

Review Article

Clinical disorders affecting mesopic vision

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Abstract

Vision in the mesopic range is affected by a number of inherited and acquired clinical disorders. We review these conditions and summarize the historical background, describing the clinical characteristics alongside the genetic basis and molecular biological mechanisms giving rise to rod and cone dysfunction relevant to twilight vision. The current diagnostic gold standards for each disease are discussed and curative and symptomatic treatment strategies are summarized.

Keywords: Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome, Bothnia dystrophy, cancer associated retinopathy, congenital stationary night blindness (CSNB), enhanced S-cone syndrome (ESCS), fundus albipunctatus, melanoma associated retinopathy, Newfoundland rod–cone dystrophy, Oguchi disease, retinitis pigmentosa (RP), retinitis punctata albescens, Sorsby fundus dystrophy, vitamin A deficiency (VAD)

Introduction

The visual system allows us to see over a remarkable range of illumination. In fact, the visual system covers approximately 11 log units change in illumination (Stockman and Sharpe, 2006). We can adapt to see in bright sunlight relying purely on the cone system, as well as in near complete darkness by switching to the more sensitive rod system. The transition from photopic (light) to scotopic (dark) vision is part of what is known as dark adaptation. Mesopic vision refers to visual function at certain light levels (twilight) at which both the cone and rod systems are active. Mesopic vision covers a luminance range from approximately 32 to 0.0032 cd m⁻². It is important to remember that dark adaptation may take up to 40 min to achieve full sensitivity. Mesopic vision depends on both the external light level and the speed of the biochemical processes providing the energy to turn the rod-system fully on. Problems in mesopic vision are related to a pathological transition from photopic to scotopic vision and may present clinically as night blindness. The

importance of rod function in mesopic conditions is exemplified by the fact that the contrast sensitivity of the rod system is highest at light levels where cones are also still contributing to vision.

The term ‘night blindness’ was introduced by Bordley and, although not strictly accurate, is now in common use (Bordley, 1908). Alternative terms include ‘nyctalopia’ (seeing at night, preferred in the French literature) or ‘hemeralopia’ (seeing in the day). Strictly speaking nyctalopia means day blindness, e.g. in blue-cone monochromacy. There is much controversy around the correct use for these terms with the Anglo-Saxon literature directly opposing the French literature (Duke-Elder, 1963; Skinner, 1970; Brouzas *et al.*, 2001). In this review we refer to ‘impaired night vision’ when we use the term ‘night blindness’.

In developed societies photopic conditions extend beyond the daylight hours. Many of us will rarely employ scotopic vision and paracentral vision in the mesopic range is only needed under certain circumstances. One of the most important situations in which most of us still rely on mesopic vision (rods and cones are active) is driving. There are however certain work environments, leisure and sport activities where *peripheral* vision and hence rod signals are important, even at high levels of scene luminance, e.g. 10 cd m⁻².

Vision in the mesopic range can be impaired in a number of diseases, some of which are inherited and

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others are acquired. Here we review these disorders and try to differentiate how they may affect mesopic vision rather than pure rod (scotopic) vision. Additionally, we discuss how cone dysfunction may also impair the early transition from photopic to mesopic vision. Finally we propose a short guideline for investigating these patients including the cardinal clinical features and history, the relevant investigations and the treatment options.

Reduced vision in the mesopic range because of rod dysfunction

Here we review the human conditions in which rod dysfunction leads to *slow* dark adaptation and consequently to impaired vision in the mesopic range. It is worth remembering that although the biochemical processes driving rod function may be slowed because of defective enzymes, in many instances the cellular metabolism permits adaptation such that normal rod function may be observed after prolonged periods of dark adaptation.

Hereditary conditions

A genetic mutation affecting any single protein or enzyme involved in the retinoid processing cycle potentially causes retinal disease (reviewed by Lamb and Pugh, 2004). The diseases relevant to the present review are retinitis pigmentosa (RP), retinitis punctata albescens (RPA), Bothnia dystrophy (BD), fundus albipunctatus (FA), congenital stationary night blindness (CSNB) and Oguchi disease. RP comprises the largest group and three genetically distinct variants, RPA, BD and Newfoundland rod-cone dystrophy (NFRCD), will be discussed separately.

Retinitis pigmentosa Retinitis pigmentosa, a clinically and genetically heterogeneous group of disorders, is the most common hereditary cause for visual impairment in all age groups. It has a prevalence of approximately 1:3500 (Pagon, 1988; Phelan and Bok, 2000).

The classical symptoms of night blindness at an early age and bilateral peripheral visual field (VF) loss are predominantly observed in patients with rod-cone RP. Although macular vision is relatively preserved, cone degeneration in the later phases of the disease will affect central visual acuity (VA) and day vision. Progression to legal blindness may happen as early as in the third, or as late as in the sixth, decade (Berson, 1996). Complete blindness occurs in a proportion of RP patients. It is not possible to predict speed and extent of visual failure. Patients who present with loss of central vision, night blindness and VF loss are likely to suffer from cone-rod dystrophy/degeneration, a RP-allied disease (Phelan and Bok, 2000).

The age of onset of symptoms is related to the mode of inheritance with children being more likely to suffer from X-linked RP, whilst younger to older adults are more likely to suffer from autosomal recessive or autosomal dominant RP, respectively (Weleber, 1994). The increasing number of RP genes (Hims *et al.*, 2003; Delyfer *et al.*, 2004) is regularly updated on RetNet (<http://www.sph.uth.tmc.edu/Retnet>). The classification of these genes into functional classes is complex. Phelan and Bok (2000) classified these into seven main functional groups (1) the visual cascade, (2) the visual cycle, (3) tetraspanins, (4) photoreceptor cell transcription factors, (5) catabolic functions in the retina, (6) mitochondrial genes and (7) genes of as yet unknown function (for review see Phelan and Bok, 2000). Kalloniatis and Fletcher (2004) recently reviewed the underlying biological mechanisms.

