Retinitis Pigmentosa and Allied Disorders

9

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Contents

Mim Number OMIM

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Synonyms

Peripheral retinal dystrophy, Rod-cone dystrophy, Tapetoretinal degeneration

9.1 Introduction

There are more than 250 entries with the term retinitis pigmentosa in OMIM. More than half of them describe a systemic disease associated with retinal dystrophy, whether central, peripheral or mixed.

A quarter deal with isolated retinitis pigmentosa, and the others correspond to different central dystrophies of the retina and of the choroid, sometimes associated with peripheral retinal involvement such as congenital stationary night blindness (CSNB), choroideraemia, gyrate atrophy, myopic choroidosis, pure cone dystrophies, Stargardt disease, pattern dystrophies and most of the fleck dystrophies.

This last group will not be discussed in this chapter. Retinitis pigmentosa is a hereditary disease which primarily affects rods and cones and is bilateral and slowly progressive. It gradually involves the different histological layers of the retina. Although the whole retina will become affected, the disease usually starts in the retinal periphery. The first signs and symptoms are haemeralopia, restriction of the visual field and peripheral pigment epithelial changes (Fig. 9.1).

A previous version of this chapter included an incorrect figure (Fig. 9.2 was represented incorrectly and was replaced by a new figure). For this reason an erratum has been published, correcting the mistake in the previous version and showing the correct figure (see DOI 10.1007/978-3-540-69466-3_54). The version readers currently see is the corrected version with the figure in chapter 2 shown correctly. The reader sees the chapter in its intended form. The Publisher would like to apologize for the earlier mistake.

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Fig. 9.1 Retinitis pigmentosa in a 25-year-old male with negative family history. The macular region is still relatively spared. The visual fields are tubular

The term *retinitis pigmentosa* introduced in 1855 by Donders reflects the end stage of various diseases, which may be vascular, inflammatory or dystrophic in origin. In 1858 von Graefe notices the hereditary characteristics and uses the name of *pigmentary degeneration* for the slowly progressive fundus condition.

Leber in 1916 prefers the name of *tapetoretinal degeneration* which will be in use till the end of the twentieth century. From then on the term of tapetoretinal degeneration will be replaced by *peripheral hereditary retinal dystrophy* and later by *rod-cone* and *cone-rod dystrophy* reflecting whether the rods or the cones are primarily involved.

By and large, the term *retinitis pigmentosa* is still used today and describes a heterogeneous group of noninflammatory peripheral retinal dystrophies which are genetically determined and affect the photoreceptors and the retinal pigment epithelium. It may appear early in life or later on; be generalised or more localised, with variable pigmentation and severity; and be isolated or sometimes associated with systemic manifestations.

9.2 Genetics

The disease is genetically transmitted [4, 5, 16, 18–22, 33, 41, 44]. The various phenotypes result from multiple mutations. About 50 genes and loci have been identified in non-syndromic forms (Retnet) (Table 9.1, Fig. 9.2). One can safely assume that many more others remain to be discovered.

The pattern of inheritance of retinitis pigmentosa can be divided in seven different types:

- *Autosomal dominant* (ADRP) 35 %.
- *Autosomal recessive* (ARRP or multiplex RP) between 19 and 45 %.
- *X-linked recessive* (XLRP) varying between 6 and 17 %.
- *X-linked dominant* extremely rare.
- *Mitochondrial* 1 %. Usually these cases present a typical fundus appearance and also associated systemic involvement.
- *Sporadic* 38 %. These are isolated cases of which the hereditary pattern has yet to be determined (simplex RP). They could result from various new mutations and be phenocopies of retinitis pigmentosa, recessive digenic or X-linked cases with insufficient familial data and cases of mistaken paternity.
- *Digenic or trigenic:* Extremely rare. The disease is the result of two or three different defective genes. In those cases, the risk for recurrence is very low.

9.3 Epidemiology

The disease is universal and heterogeneous and affects all races. It can also be found in all mammals. Its prevalence in man varies between 1/2000 and 1/4225, depending whether or not only the peripheral forms or all forms are included [4, 6, 15, 24, 32, 37, 43].

9.4 Clinical Features

The description given here corresponds to the classic form of isolated retinitis pigmentosa which is also the most common form in the heterogeneous group called retinitis pigmentosa. It represents 70–80 % of all retinitis pigmentosa cases.

