy of retinal pigment epithelium (common)

- A key feature. Depending on the mutation involved, can occur through primary retinal pigment epithelial degeneration or secondary to photoreceptor degeneration.

bone spicule pigmentation (common)

- A key feature, resulting from migration of retinal pigment epithelial cells into the photoreceptor layer of the retina, often surrounding retinal vessels.



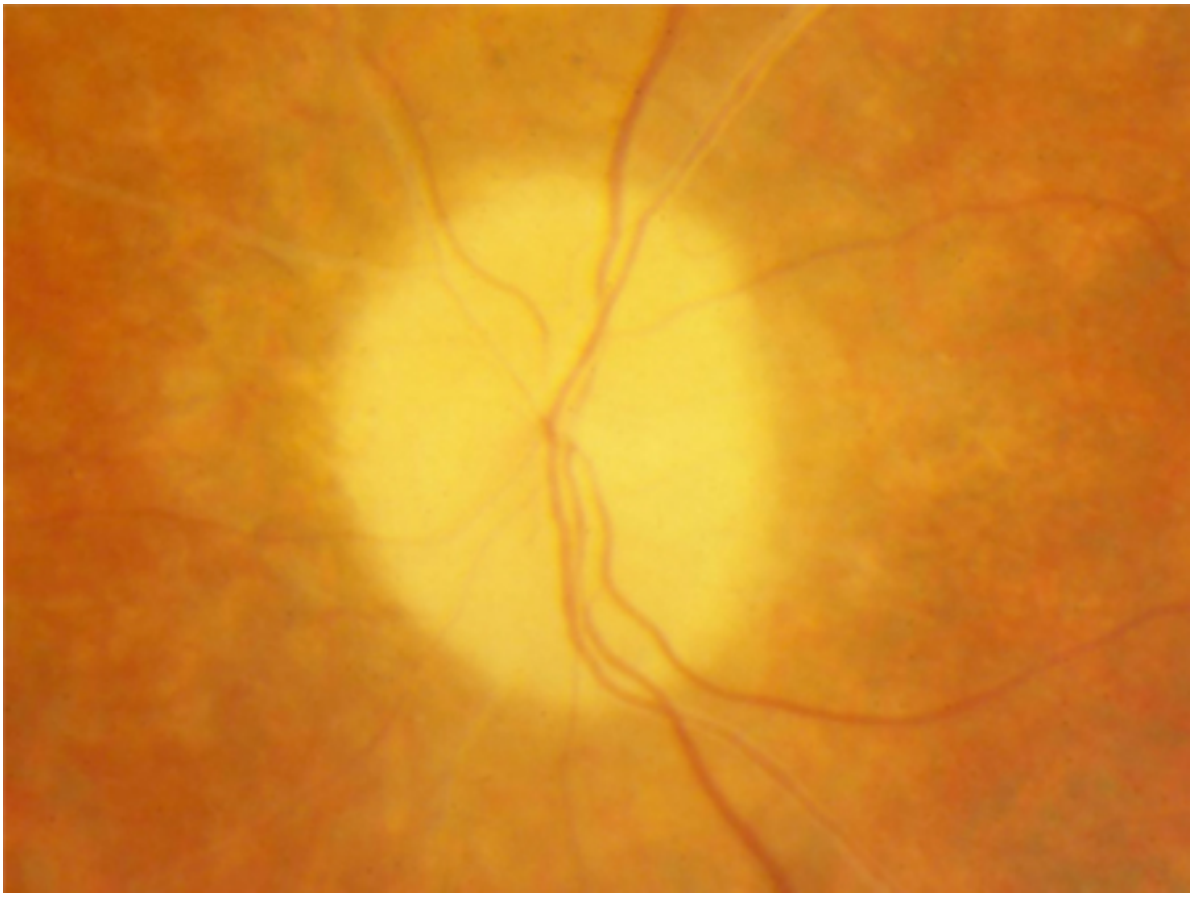
Bone spicules

From the Oregon Retinal Degeneration Center collection

Other diagnostic factors

waxy pale optic nerve (common)

- Thought to be caused by gliosis around the optic nerve.



Waxy pallor and vascular attenuation

From the Oregon Retinal Degeneration Center collection

photopsias (common)

- Continual flashes of light, and are commonly experienced. It is important to distinguish these photopsias from flashes due to a retinal detachment or association with migraine.

refractive error (common)

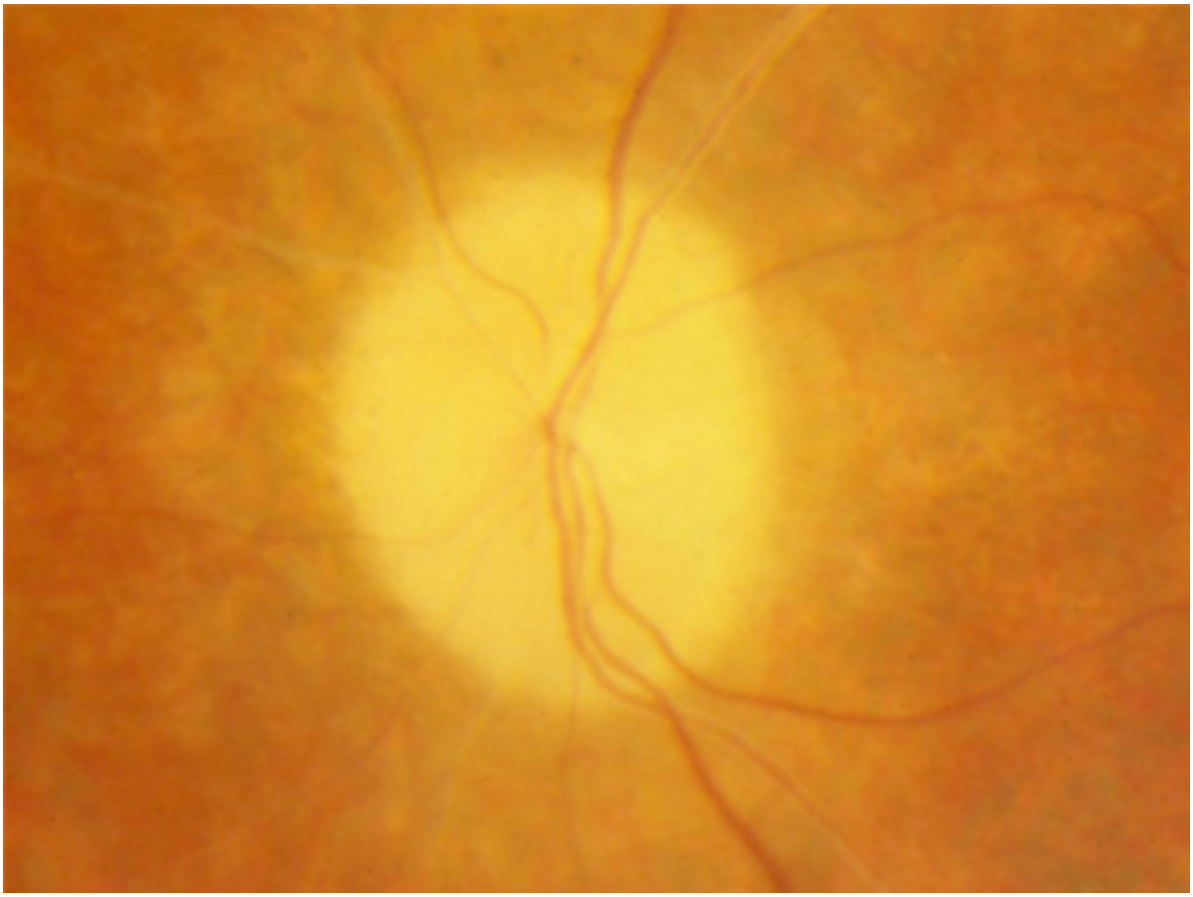
- In early severe forms of RP, such as Leber's congenital amaurosis, hyperopia predominates. In later-onset forms, myopia and astigmatism are more common.