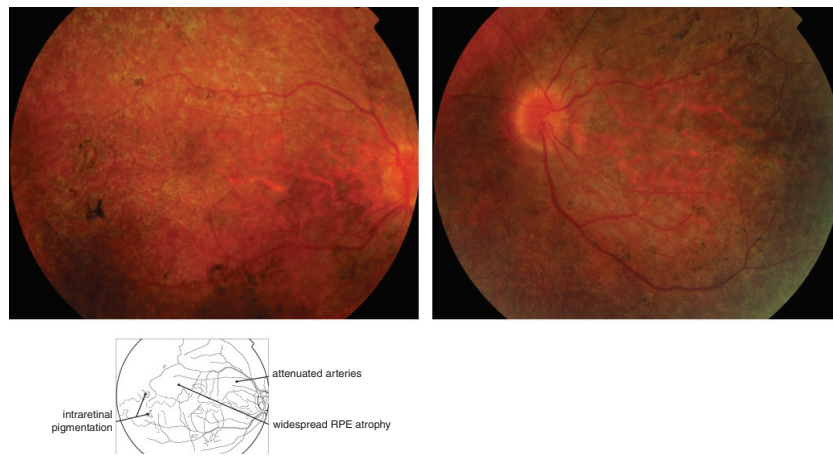


Figure 1. Retinitis pigmentosa. The fundus appearance in early disease may be variable sometimes including mild pigment epithelial atrophy in the mid-periphery and small white dots at the level of the RPE, with optic disc pallor and retinal arteriolar narrowing (reproduced with permission from Spalton *et al.*, 2005).

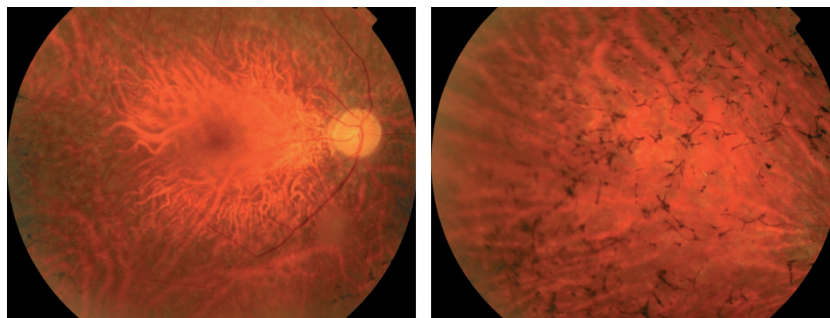


Figure 2. Retinitis pigmentosa. The typical bone spicule pigment deposition is typically seen later in the disease (reproduced with permission from Spalton *et al.*, 2005).

Fundus examination shows the typical picture of a mottled or granular appearance of the retina early in the disease (*Figure 1*) which develops into bone-spicule pigmentary deposits overlying the depigmented retina (*Figure 2*; Phelan and Bok, 2000). There is some variation in the appearance of pigmentary changes and window-like holes through the retinal pigment epithelium (RPE) are observed as are hypopigmentation, translucence and accumulation of pigment deposits of circular shape. Retinal atrophy results in attenuation of the retinal blood vessels and a pale disc because of loss of the nerve fibre layer (Heckenlively, 1988; Weleber, 1994; Phelan and Bok, 2000).

Electroretinography (ERG) plays a central role in the diagnosis of RP (Heckenlively, 1988; Marmor and Zrenner, 1998). In the classical picture of rod degeneration, abnormalities in the scotopic ERG precede those in the photopic ERG. In contrast in RP allied diseases presenting with cone-rod dystrophy the photopic ERG becomes abnormal first (Phelan and Bok, 2000). Occasionally a disproportionate disruption of the post-receptor component of the ERG b-wave is observed represented as an electronegative ERG. An absent ERG response is seen in the end-stages of the disease. There are anecdotal reports of an abnormal ERG preceding the onset of clinical symptoms later in life. In those cases where parents are affected by RP, but no gene has yet been identified this may occasionally be an issue for counselling and investigating the children.

There is no curative therapy available in RP yet. Low vision management remains one of the most valuable symptomatic treatment options (Weiss, 1991). This includes providing best refraction. The use of electronic means of magnification using special settings for the computer screen is extremely valuable and complements the common magnifying glass. Where a complaint of glare is related to cataract this is amenable to surgery. Glare may also be controlled by spectacle glasses incorporating short-wavelength filters. Care has to be taken that appropriate levels of illumination are provided for visual tasks. A range of VF-enhancing devices have been used with a varying degree of success and

other strategies such as a blind walking (long) cane or systematic scanning techniques are other alternatives. Counselling and ancillary care complement these measures (Weiss, 1991). Genetic counselling poses a particular challenge (Gross-Jendroska *et al.*, 1992). Dietary supplementation with vitamin A at a daily dose of 15 000 IU (international units) may slow the progression of RP in the early stages of the disease (Berson *et al.*, 1993). Patients should avoid taking vitamin E supplements, because this may hasten the disease, possibly by reducing the amount of vitamin A reaching the eye (Berson, 1996). There are a number of controversial treatment strategies not reviewed here (Delyfer *et al.*, 2004; Kalloniatis and Fletcher, 2004). There is experimental evidence from animals that genetherapy and specifically gene replacement therapy, may be an exciting avenue to be pursued (for review see Rolling, 2004).