9.4.1 Initial Signs and Symptoms of Typical Retinitis Pigmentosa

9.4.1.1 Age at Onset

The diagnosis can be made at every age of life, sometimes before the age of 10 years and even in infancy before the age of 2 years. In those cases one deals with Leber congenital amaurosis which will be discussed in another chapter. The other early onset cases (in the first decade of life) are often more severe in evolution and most commonly X linked. These infantile forms may be associated with systemic involvement (allied disorders) which warrant a systematic neuro-paediatric investigation. Late-onset cases are often

Table 9.1 Genes involved in non-syndromic retinitis pigmentosa and their metabolic function

Locus	Gene	Metabolism
Autosomal dominant retinitis pigmentosa		
CORD2	*CRXl*	Development
RP01	*RP1*	Connecting cilia
RP04	*RHO*	Visual transduction
RP07	*PRPH2*	Cytoskeleton of the outer segments
RP09	*PAP1*	Splicing factor
RP10	*IMPDH1*	Visual transduction
RP11	*PRPF31*	Splicing factor
RP13	*PRPF8*	Splicing factor
RP17	*CA4*	Ion transport
RP18	*HPRP3*	Splicing factor
RP27	*NRL*	Development
RP30	*FSCN2*	Cytoplasmic membrane OS
RP31	*TOPORS*	Connecting cilia
RP33	*SNRNP200*	Splicing factor
RP35	*SEMA4A*	Development
RP37	*NR2E3*	Transcription factors development
RP41	*PROML1*	Cytoplasmic membrane OS
RP42	*KLHL7*	Proteasome
RP44	*RGR*	Metabolism of retinoids
RP48	*GUCA1B*	Activates photoreceptor guanylate cyclase
RP50	*BEST1*	Ion transport
RP51	*TTC8*	Formation of cilia
RP60	*PRPF6*	Involved in pre-mRNA splicing
Autosomal recessive retinitis pigmentosa		
RP04	*RHO*	Visual transduction
RP12	*CRB1*	Development
RP14	*TULP1*	Inner segment
RP19	*ABCA4*	Visual cycle
RP20	*RPE65*	Visual cycle
RP25	*EYS*	Ion transport
RP26	*CERKL*	Ceramide
RP27	*NRL*	Development
RP36	*PCRD*	Unknown function
RP37	*NR2E3*	Development
RP38	*MERTK*	Phagocytosis
RP39	*USH2A*	Extra cellular matrix
RP40	*PDE6B*	Visual transduction
RP41	*PROML1*	Connecting cilia
	CNGA1	Visual transduction
	PDE6A	Visual transduction
	RLBP1	Visual cycle
	LRAT	Visual cycle
	SAG	Visual transduction
	CNGB1	Visual transduction
	RGR	Visual cycle
	RDH12	Metabolism of retinoids
	RBP3	Transport retinoids
X-linked retinitis pigmentosa		
RP2	*RP2*	Connecting cilia
RP3	*RPGR*	Connecting cilia
RP6	*Xp21.3-p21.2*	
RP23	*Xp22*	
RP24	*Xq26-q27*	
RP34	*Xq28-qter*	