cataracts (common)

- Early development of posterior polar or subcapsular cataracts is especially common.

retinal vascular attenuation (common)

- Thought to be secondary to retinal atrophy. Its presence can help distinguish RP from choroideraemia, which is characterised by normal retinal vessels and atrophy of choroidal vessels.



Waxy pallor and vascular attenuation

From the Oregon Retinal Degeneration Center collection

cystoid macular oedema (common)

- A common complication. Optical coherence tomography is the best method of detection.

vitreous cells (common)

- Mild vitreous cells are often observed on slit-lamp examination of the fundus. More significant inflammation should prompt suspicion for other diseases that can mimic RP.

glare from bright lights (common)

- May be a problem in advanced disease.

abnormal colour vision (uncommon)

- Can be seen early in cone-rod dystrophies or later in rod-cone dystrophies. Usually affects the blue-yellow axis, which helps distinguish it from the more common X-linked red-green colour blindness, present in about 10% of the male population.

keratoconus (uncommon)

- More common in patients with RP.

glaucoma (uncommon)

- More common in patients with RP.

optic nerve head drusen (uncommon)

- Congenital and developmental anomalies of the optic nerve head. Formed by calcific degeneration in some optic nerve axons. Often found incidentally, but more common in patients with RP. With time can grow and impinge on the retinal nerve fibre layer and cause visual field defects. A small cup-to-disc ratio may indicate buried optic drusen.

Coats-like retinopathy (uncommon)

- A rare sign in certain patients with RP. Characterised by peripheral areas of retina with abnormal vascular telangiectasias, which can leak and cause retinal exudation.

Leber's congenital amaurosis (uncommon)

- This is a severe subtype of RP, and can present in infancy with decreased vision, sluggish pupils, and nystagmus.[5]

Risk factors

Strong

family history

- Inheritance can be autosomal dominant, autosomal recessive, X-linked, or, rarely, mitochondrial or digenic. A family history can help to elicit the mode of inheritance. The prevalence of each type varies in different regions. Most patients who inherit genetic mutations will exhibit symptoms of the disease, but the severity can vary greatly, especially in autosomal dominant forms of the disease, which can show variable penetrance and expressivity.[19]

presence of an associated syndrome

- RP is usually an isolated finding but can be found as a feature of some rare genetic disorders in combination with other symptoms such as balance problems, hearing loss, and renal disease. Syndromes include Usher's, Bardet-Biedl, Alstrom's, Joubert's, Senior-Loken, neuronal ceroid-lipofuscinosis, Kearns-Sayre, Bassen-Kornzweig disease (abetalipoproteinaemia), and infantile and adult Refsum's disease.[20] [21]

Investigations

1st test to order

Test	Result
assessment of visual acuity • May be measured using a Snellen chart and can be varied depending on the type and severity of RP. It is essential to record visual acuity for both functional and legal implications and to track progress. Refractive errors may be noted, and sight may be improved by glasses if this is corrected, although underlying RP remains.	**variable**
full field perimetry • Goldmann kinetic perimetry has historically been the method for assessing a patient's full visual field; however, Octopus 900 perimetry is now capable of performing both kinetic and static full field perimetry. • Defects can start as islands in the mid-periphery, expand to form crescents, and finally result in a complete ring scotoma. In time, ring scotomas can enlarge, leaving patients with a diminishing tunnel field of vision.	**mid-peripheral visual field defects**
full field electroretinogram (ERG) • Abnormal ERGs are an essential feature of RP. Decreased amplitude and increased latency can be seen in both the dark-adapted and light-adapted ERGs. Useful in both diagnosis and monitoring progression of disease. ERGs are almost always decreased in patients with RP, but decreased ERGs alone do not make diagnosis because many other non-degenerative inherited diseases can present with ERG changes. ERGs should be measured according to the standards described by the International Society for Clinical Electrophysiology of Vision (ISCEV).[24] Each laboratory must establish normal values from a suitable age-matched population.	**decreased scotopic a-wave and b-wave with increased b-wave latencies; decreased photopic a-wave and b-wave, decreased amplitude on photopic 30 Hz flicker with increased latency**

Other tests to consider

Test	Result
elevated final dark-adapted threshold • Final dark-adapted threshold is measured by fully dark-adapting patients and then measuring the dimmest intensity of light that they can perceive.	**mirrors the symptomatic reports of impaired dark adaptation**
optical coherence tomography (OCT) • Should be considered in all patients with worsened central visual acuity. OCT of the retina can reveal retinal atrophy and is especially useful for determining the presence of cystoid macular oedema.	**retinal atrophy, possible presence of cystoid macular oedema**
genetic testing • Available for only a subset of the total genes in RP, and even testing of known genes is not always completely sensitive. Most effective when a particular gene is suspected. Performed only in certain people after consultation with a clinical geneticist when probability of identifying the responsible gene is good. May also be indicated if an underlying syndrome is suspected. Guidelines from the American Academy of Ophthalmology give specific recommendations about genetic testing.[25]	**confirmation of specific gene defect or identification of underlying syndrome**
adaptive optics imaging • Adaptive optics imaging is new technology that allows for high-resolution imaging of the photo-receptor mosaic by compensating for corneal and lenticular aberrations during imaging. Custom-built systems are capable of resolving individual cones and rods in some individuals.	**may reveal degeneration of rods and cones**
wide-field fundus autofluorescence (FAF) • Relatively new imaging modality that identifies areas of irregular lipofuscin distribution in the retinal pigment epithelium (RPE) cell monolayer of the posterior pole and peripheral retina. Irregular patterns of FAF correlate with retinal disease, retinal pigment changes, and retinal atrophy. Specific patterns of abnormal FAF are useful in the diagnosis of inherited retinal degenerations. Guidelines from the American Academy of Ophthalmology give recommendations for the clinical assessment of patients with inherited retinal degenerations.[23]	**correlates with disease-specific patterns of retinal degeneration**