Retinitis punctata albescens This is a rare progressive, autosomal recessive disorder caused by a number of different mutations in a number of genes (Weiss *et al.*, 1992; Burstedt *et al.*, 1999, 2001, 2003, 2005; Morimura *et al.*, 1999; Granse *et al.*, 2001; Fishman *et al.*, 2004; Nakamura *et al.*, 2005). The affected genes are the retinaldehyde-binding protein 1 (RLBP1) gene, the peripherin/RDS gene, the rhodopsin gene. The Arg135Trp point mutation in the rhodopsin gene was discovered by Souied in 1996 (Souied *et al.*, 1996) and the RLBP1 mutation was first described by Maw in 1997 (Maw *et al.*, 1997). Patients usually present in early childhood with night blindness (Morimura *et al.*, 1999; Nakamura *et al.*, 2005). As the disease progresses VA decreases and there is VF restriction. The examination of the fundus demonstrates whitish spots throughout the fundus (*Figure 3*), sometimes with an annulus appearance round the macula (Morimura *et al.*, 1999; Nakamura *et al.*, 2005). With loss of the nerve fibre layer the retinal vasculature becomes more attenuated (Morimura *et al.*, 1999). A fluorescein angiogram may show granular hyperfluorescence of the retina and window defects over the macula (Nakamura *et al.*, 2005). Optical

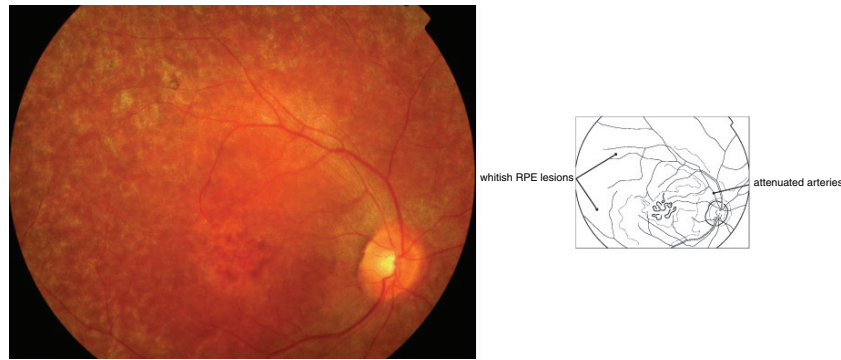


Figure 3. Retinitis punctata albescens. Multiple white deposits scattered throughout the retina are seen alongside macular atrophy (reproduced with permission from Spalton *et al.*, 2005).

coherence tomography (OCT) has been used to demonstrate thinning of the retina around the macula, mainly affecting the outer nuclear layer (Nakamura *et al.*, 2005). The ERG is severely abnormal, if not unrecordable for all modalities (photopic, scotopic and mesopic; Morimura *et al.*, 1999; Nakamura *et al.*, 2005). Scotopic blue seems to be particularly vulnerable (Morimura *et al.*, 1999).

The differential diagnosis includes RP and Nakamura *et al.* (2005) make the point that although the examination of the fundus shows distinctive subretinal flecks in FA, additional genetic analysis may be required.

Bothnia dystrophy This represents a subgroup of RPA patients with less severe disease (Burstedt *et al.*, 1999, 2001). These patients are homozygous for the RLBP1 mutation Arg234Trp and were from northern Sweden. They have a predilection to exhibit an atrophic-appearing macular lesion, particularly when over the age of 30. There is no specific treatment.

Newfoundland rod-cone dystrophy This represents another subgroup of RP patients with a particular phenotype because of a mutation in the RLBP1 gene (Eichers *et al.*, 2002). The onset of the disease is early (< 10 years of age) and rapidly progresses so that legal blindness is usually reached between 40 and 50 years of age. Night blindness is the earliest symptom, followed by progressive loss of peripheral, central and colour vision. The fundus appearance is somehow distinct to what is observed in RP or BD. In contrast to RP, there are usually no bone spicule pigmentations until late in the disease. In contrast to BD the macula appears normal or shows a 'beaten-bronze' atrophy (Eichers *et al.*, 2002). The observed white stippling of the retina and annulus around the macula is similar to that observed in RPA. The rod ERG is affected early in the disease, followed by an abnormal cone ERG (Eichers *et al.*, 2002). There is no specific treatment.

Congenital stationary night blindness This is an umbrella term for a heterogeneous, non-progressive group of disorders presenting in childhood with night blindness and occasionally other ocular symptoms such as nystagmus, decreased VA, myopia and hyperopia (Lorenz *et al.*, 1996; Weleber, 2002; Wutz *et al.*, 2002; Abramowicz *et al.*, 2005; Zeitz *et al.*, 2005). The autosomal dominant variant of CSNB was first described in the Nougaret family by the Belgian ophthalmologist Florent Cunier (Cunier, 1838; Wayenborgh, 2001) in collaboration with a local antiquarian (M Chauvet) from a small village near to Montpellier. The founder of this family was a French butcher by the name of Jean Nougaret born in Provence in 1636. The Nougaret family was followed up by Nettleship (1907).

Whilst many genes are described the underlying biochemical features are not yet unravelled and more functional studies are needed (Muradov *et al.*, 2003; Mansergh *et al.*, 2005). There is a recent report of benign familial myoclonic epilepsy in three patients with CSNB suggesting that some of these patients may suffer from a channelopathy (Manabe *et al.*, 2002), which is consistent with the findings in a new animal model (Mansergh *et al.*, 2005). The fundus may appear normal and this variant is referred to as the Schubert-Bornschein variant (Schubert and Bornschein, 1952).