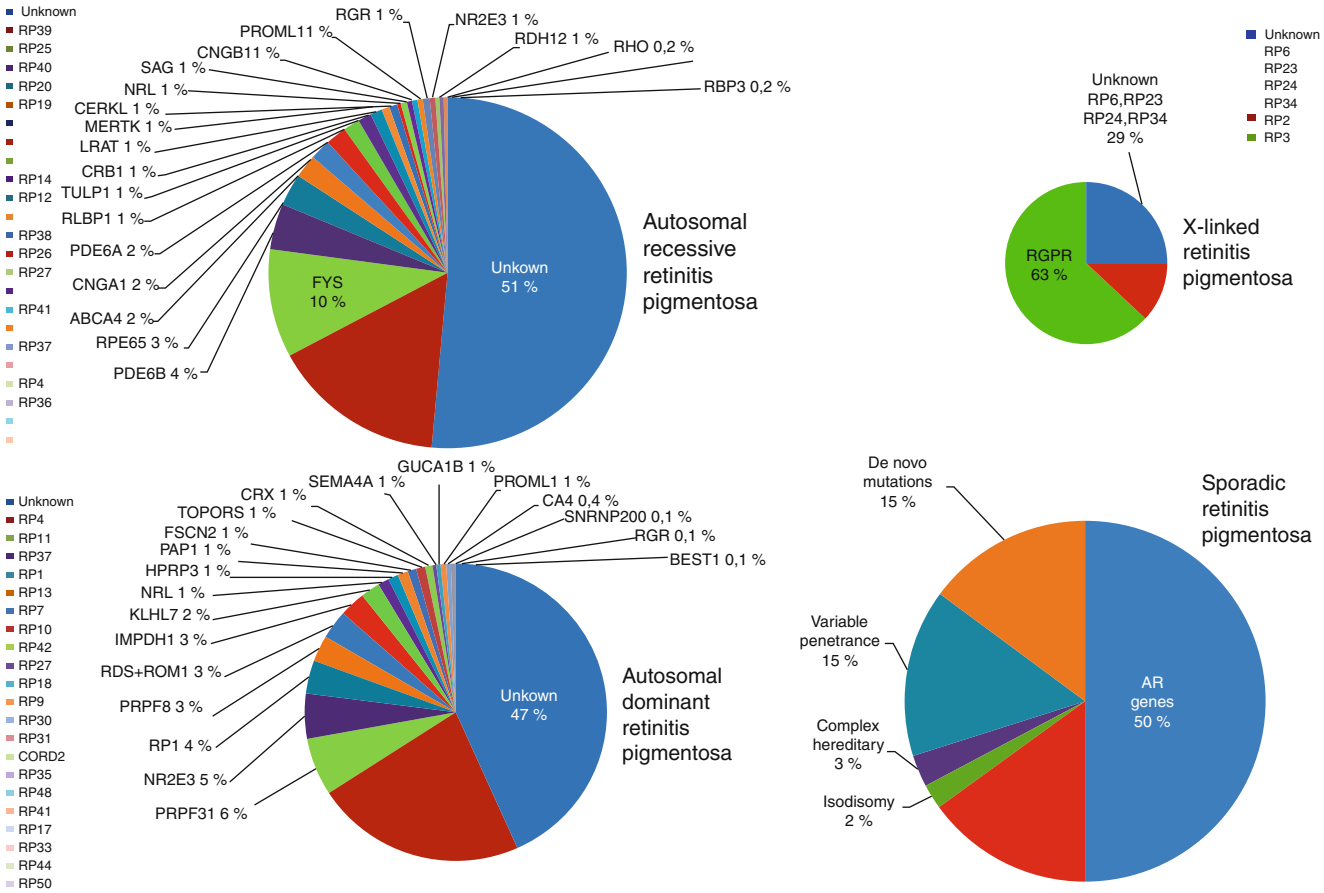

Fig. 9.2 Distribution of the genes in non-syndromic retinitis pigmentosa (Hamel 2010, personal communication). Genes with a prevalence of 1 % or less are either genes which have been recently discovered or of which the prevalence has not yet been studied. The Usher 2A gene may express RP without deafness, and possibly other more exceptional Usher 2 genes may provoke non-syndromic RP. The columns to the left indicate the colour code for the genes in the charts

autosomal dominant in inheritance and have a less severe and slower progression [42]. In most cases, the disease has started in an insidious way years before the diagnosis was made.

9.4.1.2 Nyctalopia

Loss of night vision is often the first symptom noticed by the patient. This already can start in early childhood or during adolescence. Nyctalopia is not unique to retinitis pigmentosa as it can be found in congenital haemeralopia and some severe choroidopathies or result from intoxication by some drugs, vitamin deficiencies or paraneoplastic processes.

9.4.1.3 Central Visual Acuity

Central vision may be preserved till late in the disease process. Some X-linked cases of retinitis pigmentosa associated with high myopia will provoke an early loss of central vision [11]. Progressive central visual loss in rod-cone dystrophies may result from cystoid macular oedema and central areolar atrophy or from an epiretinal membrane.

9.4.1.4 Photopsia and Other Symptoms

A number of patients complain of light flashes either in the centre or in the periphery, sometimes undulating and sometimes rotatory with variable intensity. These phenomena can be discrete or more diffuse, similar to what is sometimes observed in ophthalmic migraine. They could result from vitreoretinal traction. These subjective phenomena will regress when the retina is further affected.

9.4.1.5 Colour Vision

Colour vision may be normal when the central visual acuity is still normal. When the central vision is affected, usually a blue-yellow dyschromatopsia is found (acquired tritanopia). If a red-green deficiency is found, one has first to consider X-linked colour blindness (5–8 % of the male population) or cone or cone-rod dystrophy [9].

9.4.1.6 Photopic Visual Fields

The visual field is always affected. The initial alteration is related to the nyctalopia thus in scotopic conditions. The