Emerging tests

Test	Result
whole exome sequencing • Whole exome sequencing is now becoming available and allows testing of many genes at one time. This technology offers the hope of finding new genes for RP.	**may reveal novel genes for RP**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Congenital rubella	• Granular pigmentary changes on funduscopy. These tend to be more granular than the bone spicules seen in RP, but funduscopy alone cannot reliably distinguish the difference. Congenital deafness may also be present. Other features include microcephaly, intellectual disability, microphthalmia, and congenital cataracts.	• Normal electroretinogram (ERG). • Positive blood test for rubella antibodies confirms infection.
Syphilis	• Pigmentary changes, evidence of retinal vasculitis (such as sheathed vessels), and placoid (plate-like) areas of chorioretinal inflammation. Other features include a firm painless chancre at the site of infection, skin rash, and general symptoms of fatigue, weight loss, and lymphadenopathy. • In congenital syphilis there may be a rash, swollen liver, anaemia or jaundice, and rhinitis.	• Serum Venereal Disease Research Laboratory test (VDRL) will be positive. • Serum rapid plasma regain test (RPR) will be positive.
Vitamin A deficiency	• Presents with night blindness and malnutrition. Particularly seen in pregnant women in developing countries.	• Reversibility of night blindness with high-dose vitamin A (retinol) supplementation.
Ophthalmic artery occlusion	• Sudden-onset, severe, unilateral but painless loss of vision. May have history of amaurosis fugax.	• Fundus angiography showing impaired choroidal perfusion. • Carotid Doppler scans demonstrating high-risk plaques.
Posterior uveitis	• A greater degree of inflammation and signs of chronic inflammation such as posterior synechia, choroidal infiltrates in active phase, asymmetrical changes, and presence of vascular cuffing indicating vasculitis.	• Elevated WBC/CRP and ESR, non-specific markers of inflammation. • Further tests depend on likely underlying cause: Lyme titre (can cause uveitis in endemic areas); PPD test (positive for patients with

Condition	Differentiating signs / symptoms	Differentiating tests
		suspected tuberculosis); antinuclear cytoplasmic antibodies positive in 90% of patients with granulomatosis with polyangiitis.
Retinal detachment	• May have history of risk factors, including ocular trauma, previous detachment, or cataract surgery. History of sudden-onset central visual loss, possibly with preceding flashes of light. On examination there is subretinal fluid and cystic degeneration in an asymmetrical pattern.	• Slit-lamp examination and indirect ophthalmoscopy: retinal detachment; retinal break; vitreoretinal pathology (traction or presence of pigment).
Diffuse unilateral subacute neuroretinitis	• Usually a unilateral condition; patient may report floaters or conjunctivitis in the early stages with mild visual loss. More severe visual loss and central scotomas may be evident in later disease. On funduscopic examination crops of yellow creamy-appearing choroidal infiltrates can be seen in the active phase, caused by a nematode worm. Late changes are indistinguishable from RP.	• Funduscopic examination is usually sufficient. • Scanning laser ophthalmoscope: an infrared laser that is good for identifying live worms in young patients.
Autoimmune retinopathy	• Symptoms depend on whether rods or cones are predominantly affected and are clinically indistinguishable from RP. On funduscopic examination there is retinal vascular atrophy but without pigmentary changes.	• Positive serum anti-retinal antibodies.
Congenital stationary night blindness	• Relatively normal-appearing fundus; night blindness is non-progressive. High myopia and nystagmus are frequent features.	• Decreased b- to a-wave ratio on ERG. • Genetic testing confirms diagnosis.
Fundus albipunctatus	• Also presents with symptoms of night blindness but on	• Elevated final dark-adapted threshold: impaired dark adaptation that recovers with prolonged time in the dark.

Condition	Differentiating signs / symptoms	Differentiating tests
	examination there are small white spots on the retina.	• Genetic testing confirms diagnosis.
Achromatopsia	• Typically diagnosed at about 6 months of age. Decreased visual acuity with photophobia and complete colour blindness. Nystagmus becomes less noticeable with age.	• Severely diminished photopic ERG but normal scotopic ERG. • Genetic testing confirms diagnosis.
X-linked retinoschisis	• Variable history can be mild gradual loss of central vision or sudden severe visual loss with a vitreous haemorrhage. Foveoschisis (splitting of the retinal layers) can appear similar to cystoid macular oedema on funduscopy. Peripheral retinal schisis may also be seen.	• Decreased b- to a-wave ratio on ERG.
Choroideraemia	• X-linked disorder, so usually only males are affected. Extensive chorioretinal atrophy with sparing of the macula until late stages. Normal-appearing retinal vessels and optic nerve.	• Genetic testing confirms diagnosis.
Gyrate atrophy	• Total blindness usually occurring in middle age (40-60 years). • Peripheral areas of chorioretinal degeneration in gyrate patterns. • Associated with early-onset cataract requiring surgery by 18-20 years of age.	• Elevated blood ornithine levels. • Genetic testing confirms diagnosis.

Screening

RP is a heterogeneous disease caused by mutations in over 100 genes. Screening of an asymptomatic population without a family history of disease is not useful or cost-effective. Screening of asymptomatic family members by clinical evaluation may follow an informed discussion between patient and physician. Due to the lack of effective treatment for most forms of RP, the testing of asymptomatic children with a family history of RP must take into account the psychological ramifications versus the benefit of such testing. In general, testing is not recommended unless children manifest symptoms. Furthermore, due to variable age of onset even within families, a normal test in a child does not exclude the diagnosis.

For asymptomatic adults who are 65 years or older, the US Preventive Services Task Force concluded that the current evidence is insufficient to recommend for or against screening for impaired visual acuity.[26] [27]

Approach

While RP has no cure, many patients can significantly benefit from optimising their remaining vision. All patients should undergo a sight test to have their refractive ability checked. Many patients will benefit from assistance from a low-vision consultant (either an ophthalmologist or optometrist), who can help them obtain various visual aids such as glasses, magnifiers, or telescopes.