The ERG responses in X-linked and autosomal recessive CSNB show a selective reduction of the b-wave, whilst the a-wave is almost completely normal, giving rise to the typical picture of the a-wave being larger than the b-wave (Miyake *et al.*, 1986, 1994; Langrova *et al.*, 2002; Bradshaw *et al.*, 2004), a so-called 'negative' ERG. Differences in the rod and cone b-wave responses permit CSNB1 to be distinguished from CSNB2 (Zeitz *et al.*, 2005). The ERG allows for further sub classification of the Schubert-Bornschein variant dependent on whether the defect of the bipolar cells is complete or incomplete (Schubert and Bornschein, 1952; Miyake *et al.*, 1986).

The discovery of new phenotypes makes the interpretation of the ERG more complex and there is no clear genotype-phenotype correlation (Allen *et al.*, 2003; Kabanarou *et al.*, 2004).

Fundus albipunctatus Fundus albipunctatus, first described by Lauber (1910) presents with non-progressive, or very slowly progressive night-blindness without associated retinal dystrophy. The typical clinical findings are multiple whitish yellow spots in the fundus, which tend to be scattered as an annulus around the macular (Figure 4). Fundus albipunctatus can present with and without macular atrophy (Nakamura *et al.*, 2003).

Fundus albipunctatus is caused by a number of distinct mutations in the RDH5 gene, which encodes for the 11-cis retinol dehydrogenase of the retinal pigment epithelium (Nakamura and Miyake, 2002; Nakamura *et al.*, 2003). The biological function of this enzyme is to oxidize the alcohol 11-cis retinol to the aldehyde 11-cis retinal. Impairment of this process results in reduced retinol delivery and prolonged dark-adaptation.

The interesting finding is that patients suffer from severely depressed rod-function in the early stages of dark adaptation. However, rod function starts to improve within about 30 min of adaptation and returns to near normal levels after 2–3 h of adaptation (Carr *et al.*, 1974). The biochemical basis for this phenomenon is delayed regeneration of rod visual pigment. It is of note that this also delays the regeneration of cone visual pigments. In fact cone dysfunction can be demonstrated in about 38% of patients with FA (Cideciyan *et al.*, 2000; Niwa *et al.*, 2005). Macular lesions are not required for reduced cone function. There is no specific therapy for FA.

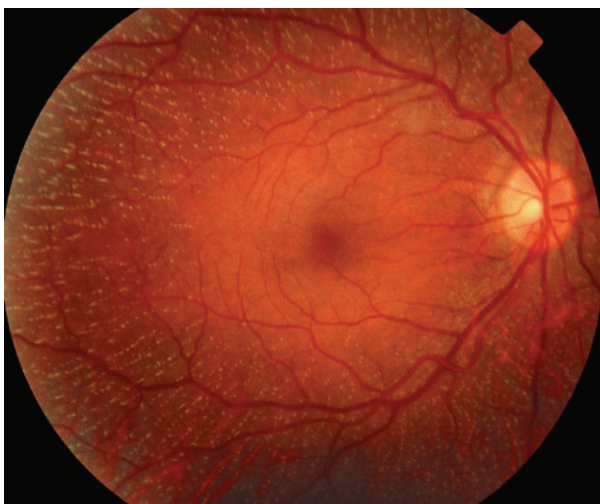


Figure 4. Fundus albipunctatus. The characteristic fundus appearance with multiple white dots scattered over the retina with macular sparing is shown (reproduced with permission from Spalton *et al.*, 2005).

Oguchi disease This is a non-progressive disorder first described by Oguchi (1912) in which dark adaptation is eight- to 10-times slower than normal (Carr and Ripps, 1967; Sharp *et al.*, 1990; Cideciyan *et al.*, 1998). Mizuo (1913) observed in these patients by examination of the fundus that under light adapted conditions the retina had a metallic, phosphorescent-like sheen which disappears with prolonged dark adaptation, a phenomenon which has since carried his name. Interestingly pigment regeneration appears to be normal despite a severely reduced dark adaptation (Lamb and Pugh, 2004). Oguchi disease is caused by mutations in genes encoding either of two proteins, RR or Arr (reviewed in Dryja, 2000). These mutations are more common in the Japanese compared with the European population.

Standard full-field scotopic ERG shows absent rod responses and a reduced a-wave. The cone and flicker ERG is normal. The photopic ERG permits differentiation of patients with Oguchi disease from complete CSNB where the ON-response is reduced (Miyake *et al.*, 1996).

Acquired conditions

Vitamin A deficiency Vitamin A deficiency, defined by serum retinol concentration $<0.7 \mu\text{mol L}^{-1}$ is world wide the most common cause for xerophthalmia (*xeros*, dry, *ophthalmia* inflamed eye) which is followed by night blindness (Tielsch and Sommer, 1984). Although recognized since the early Egyptian times (Wolf, 1978), the typical fundus appearance was not described until 1928 by Uyemura (Uyemura, 1928). Fuchs subsequently proposed to name the disease Uyemura syndrome (Fuchs, 1928, 1959).

Vitamin A deficiency is a public health issue in countries where part of the population faces nutritional problems. VAD has recently been described in Afghanistan (Mihora *et al.*, 2004), Bangladesh (Ahmed, 1999; Ahmed *et al.*, 2000; de Pee *et al.*, 2003; Singh and West, 2004), Bhutan (Singh and West, 2004), Brazil (Ramalho *et al.*, 2002; Saunders *et al.*, 2004), Cambodia (Christian, 2002; Semba *et al.*, 2003), Djibouti (Resnikoff *et al.*, 1992), Ethiopia (Haidar and Demissie, 1999; Asrat *et al.*, 2002), India (Christian, 2002; Singh and West, 2004; Shaw *et al.*, 2005), Indonesia (Mele *et al.*, 1991; de Pee *et al.*, 2003; Singh and West, 2004), Iraq (Al-Kubaisy *et al.*, 2002), Java (Bergen *et al.*, 1988), Kenya (Nabakwe *et al.*, 2005), Kiribati (Schaumberg *et al.*, 1996), Malawi (Tielsch *et al.*, 1986), Malaysia (Nghah *et al.*, 2002), Mali (Farbos *et al.*, 2000; Schemann *et al.*, 2002), the Marshall Islands (Maqsood *et al.*, 2004), Myanmar (Singh and West, 2004), Nepal (Singh and West, 2004; Taren *et al.*, 2004), Niger (Blum *et al.*, 2004), Nigeria (Oso *et al.*, 2003), Philippines (Rosen *et al.*, 1994), Sri Lanka (Brink *et al.*, 1979; Singh and