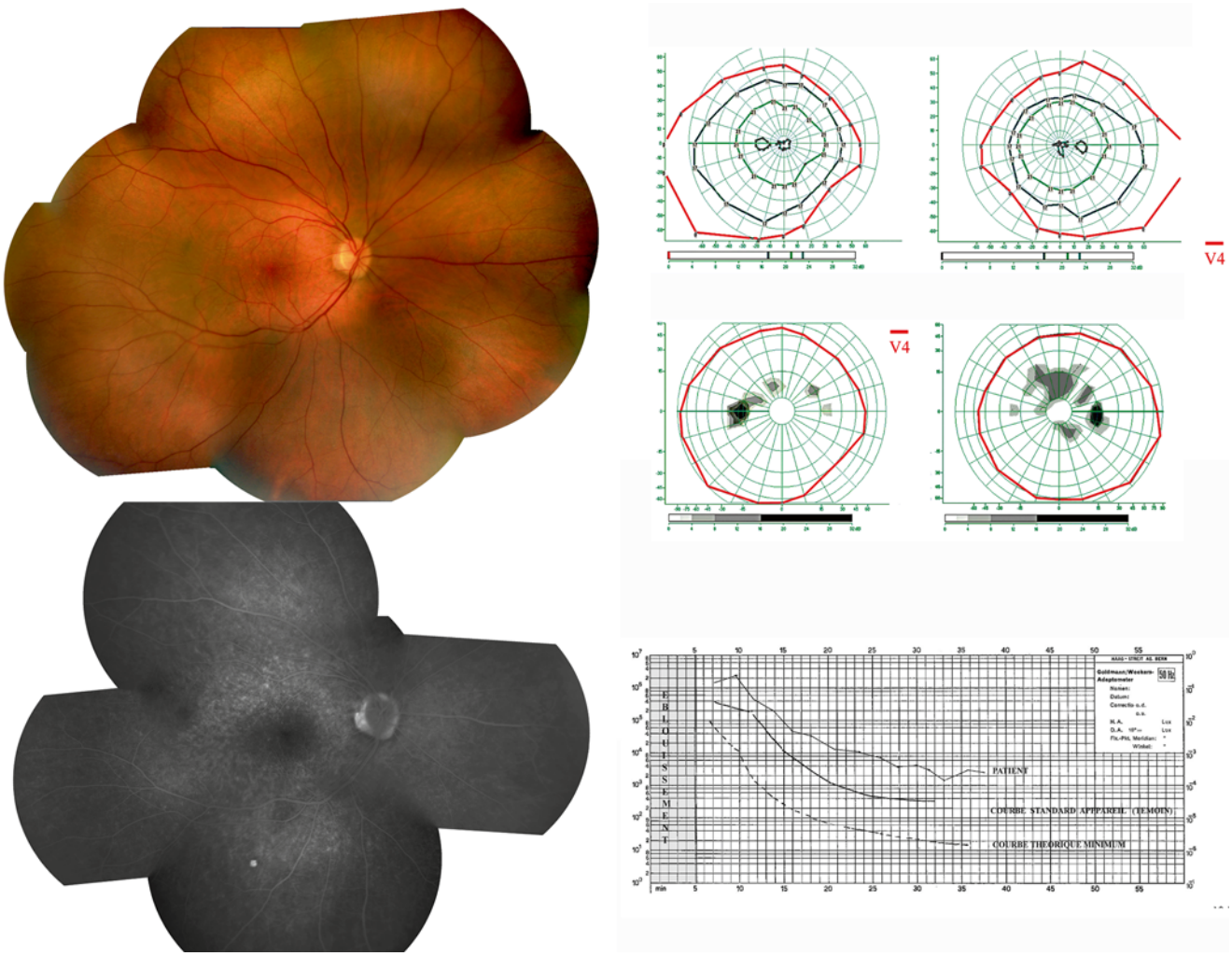

Fig. 9.3 Paucipigmentary form. A 53-year-old man from a family with an aggressive form of retinal dystrophy. Visual acuity is 2/10 ODS. The dark adaptation curve, the ERG and the EOG are markedly affected. His first symptoms started about the age of 50 years with photophobia, mild nyctalopia and the appearance of white dots in the posterior pole. These dots progressed to areas of chorioretinal atrophy [34]

photopic visual field may seem complete for the patient in the early stages of the disease although small relative scotomata may be present in the area between 20° and 40° from the fixation point. They can be detected in supraliminary static perimetry. On Goldmann kinetic perimetry, the central isopters seem to contract, and local depressions may indicate a more or less dense annular scotoma (Fig. 9.3). These small scotomas will fuse progressively, and a more or less dense annular scotoma will appear in the area between 20° and 45° from the fixation point. This annular scotoma will extend both towards the centre and towards the periphery (Figs. 9.4, 9.5 and 9.6).

The progressive disappearance of the peripheral visual field will take a few decades, whereas the central visual field appears more resistant, and although it will narrow progressively, a useful central vision can persist for four to five decades. Ultimately the patient will have tunnel vision, with a central field of 5–10° around the fixation point. Sometimes at that stage a visual acuity of 10/10 can still be obtained.