Vitamin A (retinol) and docosahexaenoic acid (fish oils)

High doses of oral vitamin A (retinol) slow the rate of decline of retinal function, as measured by electroretinogram responses.[28] Vitamin A (retinol) supplementation is routinely recommended by some centres but opposed by others. Patients with cone-rod dystrophy should avoid vitamin A (retinol), due to the potential hazards that have been observed in mice with ABCA4 mutations, which had more accumulation of phototoxic A2-E (N-retinylidene-N-retinylethanol-amine) compounds.[29] A2-E is detrimental to retinal pigment epithelial (RPE) cell function by a variety of mechanisms, including inhibition of lysosomal degradative capacity, loss of membrane integrity, and phototoxicity.[30] Long-term high-dose vitamin A (retinol) supplementation seems safe for other variants of RP, but it can elevate liver enzymes and triglycerides and increase the risk of osteoporosis.[31] Patients receiving vitamin A (retinol) should be monitored by their physician for these potential adverse effects. The decision to use or not use vitamin A (retinol) will depend on the centre and patient preference. The use of vitamin A (retinol) has not been studied in children with RP and therefore is usually avoided. Beta-carotene (a precursor of vitamin A) has been suggested to be beneficial in the treatment of retinitis pigmentosa, but these results are still preliminary and require further study before a formal recommendation can be made.[32] [33]

Docosahexaenoic acid (DHA) is a fatty acid present in high concentrations in the photoreceptors and may be a precursor for neuroprotective factors. Two randomised studies in patients with RP did not show a significant benefit of DHA supplementation.[34] [35] One 4-year single-site phase II clinical trial evaluating the efficacy of DHA in patients with X-linked RP also showed no therapeutic benefit in slowing the rate of cone electroretinography (ERG) functional loss.[36] Many centres still recommend DHA supplementation due to the theoretical benefit, low risk, and minimal side effect profile.[37]

Lutein

Lutein is a carotenoid, found in the human retina and dark green leafy vegetables. A randomised controlled trial examined the efficacy of lutein to slow visual field loss in patients with RP who were taking vitamin A.[38] The study showed a reduction in the loss of mid-peripheral visual fields.[38] However, others have challenged the conclusions of this study.[39]

Cystoid macular oedema (CMO)

Carbonic anhydrase inhibitors such as topical dorzolamide or oral acetazolamide are effective for treatment of CMO in some patients.[40] [41] Patients must often remain on these medicines for several months before an effect is seen. The effect can wear off with time, and some patients do not benefit. Furthermore, some patients cannot tolerate the adverse effects of these medicines such as paraesthesias and frequent urination.

Cataracts

Posterior subcapsular cataracts are especially common and often affect central vision. Cataract extraction can benefit many patients, especially if the degeneration has not involved the central macula. It is

important to rule out the presence of cystoid macular oedema before cataract extraction because this can worsen after surgery. Occult weak zonules require appropriate surgical precautions to minimise the risks of complications during cataract surgery.

Gene replacement therapy

Voretigene neparvovec, a recombinant adeno-associated virus vector carrying a normal copy of the RPE65 gene, has demonstrated improved vision in patients with Leber congenital amaurosis secondary to mutations in the RPE65 gene when injected into the subretinal space.[42] [43] [44] [45] [46] [47] A subsequent phase 3 trial showed improved functional vision in patients with RPE65-mediated inherited retinal dystrophy who were treated with the AAV vector-based gene therapy, voretigene neparvovec.[48] Follow-up studies of the phase 3 trial and an earlier phase 1 trial demonstrated a consistent safety profile and developing longer-term efficacy.[49] Voretigene neparvovec is approved for the treatment of biallelic RPE65 mutation-associated retinal dystrophy. It is available through the NHS in the UK.[50] Voretigene neparvovec is not only the first approved treatment for retinal dystrophy, but is the first approved gene therapy for the eye. Other clinical trials for Usher syndrome type 1 due to mutations in MYO7A, and X-linked RP due to mutations in RPGR are underway.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)			
all patients			
		1st	assessment of refractive ability ± visual aids
		adjunct	vitamin A (retinol) supplementation
		adjunct	fish oils
		adjunct	lutein
	with cataracts	adjunct	surgery
	with cystoid macular oedema	adjunct	carbonic anhydrase inhibitor
	with biallelic RPE65 mutations	adjunct	voretigene neparvovec

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

all patients

1st **assessment of refractive ability ± visual aids**

» An assessment with a low-vision consultant (ophthalmologist or optometrist) is recommended to accurately determine and optimise visual ability. Visual aids such as glasses, magnifiers, or telescopes may be helpful.

adjunct **vitamin A (retinol) supplementation**

Treatment recommended for SOME patients in selected patient group

Primary options

» vitamin A: adults: 15,000 units orally once daily

» Routinely recommended by some centres but opposed by others.

» Should be avoided in patients with cone-rod dystrophy based on more rapid retinal degeneration seen in experiments with mice.

» Long-term high-dose vitamin A (retinol) supplementation seems safe but can elevate liver enzymes and triglycerides and increase the risk of osteoporosis.[31] Patients receiving vitamin A (retinol) should be monitored by their physician for these potential adverse effects.

» The use of vitamin A (retinol) has not been studied in children with RP and therefore is usually avoided.

adjunct **fish oils**

Treatment recommended for SOME patients in selected patient group

» Three randomised studies in patients with RP did not show a significant benefit, but many centres still recommend supplementation due to the low risk and potential benefit.[34] [35] [36] [37]

adjunct **lutein**

Treatment recommended for SOME patients in selected patient group

Primary options

Acute

» lutein: consult specialist for guidance on dose

» Is a carotenoid, found in the human retina and dark green leafy vegetables. A randomised controlled trial examined the efficacy of lutein to slow visual field loss in patients with RP who were taking vitamin A.[38] The study showed a reduction in the loss of mid-peripheral visual fields.[38] However, others have challenged the conclusions of this study.[39]

with cataracts — **adjunct** — **surgery**

Treatment recommended for SOME patients in selected patient group

» Cataract extraction can benefit many patients, especially if the degeneration has not involved the central macula. It is important to rule out the presence of cystoid macular oedema before cataract extraction because this can worsen after surgery. Occult weak zonules require appropriate surgical precautions to minimise the risks of complications during cataract surgery.

with cystoid macular oedema — **adjunct** — **carbonic anhydrase inhibitor**

Treatment recommended for SOME patients in selected patient group

Primary options

» dorzolamide ophthalmic: (2%) 1 drop into the affected eye(s) three times daily

OR

» acetazolamide: 500 mg orally (extended-release) once daily initially, adjust dose according to response

» Inhibitors such as topical dorzolamide or oral acetazolamide are effective at treating cystoid macular oedema in some patients. May need several months of treatment before an effect is seen.[40] [41]

» Effects can wear off with time, and some patients do not benefit. Furthermore, many patients cannot tolerate the adverse effects of these medicines such as paraesthesias and frequent urination.

with biallelic RPE65 mutations — **adjunct** — **voretigene neparvovec**

Treatment recommended for SOME patients in selected patient group

Primary options

Acute

» voretigene neparvovec subretinal: consult specialist for guidance on dose

» Voretigene neparvovec, an adeno-associated virus vector carrying a normal copy of the RPE65 gene, has been shown to improve functional vision in patients with RPE65-mediated inherited retinal dystrophy.[48] It is administered as a subretinal injection. Patients must have sufficient viable retinal cells to be considered for this treatment.[48]