West, 2004), Tanzania (Wedner *et al.*, 2000), Thailand (Bloem *et al.*, 1989; Singh and West, 2004), Yemen (Rosen *et al.*, 1996) and Zaire (Donnen *et al.*, 1996). Xerophthalmia remains the leading cause of acquired pediatric blindness. The WHO estimates that about 140–250 million worldwide are at risk of a VAD disorder (Underwood, 2004).

The earliest symptom of VAD is night blindness, followed by peripheral and central VF constriction (McBain *et al.*, 2005), photophobia and reduced VA. The revised WHO (Somner, 1995) clinical classification of xerophthalmia includes night blindness, conjunctival xerosis, Bitot spots, corneal xerosis, corneal ulceration/keratomalacia, corneal scarring, xerophthalmia fundus (Sommer, 1982). Photopic stress to the rods can exacerbate night blindness by up-regulating the rhodopsin turnover (Baillie, 1816; Stephenson, 1896).

Vitamin A is one of the five fat-soluble vitamins essential to human metabolism. Amongst other functions it is needed to synthesize rhodopsin, the visual pigment used in the rods and cones (McBain *et al.*, 2005).

The differential diagnosis for VAD is wide and apart from patients suffering from malnutrition in the above-mentioned countries, one needs to consider diseases such as Crohn disease (Main *et al.*, 1983; McBain *et al.*, 2005), surgical intervention (Parker *et al.*, 1985; Purvin, 1999; Lee *et al.*, 2005; McBain *et al.*, 2005) including bowel surgery for severe obesity (Spits *et al.*, 2004; McBain *et al.*, 2005), eating disorders (Velasco Cruz *et al.*, 2005), malabsorption (Perlman *et al.*, 1983), alcohol-induced chronic pancreatitis (Ruiz-Martin *et al.*, 2005), cirrhosis (Onder *et al.*, 2005), a mutation to the plasma retinol binding protein (I41N and G75D; Bennett *et al.*, 2004; Folli *et al.*, 2005), common variable immunodeficiency (Kilic *et al.*, 2005) and pregnancy (Saunders *et al.*, 2004).

Vitamin A deficiency can also be observed as a result of an acute phase response induced by infection (Nabakwe *et al.*, 2005) in an at-risk population (Brink *et al.*, 1979; Tielsch *et al.*, 1986; Bergen *et al.*, 1988; Bloem *et al.*, 1989; Mele *et al.*, 1991; Resnikoff *et al.*, 1992; Rosen *et al.*, 1994; Donnen *et al.*, 1996; Rosen *et al.*, 1996; Schaumberg *et al.*, 1996; Ahmed, 1999; Haidar and Demissie, 1999; Ahmed *et al.*, 2000; Farbos *et al.*, 2000; Wedner *et al.*, 2000; Al-Kubaisy *et al.*, 2002; Asrat *et al.*, 2002; Christian, 2002; Christian, 2002; Ngah *et al.*, 2002; Ramalho *et al.*, 2002; Schemann *et al.*, 2002; Oso *et al.*, 2003; de Pee *et al.*, 2003; Semba *et al.*, 2003; Blum *et al.*, 2004; Maqsood *et al.*, 2004; Mihora *et al.*, 2004; Saunders *et al.*, 2004; Singh and West, 2004; Taren *et al.*, 2004; Nabakwe *et al.*, 2005; Shaw *et al.*, 2005).

The fundus is normal in early VAD, but later on may show multiple white or grey–white spots in the periph-

eral retina (Uyemura, 1928), which usually disappear with vitamin A supplementation (Apushkin and Fishman, 2005; McBain *et al.*, 2005).

The ERG response shows elevated thresholds for both rods and cones, with the rods being more severely affected (Perlman *et al.*, 1983). In severe cases the rod ERG can be undetectable. The ERG generally normalizes with treatment. McBain and colleagues describe an interesting patient who reported she would see ‘white as green’ and had a selective loss of the S-cone function (McBain *et al.*, 2005). One of the two cases reported by Bennett *et al.* (2004) was a photographer by profession and reported that colours appeared as if seen through a yellow filter, with the other patient reporting that colour appeared as if seen through a red screen. Fluorescein angiography suggests that the white areas in the fundus represent loss of pigment from the retinal pigment epithelium (Sommer, 1982).

The treatment of VAD is straightforward by supplementing vitamin A. An interesting new approach using genetically modified rice and maize may eventually contribute enriching vitamin A in the food, but logistic problems and controversial economical issues need to be addressed (Anon, 2005). VAD and xerophthalmia were already known to the ancient Egyptians and Greeks who treated it with calf or goat liver, both of which have a high vitamin A content (Wolf, 1978; for a historical review see Wolf, 1996). However and sadly it needs to be remembered that most of the children affected by VAD will receive treatment too late to make a full recovery.