There is a vast literature on the progression of visual field loss. Berson et al. [2] estimated the loss at 4.6 % per year. Massof et al. [27] described retinitis pigmentosa patients with 50 % visual field loss within 4 or 5 years. One has to take into account the normal 10–15 % fluctuations from one field to the other regardless of the fact that the fields are measured in the same patient by the same or by different examiners [39]. There is also a high variability of the progression even in the same family.

9.4.2 Anterior Segment

After 10–15 years evolution, a subcapsular posterior cataract can be seen. It is especially visible in

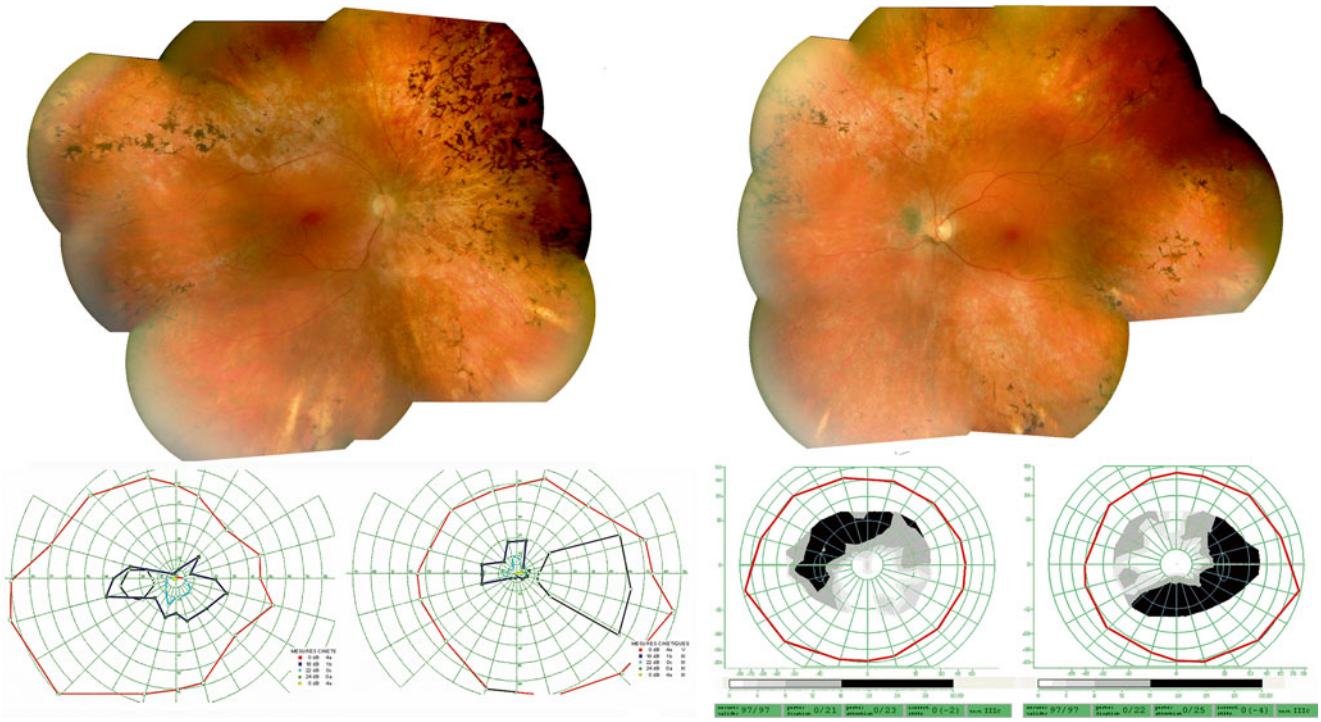

Fig. 9.4 Other paucipigmentary formed in a 16-year-old male with 10/10 vision ODS and nyctalopia. The family history is negative. Only few pigmentary changes, but already an incomplete annular scotoma. The ERG and the EOG are affected