Emerging

General considerations

Current strategies for novel therapies include neuroprotection, small-molecule medications, stem-cell based therapy, and retinal prosthesis. As with all emerging therapies, care must be taken to account for biased investigator observations and placebo effect in the design of clinical trials, as well as the critical analysis of data and responsible promotion of any potential treatment.[51]

Neuroprotection

The goal of neuroprotection is to deliver factors that prevent retinal neurons from degenerating. One potentially successful compound in animal studies has been ciliary neurotrophic factor (CNTF). A study in patients with geographic atrophy due to age-related macular degeneration showed that a subgroup of patients with CNTF implants retained better visual acuity than those who received sham treatment.[52] One large multicentre sham-surgery-controlled dose-ranging clinical trial investigated the long-term delivery of CNTF to the retina, using an encapsulated cell technology, for the treatment of RP.[53] [54] Patients were randomly assigned to receive a high- or low-dose implant in one eye and sham surgery in the other eye. The results demonstrated a dose-dependent increase in retinal thickness without any serious adverse events related to either the encapsulated cell implant or the surgical procedure; however, there was no therapeutic effect on visual acuity or visual-field sensitivity after 12 months in late-stage and early-stage disease, respectively. Additional longitudinal follow-up studies using more sensitive measures will be required to assess for any long-term benefits of CNTF treatment. A trial using the calcium-channel blocker nilvadipine demonstrated preservation of central visual fields in a small group of patients with RP.[55] Similarly, topical unoprostone isopropyl has been shown to preserve macular sensitivity after one year of treatment in a small group of patients with RP.[56] Larger multicentre double-blinded clinical trials are needed to confirm the efficacy of these neuroprotective agents.

Cell- and stem cell-based therapy

Transplantation of various precursor cells into the subretinal space has been attempted to regenerate retinal pigment epithelial cells.[57] One study demonstrated the safety of injecting autologous bone-marrow-derived mononuclear cells in 5 patients with retinal degeneration; further studies are needed to evaluate the efficacy and safety of cell-based therapies.[58] With the advent of induced pluripotent stem cells (iPSCs) that can be generated from the adult cells of patients with RP, not only can future cell-based replacement strategies be tailored to each individual but also new in-vitro techniques can be developed to better understand specific disease mechanisms and test the efficacy of therapies prior to clinical trials.[59]

Electronic retinal implants

Several groups are developing silicon microelectrodes for patients with profound vision loss from diseases such as RP. Such devices convert visual stimuli into electronic signals, which can stimulate postreceptor cells in the retina.[60] [61] [62] These implants are best suited to treatment of advanced disease where patients have residual visual acuity of residual light perception in their better eye. Although there is severe attenuation of the outer retina and disorganisation of the inner retina in late-stage RP, the residual retinal nerve fibre layer is relatively preserved and susceptible to electrical stimulation, which can produce artificial vision in the form of perceived phosphenes. The US Food and Drug Administration (FDA) approved the Argus II device for use within the US in February 2013. One single-centre study evaluating 12-month safety and efficacy outcomes in 6 patients with RP showed the Argus II device to be well-tolerated.[63] With rigorous rehabilitation, the patients generally experienced limited improvement in visual function. Longitudinal studies of larger cohorts will be needed to confirm these findings.

Beta-carotene

Beta-carotene (a precursor of vitamin A) has been suggested to be beneficial in treating RP. However, results remain preliminary and require further study before a formal recommendation can be made.[32] [33]

Patient discussions

Patients are encouraged to maintain regular follow-up with an ophthalmologist and report any significant changes in their vision. [Royal College of Ophthalmologists: understanding retinitis pigmentosa] (https://www.rcophth.ac.uk/wp-content/uploads/2017/10/2017_Understanding-Retinitis-pigmentosa.pdf)

FOLLOW UP

Monitoring

Monitoring

Patients are encouraged to follow up with a consultant in retinal degeneration every 1 to 2 years. This provides the opportunity for the physician to update the patient on the state of research in the field, ensure that any refraction errors are corrected, and address any concerns. Serial visual fields are more useful for following the disease from year to year than electroretinograms. Patients who have chosen to take high doses of vitamin A (retinol) should be monitored by their primary care physician for possible adverse effects of liver damage and hyperlipidaemia.

Complications

Complications	Timeframe	Likelihood
cataracts	**variable**	**high**
Cataracts, especially posterior polar or subcapsular, are common in patients with RP. Cataract extraction can improve vision in many cases, but patients should be informed that, with severe cases of retinal degeneration, cataract extraction may not improve and may even worsen vision.		
cystoid macular oedema (CMO)	**variable**	**medium**
Common in patients with RP and has been recognised more frequently with the advent of optical coherence tomography. Patients can benefit from carbonic anhydrase inhibitors, such as acetazolamide or dorzolamide, but some patients cannot tolerate the adverse effects.		
blindness	**variable**	**medium**
RP is a slowly progressive disease, which manifests over years. Visual field loss begins in the mid-periphery and then expands to the periphery and centrally. Patients tend to lose about 50% of their remaining visual field every 5 years.[64] Good central visual acuity is often maintained even when visual fields have diminished to small tunnel fields. Complete visual loss is rare, with <0.5% of patients in one study measuring no light perception.[65]		

Prognosis

RP is a slowly progressive disease, which manifests over years. There is no cure for RP, and most treatments have been shown to only modestly slow the degeneration of the disease. While the age of onset is quite variable, the rate of degeneration once it begins seems similar across the different forms of the disease. Visual field loss begins in the mid-periphery and then expands to the periphery and centrally. Patients tend to lose about 50% of their remaining visual field every 5 years.[64] Good central visual acuity is often maintained even when visual fields have diminished to small tunnel fields. An abrupt loss of central acuity can result from the development of cystoid macular oedema and should be brought to the attention of the patient's physician. Many patients with advanced disease will eventually lose central acuity as the macular cones degenerate, but some patients will maintain central vision until the end of their life. Complete visual loss is rare with <0.5% of patients in one study measuring no light perception.[65]

The ability to drive is a common issue. Guidelines for driving vary from state to state, as well as by country. In general, measurements of central visual acuity and visual fields are incorporated in most guidelines. A consultation with a low-vision consultant is often helpful for maximising remaining vision. Additionally, many patients with RP will eventually be entitled to register as legally blind, entitling them to specific benefits and protection under the law.