Melanoma associated retinopathy (MAR) This belongs to the paraneoplastic syndromes and is characterized by the combination of night blindness, phosphenes (the subjective appearance of flickering lights), colour deficits on the tritan axis, reduced VA and central VF loss occurring in patients with metastatic cutaneous melanoma (Sawyer *et al.*, 1976; Gass, 1984; Weinstein *et al.*, 1994; Kellner *et al.*, 1995; Jacobson, 1998; Pfohler *et al.*, 2003; Petzold and Plant, 2005). Visual symptoms frequently start with night blindness and shimmering, flickering, or pulsating photopsias followed by progressive loss of VA (Keltner *et al.*, 2001). The occurrence of photopsias is very sudden and indicative of loss of vision.

Sawyer *et al.* (1976) were probably the first to recognize the relationship between a non-ocular cancer and retinal pathology. Ripps and colleagues were the first to describe the occurrence of night blindness and photopsias in a 30-year-old man with melanoma, but they suggested that toxic properties of the chosen chemotherapy (vincristine) were causative (Ripps *et al.*, 1984). Gass (1984) is credited with recognizing the MAR syndrome.

The mostly accepted pathophysiological mechanism is that (perhaps in an attempt to limit tumour growth) the human immune-system produces antibodies which cross-react with bipolar cells of the retina (Milam *et al.*, 1993; Weinstein *et al.*, 1994; Keltner *et al.*, 1995; Boeck *et al.*, 1997; Klopfer *et al.*, 1997), although this could not be shown in all cases (Rougier *et al.*, 1995; Bret-Dibat *et al.*, 1996; Fishman *et al.*, 1996), and cross-reactivity with other retinal cells is also observed (Keltner *et al.*, 2001). One group provided some experimental evidence that the transfer of human IgG from MAR patients into the vitreous of the monkey induces the ERG changes also seen in MAR (Lei *et al.*, 2000).

The fundus has been reported as normal in 19 (44%) of 43 patients. Some cases show a pale optic disc, attenuation of retinal vessels including retinal periphlebitis, changes of pigmentation or occasional vitreous cells (see *Table 6* in Keltner *et al.*, 2001). The inflammatory changes may be more widespread, involving larger parts of the posterior uvea.

Nyctometry (see Assessment, below) is abnormal in MAR patients (Pfohler *et al.*, 2003). Psychophysical tests suggest a specific M-cell dysfunction with preservation of P-cell function (Wolfe *et al.*, 1996).

The ERG typically shows a markedly reduced b-wave because of the defunct bipolar cells. A normal a-wave indicates normal functioning of the photoreceptors (Fishman *et al.*, 1996; Barnes *et al.*, 2002). The ERG pattern resembled the one found in CSNB patients in 54 of 56 patients recently reviewed by Keltner *et al.* (see *Table 7* in Keltner *et al.*, 2001).

Treatment of the underlying melanoma is the primary concern to the physician. With regard to the MAR syndrome there are anecdotal reports that corticosteroids, plasmapheresis, intravenous immunoglobulins (IVIg), azathioprine, gabapentin, radiation and cytoreductive surgery may be of some benefit (Guy and Aptsiauri, 1999; Keltner *et al.*, 2001).

Cancer associated retinopathy This is another cancer associated paraneoplastic retinal degeneration (Sawyer *et al.*, 1976). Cancer associated retinopathy (CAR) can be seen with tumours such as pulmonary small cell carcinoma, breast and other gynaecological cancers, endocrine and other malignancies (Keltner *et al.*, 2001).

The main symptoms are loss of VA associated with photopsias which can precede the detection of the cancer by many months. Rod dysfunction is the cause for night blindness, prolonged dark adaptation, peripheral and ring scotomata. Cone dysfunction results in photosensitivity, decreased colour vision and VA and central scotomata (Keltner *et al.*, 2001; Petzold and Plant, 2005).

Over 15 different types of antibodies are described with the 23-kDa protein recoverin being the most

commonly found antigen, followed by the 46-kDa protein α -enolase and others (i.e. neurofilaments, heat shock protein 70, TULP1, etc.) (Thirkill *et al.*, 1992; Polans *et al.*, 1995; Keltner and Thirkill, 1998; Adamus *et al.*, 2004). The ERG can be abnormal either for cone- or rod-function, or for both, presumably dependent upon the proteins targeted by the antibodies. Treatment of the underlying cancer is the main problem.

Autoimmune-related retinopathy and optic neuropathy syndrome This syndrome represents a rare and heterogeneous group of patients with retinal degeneration and optic neuropathy thought to be associated to autoimmune antibodies without evidence of cancer, but rather to a systemic autoimmune disease (Keltner *et al.*, 2001). The symptoms frequently resemble those observed in CAR patients. Indeed, antibodies against similar antigens (i.e. recoverin) are found in autoimmune-related retinopathy and optic neuropathy (ARRON) and CAR (Keltner *et al.*, 2001; Adamus *et al.*, 2004). The ERG resembles that seen in CAR patients. No specific treatment is known and various immunosuppressive strategies have been tried.

Reduced vision in the mesopic range related to cone dysfunction

The relevance of cone disease

The human retina comprises three types of cones, which vary in their absorption spectra. The S-cones are most sensitive in the short wavelength spectrum, the M-cones in the middle wavelength spectrum and the L-cones in the long wavelength spectrum. Cone disease may cause problems on first entering the dark.

Enhanced S-cone syndrome

This is a progressive autosomal recessive disorder which can be caused by a large number of mutations in the NR2E3 gene (synonymous to PNR; Haider *et al.*, 2000; for review of these mutations see Wright *et al.*, 2004; Hayashi *et al.*, 2005). Marmor *et al.* (1990) coined the term enhanced S-cone syndrome (ESCS). Inherited retinal dystrophies generally affect the rods and all three cone types (S-cones, M-cones and L-cones). ESCS represents a rare exception because only M- and L-cones are affected, whilst the S-cones or blue cones exist in excess (Peng *et al.*, 2005). It has been suggested that NR2E3 may be important during retinal development (Milam *et al.*, 2002; Bumsted O'Brien *et al.*, 2004).