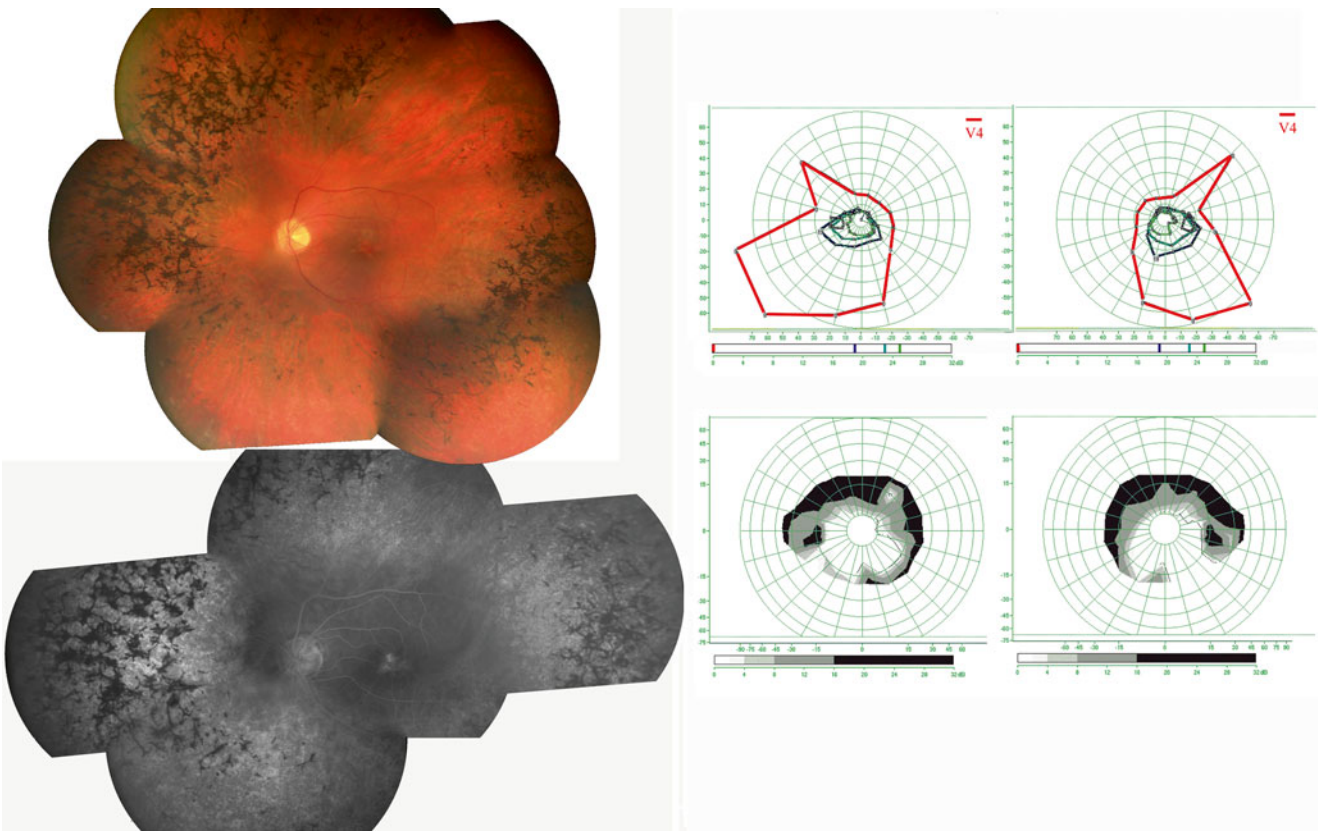

Fig. 9.5 A 47-year-old female. Negative family history. Visual acuity of 7/10 ODS. She complained since years of nyctalopia. Extensive visual field loss. Both cone and rod ERG responses are severely affected

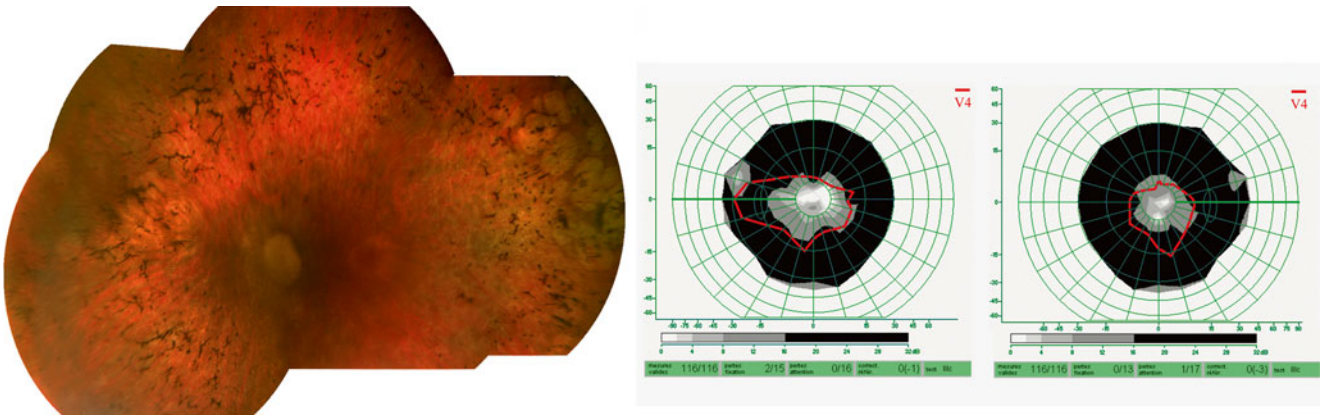

Fig. 9.6 Autosomal dominant retinitis pigmentosa in a 70-year-old pseudophakic woman She also has type II diabetes and is treated for glaucoma. Visual acuity of 5/10 RE and 6/10 LE. She complained of nyctalopia since early childhood. Tubular visual field. Ophthalmoscopy shows numerous pigment clumps and round areas of chorioretinal atrophy in the periphery. The macula is surrounded by a depigmented halo (Bull's eye maculopathy). No signs of diabetic retinopathy despite a hyperglycaemia of more than 2 g