Diagnostic guidelines

North America

Guidelines on clinical assessment of patients with inherited retinal degenerations (https://www.aao.org/education/guidelines-browse)

Published by: American Academy of Ophthalmology **Last published:** 2022

Pediatric eye evaluations preferred practice pattern (https://www.aao.org/education/guidelines-browse)

Published by: American Academy of Ophthalmology **Last published:** 2022

Comprehensive adult medical eye evaluation preferred practice pattern guidelines (https://www.aao.org/education/guidelines-browse)

Published by: American Academy of Ophthalmology **Last published:** 2020

Recommendations for genetic testing of inherited eye diseases (https://www.aao.org/education/guidelines-browse)

Published by: American Academy of Ophthalmology **Last published:** 2014

Online resources

1. Royal College of Ophthalmologists: understanding retinitis pigmentosa (https://www.rcophth.ac.uk/wp-content/uploads/2017/10/2017_Understanding-Retinitis-pigmentosa.pdf) *(external link)*

Key articles

- American Academy of Ophthalmology. Comprehensive adult medical eye evaluation PPP. Nov 2020 [internet publication]. Full text (https://www.aao.org/education/preferred-practice-pattern/comprehensive-adult-medical-eye-evaluation-ppp)
- American Academy of Ophthalmology. Guidelines on clinical assessment of patients with inherited retinal degenerations - 2022. Oct 2022 [internet publication]. Full text (https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with)
- Robson AG, Frishman LJ, Grigg J, et al. ISCEV Standard for full-field clinical electroretinography (2022 update). Doc Ophthalmol. 2022 Jun;144(3):165-77. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9192408) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35511377?tool=bestpractice.bmj.com)
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Images

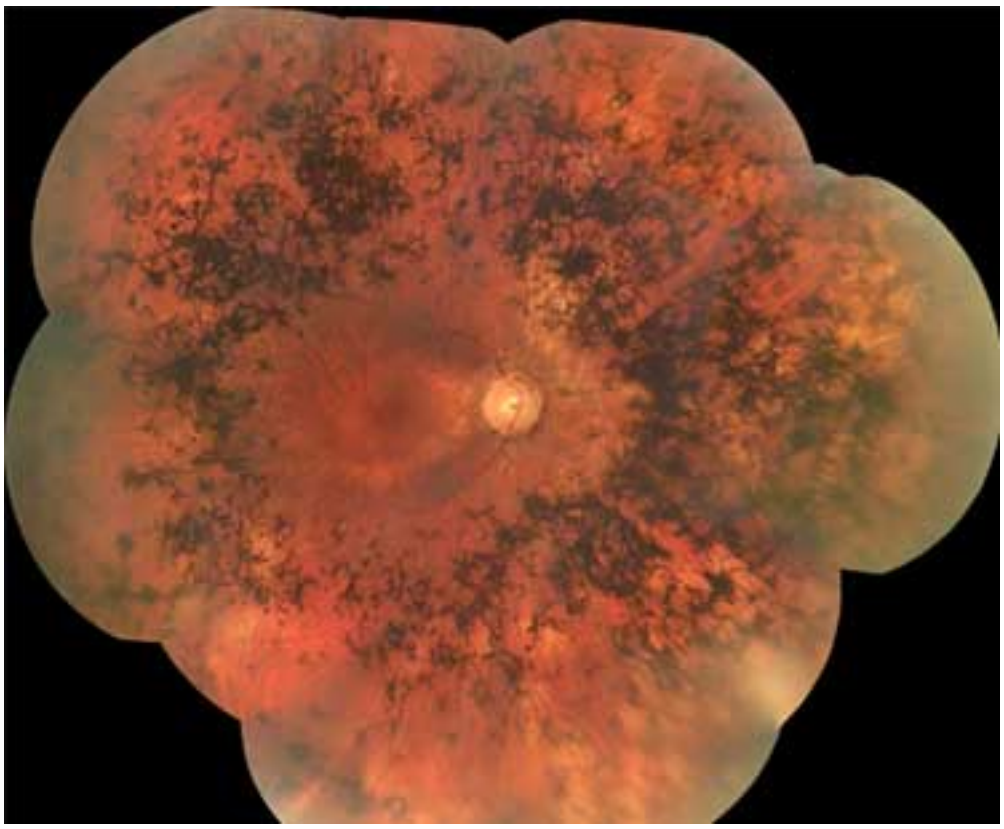

Figure 1: Retinitis pigmentosa

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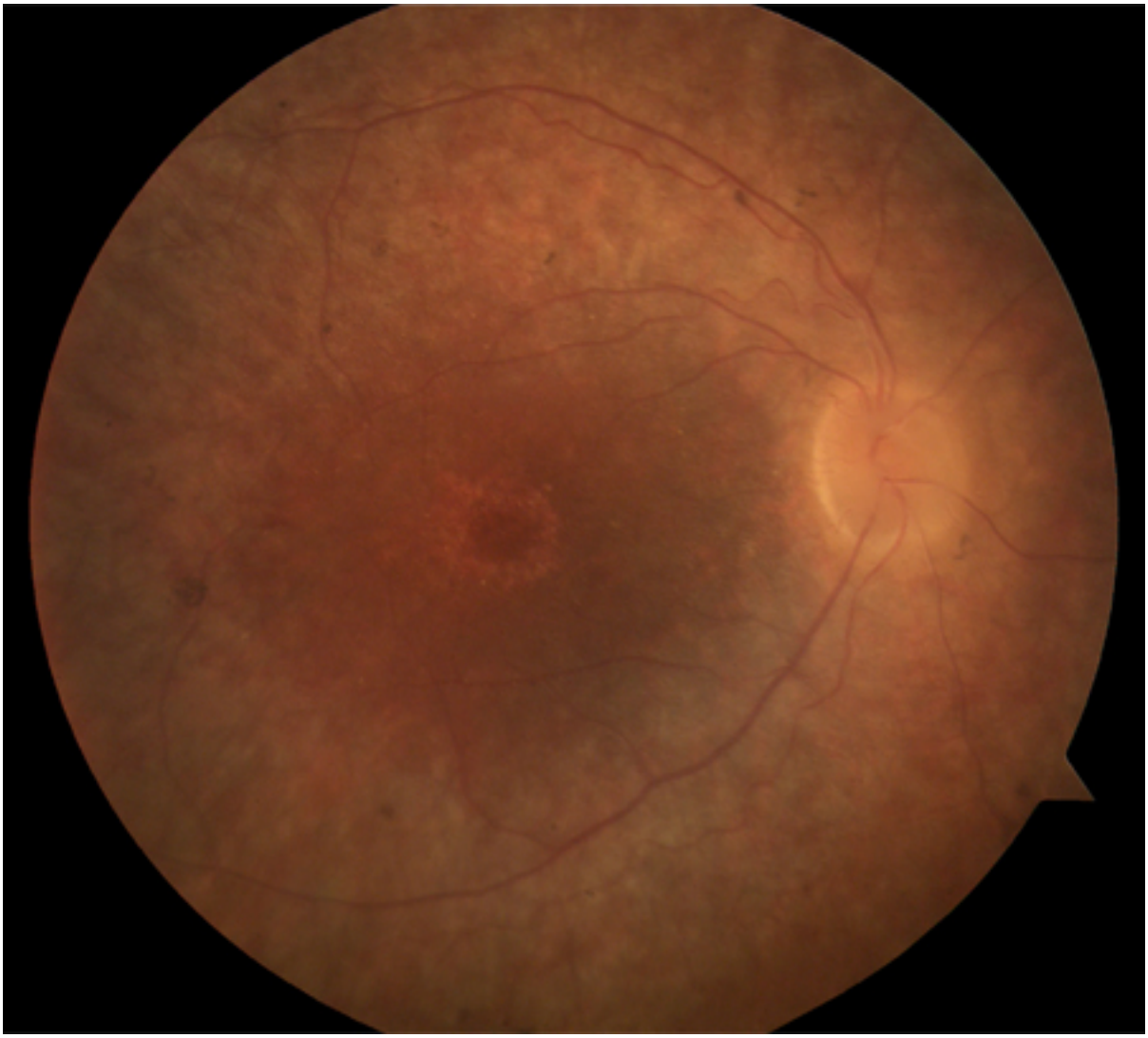