Patients with ESCS suffer from night blindness because of rod dysfunction. Most young patients suffer from bilaterally reduced VA to <0.8 (Snellen decimal), which decreases further with age so that by the age of 20,

VA is generally <0.4 (Yamamoto *et al.*, 1999; Nakamura *et al.*, 2002, 2004; Sharon *et al.*, 2003; Usui *et al.*, 2004). The peripheral VF is reduced and ring scotomata can be observed (Hayashi *et al.*, 2005). Colour vision may or may not be impaired, dependent on severity. The severity and prognosis of ESCS varies from very mild (Hayashi *et al.*, 2005) to severe (Nakamura *et al.*, 2004), dependent on the underlying mutation.

The pathognomonic finding in ESCS is the ERG demonstrating ‘hyperfunction’ of S-cones (Marmor *et al.*, 1990, 1999, 2004; Hood *et al.*, 1995). They are probably not truly hyperactive, but just exist in excess resulting in the stronger electrical response. The diagnosis of ESCS is frequently based on the typical findings in the spectral ERG, which combines hypersensitivity to blue stimuli with a hyposensitivity to red stimuli (Marmor *et al.*, 1990; Hayashi *et al.*, 2005). In most patients there is no recordable rod function on ERG, but in the very mild form of ESCS the rod ERG shows low rod b-waves (Hayashi *et al.*, 2005).

The fundus findings include cystoid changes in the macula and may also show degenerative changes in the vascular arcade to the mid-peripheral retina. Pigmented spots can also be seen in degenerating areas (Marmor *et al.*, 1990; Jurklies *et al.*, 2001; Nakamura *et al.*, 2002; Hayashi *et al.*, 2005). OCT may show large macular retinoschisis and an abnormal laminar retinal architecture (Jacobson *et al.*, 2004; Hayashi and Kitahara, 2005). Fluorescein angiography (midphase) may reveal hyperfluorescence of the degenerative regions and temporal hypofluorescence in areas where pigmented spots are seen by direct examination of the fundus (Hayashi *et al.*, 2005).

The differential diagnosis of mutations to the NR2E3 gene includes Goldmann–Favre syndrome (Sharon *et al.*, 2003), autosomal recessive RP (Gerber *et al.*,

2000) and clumped pigmentary retinal degeneration (Sharon *et al.*, 2003).

Sorsby fundus dystrophy

This represents a rare autosomal dominant macular degeneration, first described by Sorsby and Mason (1949), which presents with bilateral loss of central vision in the adult. Some patients may present with nyctalopia prior to the development of the maculopathy (Capon *et al.*, 1988; Polkinghorne *et al.*, 1989). Pigment dispersion glaucoma is also observed.

Sorsby fundus dystrophy (SFD) is caused by a mutation on chromosome 22q12-q13 resulting in decreased activity of TIMP3, the inhibitor to the metalloproteinase 3 (MMP3; Weber *et al.*, 1994). The condition is progressive (Weber *et al.*, 1994).

The TIMP3 and MMP3 participate in a complex network of enzymes needed for the normal remodelling of the extracellular matrix (ECM) (Bergers and Coussens, 2000). The degrading activity of MMPs is high and MMPs are tightly controlled by their specific tissue inhibitors (TIMP). A range of disorders has been related to MMPs, but of the TIMPs only TIMP3 has so far been related to disease (Klenotic *et al.*, 2004). In SFD Ser–Cys mutants of TIMP3 accumulate in drusen and in Bruch’s membrane similar to what is seen in the more common age-related macular degeneration (AMD) (Weber *et al.*, 1994; Tabata *et al.*, 1998; Kamei and Hollyfield, 1999). The mechanism leading to TIMP3 accumulation remains unknown but is likely to be related to impaired degradation of the protein (Chong *et al.*, 2003).

Fundus examination in the earlier stages shows juxtafoveal choroidal neovascularization (Barbazetto



Figure 5. Sorsby fundus dystrophy. There is widespread RPE atrophy with an island of RPE preserved centrally. The optic disc is atrophied and the yellowish–white deposits represent drusen (reproduced with permission from Spalton *et al.*, 2005).

et al., 2005) and diffuse fine yellowish-white deposits. Retinal haemorrhages may be present (Ayyagari *et al.*, 2000). Later the picture is dominated by retinal and macular atrophy (Figure 5; Atan *et al.*, 2004). Fluorescein angiography shows the classical features of choroidal neovascularization, that is to say delayed choroidal filling and retinal pigment epithelial mottling (Atan *et al.*, 2004; Barbazetto *et al.*, 2005).

There is no specific treatment, but retinal neovascularization may be limited by photodynamic therapy or steroids (Atan *et al.*, 2004; Peiretti *et al.*, 2005). On a very short term basis vitamin A supplement may improve the symptoms (Berson, 2000). The differential diagnosis includes other conditions with early onset retinal and macular degeneration.

Assessment

The most important, easiest and most economical approach is to ask the patient if he/she experiences any problems with his/her night vision. Patients who drive may be particularly aware of impaired vision in the mesopic range. Accurate and reproducible quantification of mesopic vision and changes in mesopic vision over time, are very difficult. Discussion of the complexities of mesopic photometry is beyond the scope of this review and the interested reader is referred to the paper by Stockman and Sharpe (2006). Here we restrict the discussion to some pragmatic assessments, which are relevant for assessment of night driving abilities in some countries.