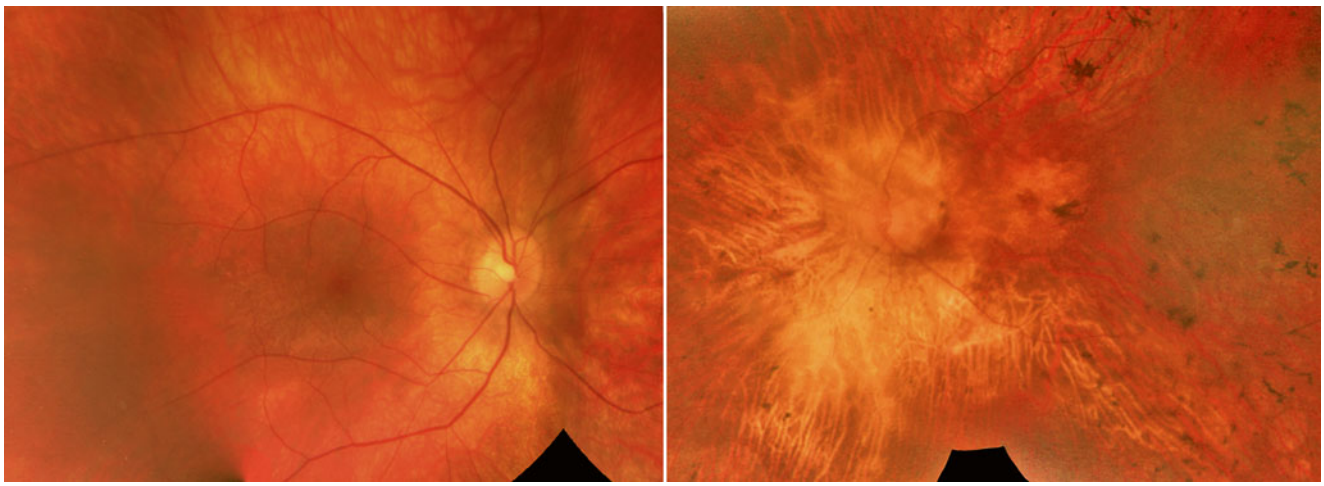

Fig. 9.7 A young 7-year-old girl with a −10 myopia and VA of 8/10 RE and 7/10 LE and her 78-year-old grandmother who has been operated of cataract but was also −10 D myopic. The vision of the grandmother is reduced to finger counting in the right eye and 4/10 in the left eye. Both are carriers of X-linked retinitis pigmentosa. In the grandmother large areas of chorioretinal atrophy and pigment clumping are seen. Heterozygotic mutation ORF15+875_876del GG in exon ORF15 of the RPGR gene

retro-illumination and will only progressively affect central vision after several decades of evolution. This slowly progressive cataract filters and reduces the light intensity and plays possibly a mild protective role against the deleterious effects of light**.**

9.4.3 Fundus Appearance

The fundus lesions affect both eyes and are symmetrical [25]. One can observe various manifestations.

- The retina may look *discoloured* especially in the posterior pole, around the optic disc and under the temporal vessel arcades (Fig. 9.7).
  This discoloration may be absent in highly pigmented individuals; the retina has a marbleized aspect due to a better visibility of the choroidal vessels. In far progressed stages, small round, more or less, confluent chorioretinal atrophic lesions may be seen.
- The *optic disc* can sometimes be pink and sometimes grey-yellow or waxy. When the disease progresses, a discoloration of the temporal sector is seen, and the optic disc is surrounded by chorioretinal atrophy. The aspect could be the result of the presence of astroglial fibrous tissue. Drusen of the optic disc or hamartomas may be present.
- Optic disc drusen are however not more commonly found in retinitis pigmentosa patients than in the general population.
  - *Narrowing of the arterioles* is sometimes associated with a discrete sheathing. When the arterioles become filiform, they are hardly visible especially in the retinal