Figure 2: Bull's-eye appearance in RP

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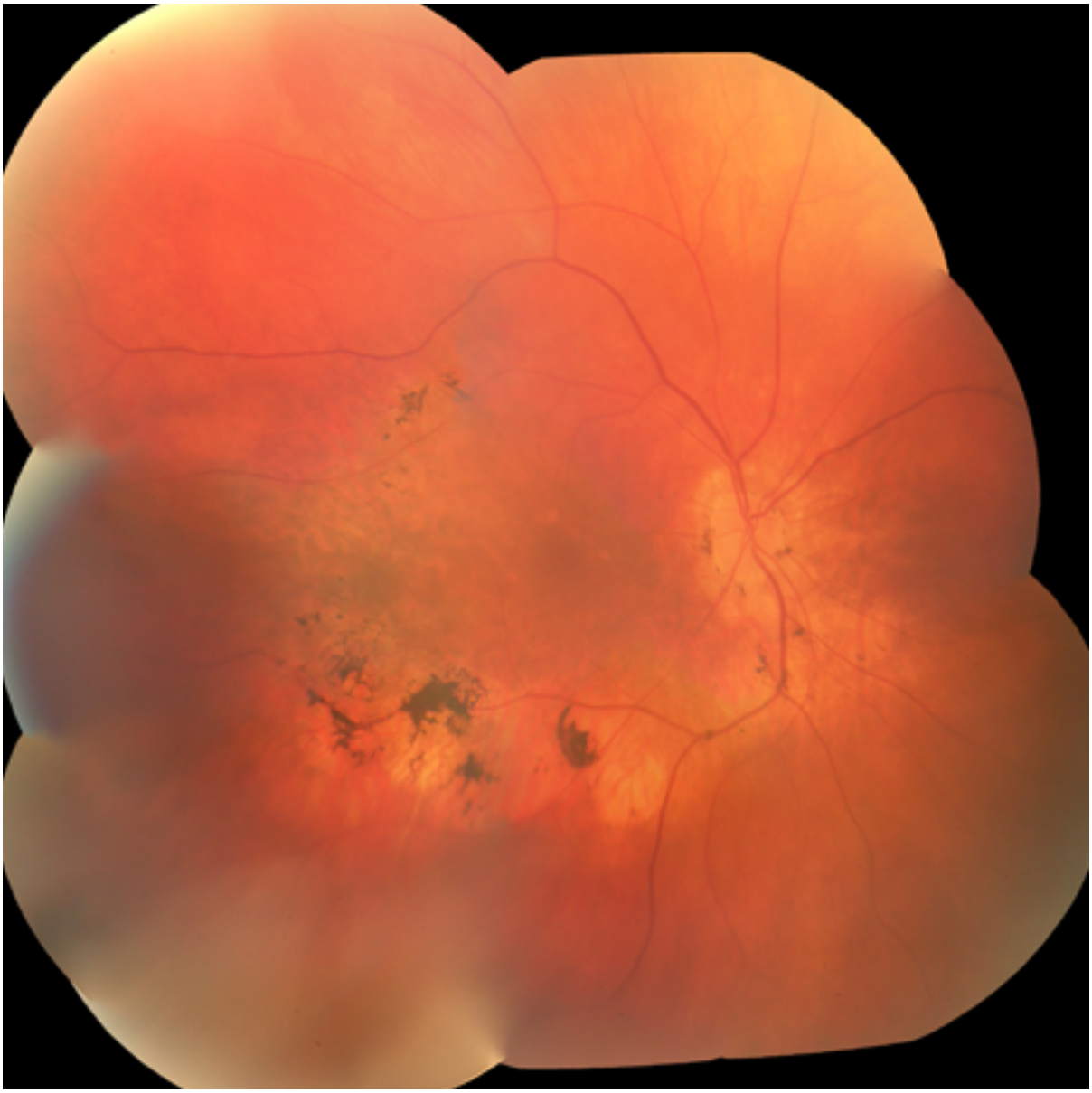

Figure 3: Sector RP

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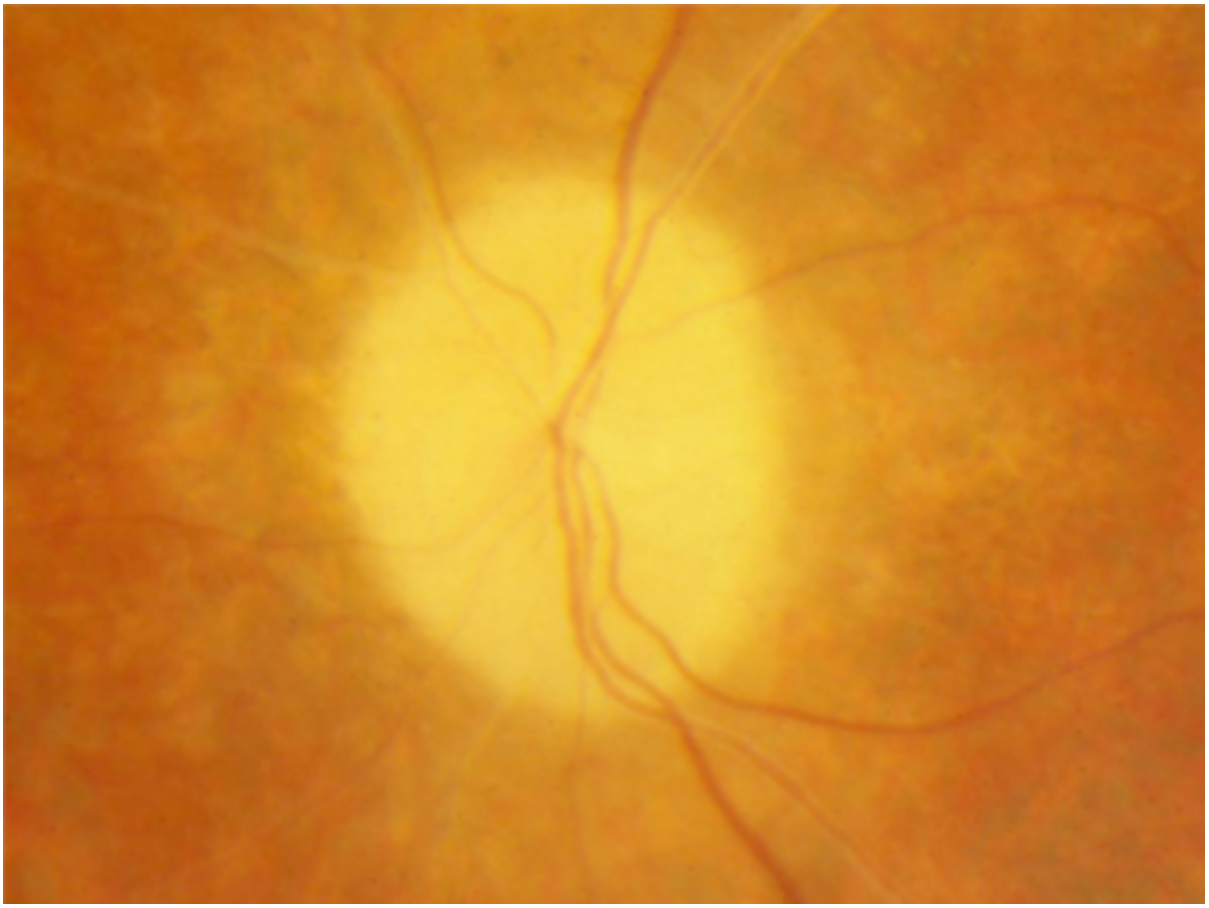