Historically the Nyktometer (Rodenstock) was probably the most frequently used instrument for assessment of VA under mesopic conditions (Hartmann and Wehmeyer, 1980; Kolling and Schratz, 1991; Schlag, 1993). Several developments have been made and the Mesotest II (Oculus), the Kontrastometer (BKG Medizin Technik GmbH) and the Nyktometer 500 (Rodenstock) may currently be the most frequently used instruments

(Kolling and Schratz, 1991; Schlote *et al.*, 1997; DOG, 2003; Puell *et al.*, 2004).

The Nyktometer 500 allows for the assessment of monocular and binocular VA under mesopic conditions using Landolt rings (the use of plate 505 is recommended). The forehead is rested against a flexible, soft plastic cover, which shields the eyes from any stray light. It is possible to keep the spectacles on during the test. The apparatus allows for correction of night myopia by adding minus lenses.

The Mesotest II is very similar to the Nyktometer. One additional feature is that the rear wall of the apparatus can be removed allowing for vision through a semi-reflecting mirror. The idea is that this may avoid night myopia. If this option is used care needs to be taken that the apparatus points towards a non-reflecting wall and that the illumination in the room is kept constant.

The Kontrastometer is again very similar to the Nyktometer. An advantage of this apparatus is that VA is tested using Landolt rings, which are illuminated from behind and also from the side allowing for variation of contrast, which is of use for those patients who suffer from very poor mesopic vision. Additionally the Landolt rings can be turned so that the patient cannot memorise the gap position of the ring. The core features of these three apparatuses are summarized in Table 1.

Other tests include the Pelli–Robson letter contrast sensitivity (Wood and Owens, 2005), low-contrast letters (Smith, 1973; Pesudovs *et al.*, 2004) and a new automated test developed by Chisholm *et al.* (2003).

The relationship between mesopic vision and dark adaptation is of particular importance for drivers, pilots, etc. and a number of tests assess this function (Reiner, 1997; Babizhayev, 2003; Plainis *et al.*, 2005). Other visual functions affected by reduced vision in the mesopic range are motion (Takeuchi *et al.*, 2001) and distance judgment (Bourdy *et al.*, 1991).

Table 1. Characteristics of the Nyktometer 500, Mesotest II and Kontrastometer (adapted from DOG, 2003)

Characteristic	Nyktometer 500	Mesotest II	Kontrastometer
Producer	Rodenstock GmbH	Oculus Opticgeräte	BKG Medizin Technik
URL	http://www.rodenstock.com	http://www.oculus.de	http://www.bkg-medizintechnik.de
Optics	Binocular	Binocular ¹	Binocular
Field illumination (cd)	0.032–0.1	0.032–0.1	0.032–0.1
Stimulus presentation	Pre-programmed ²	Choice	Random
Contrast (range)	Plate dependent ³	2:1–23:1	1–14:1–5:1
Monocular testing	Yes	Yes	Yes
Correction for night myopia	Yes	Yes	Yes

¹Optional see-through field.

²Three plates are available: 501, 502 and 505. A potential pitfall with the pre-programmed presentation is that the patient may memorize the stimulus position, which causes a problem for repeated measurements.

³Plate 501, 1.46 : 1 to 23 : 1; plate 502, 1.14 : 1 to 23 : 1; plate 505, 2 : 1 to 23 : 1.

Electroretinography

Electroretinography has a central role in the diagnosis of all diseases described in the review. It permits testing of rod function during dark adaptation by providing a white flash of light (scotopic ERG), cone function adapted to specific light levels (photopic ERG) and both rods and cones if a sufficiently bright light flash is given under dark adaptation (mesopic ERG). At intermediate light levels cone function can be isolated by recording the ERG to rapid flicker or a long wavelength stimulus, as the rods will not respond to either of these.

The ERG recordings show an initial negative deflection (downwards on the y-axis) because of closure of cation channels in the outer segment membrane. This is followed by a positive deflection (upwards on the y-axis) because of activity of the photoreceptors and retinal neurons. In this review we frequently refer to the ERG b-wave, which reflects the transmission of the signal from the photoreceptors to the second-order neurons.

In diseases with predominant or early degeneration of the rods, pathological changes in the scotopic ERG precede those of the photopic ERG. Conversely diseases affecting predominantly the cones mainly change the appearance of the photopic ERG. In cone-rod dystrophy the photopic ERG is affected first, but the scotopic ERG is usually pathological as well. It needs to be remembered that the standard ERG is not sensitive enough to detect diseases limited to the macula with a limited amount of cone loss.

Conclusions

Impaired vision in the mesopic range is probably the most sensitive and earliest sign of a range of diseases. Frequently taking a history and asking about problems with night vision is sufficient to identify affected patients. Simple tests for assessing mesopic vision have been established and have been recommended as screening tests particularly for VAD, which remains the most frequent cause for acquired blindness. More detailed tests of mesopic vision include the nyctometer, ERG, contrast sensitivity, dark adaptation and others; the results contribute to unravelling the function of the visual pathways and their genetic and molecular biological basis.

It is important to remember that disorders of both the rod and cone systems can affect vision at mesopic levels. However, relatively little is known about how the interactions between the two systems, which only occur at mesopic light levels, can be modified in disease and how this may be manifested in the symptomatology. Even less is known about optic nerve and cerebral disease as in those disorders visual function is almost exclusively studied under photopic conditions. And yet

patients with optic nerve disease, for example, will often report that they see better in bright than dim light or vice versa. Patients with bilateral occipital dysfunction may report that their visual world appears abnormally dark, and that 'if only there were more light' they would be able to see.

There is increasing realisation that mesopic vision is important in the everyday life of patients, particularly where driving at night is concerned. In this review we have attempted to provide an understanding of the range of rod and cone system disorders which may result in impaired vision in the mesopic range. In the coming years a greater understanding of the consequences of these for mesopic vision will emerge.

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