Figure 4: Waxy pallor and vascular attenuation

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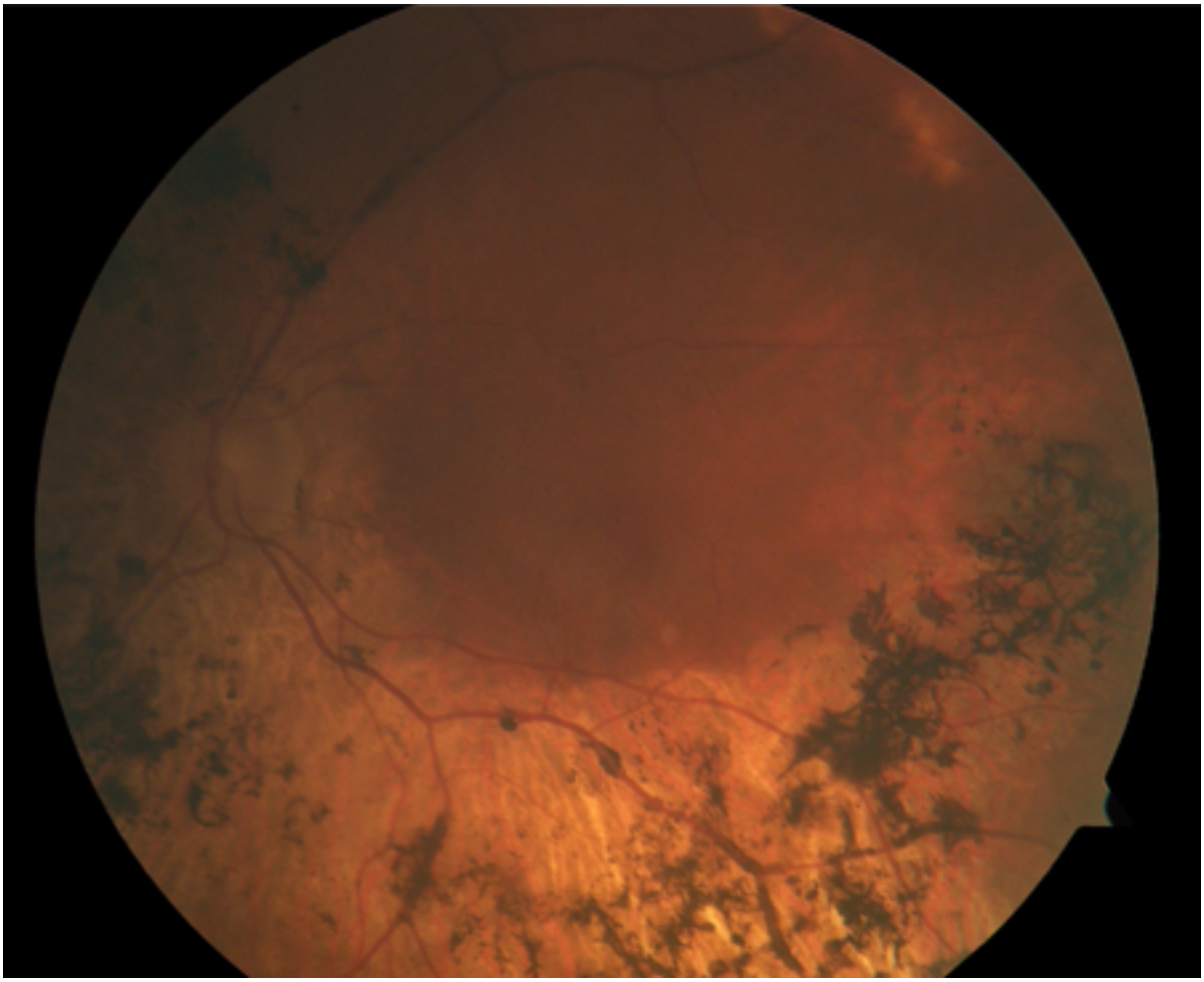

Figure 5: Bone spicules

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Figure 1 – BMJ Best Practice Numeral Style

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Mark E. Pennesi, MD, PhD

Professor
Casey Eye Institute, Oregon Health and Sciences University, Portland, OR
DISCLOSURES: MEP serves on the scientific advisory board and executive committee for the Foundation Fighting Blindness.

Paul Yang, MD, PhD

Associate Professor
Casey Eye Institute, Oregon Health and Sciences University, Portland, OR
DISCLOSURES: PY acted as a consultant for Applied Genetic Technologies Corp in 2019 and was paid for a meeting regarding XLRP gene therapy, for which there was no agreement to disseminate information.

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// Peer Reviewers:

Scott Fraser, MD, FRCS (Ed), FRCOphth

Consultant Ophthalmologist
Sunderland Eye Infirmary, Sunderland, UK
DISCLOSURES: SF declares that he has no competing interests.

Elias Traboulsi, MD

Professor of Ophthalmology
Director, Center for Genetic Eye Diseases, Cole Eye Institute, Cleveland Clinic, Cleveland, OH
DISCLOSURES: ET declares that he has no competing interests.