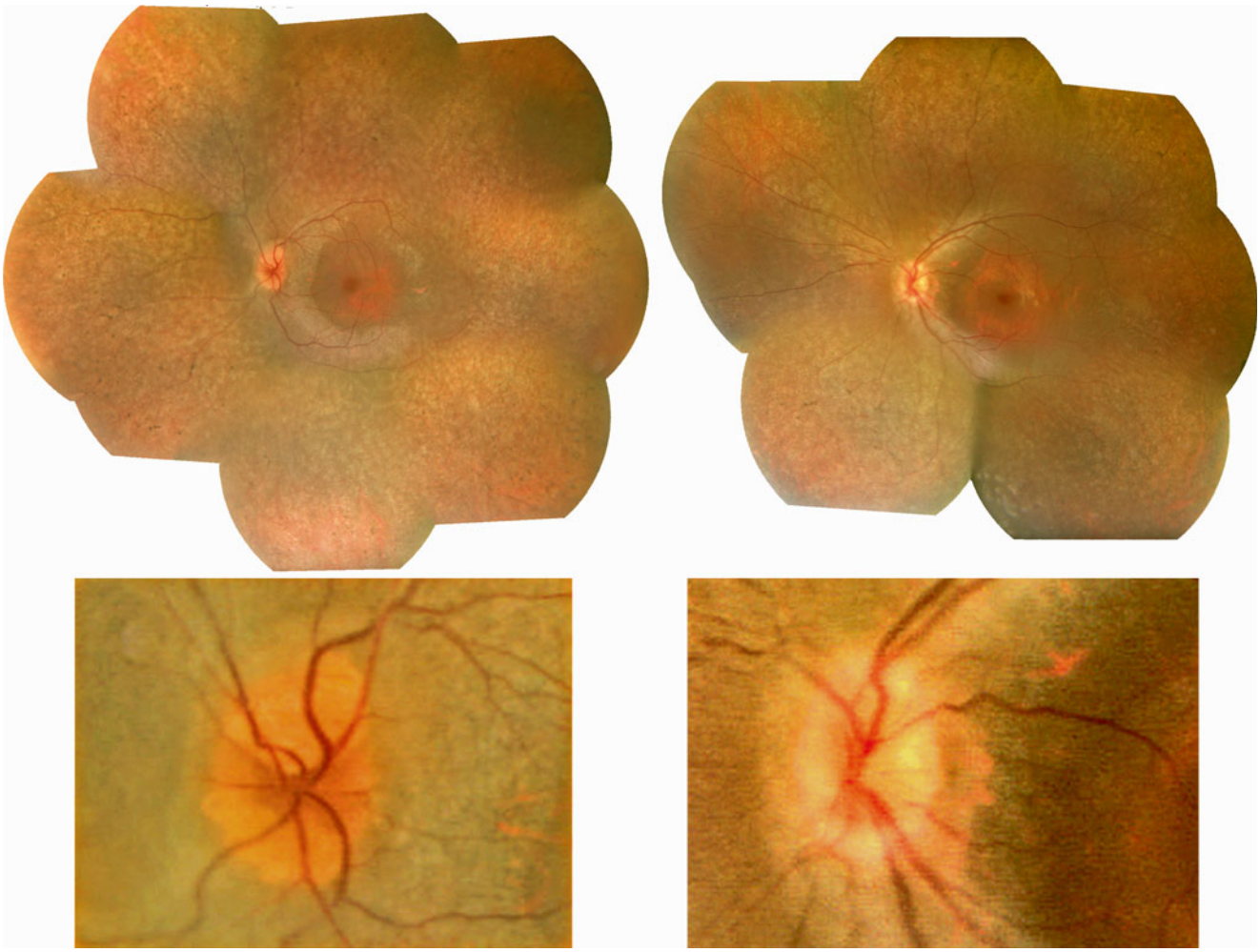

Fig. 9.8 Brother (*left pictures*) and sister(*right pictures*) with retinitis pigmentosa and extinguished ERG. The left pictures show only few bone spiculae but multiple whitish dots as well as a floater in contact with the disc and a parapapillary hamartoma. Right pictures: fundus in the sister with optic disc hamartoma

periphery. An aspect of vascular sclerosis of the choroidal vessels may be obvious most often in the peripapillary region.

  - *Pigment clumping*, sometimes as small round lesions, is more often in a pattern similar to the histological aspect of osteoblastic cells. These pigmentations may be dispersed in the fundus periphery but are more often to be seen around the retinal vessels or even in front of the vessels. They tend to increase in number and towards the posterior pole with progression of the disease.
  - Multiple *white dots* may precede or accompany the bone spiculae. They extend from the posterior pole up to the periphery and are quite often misdiagnosed as retinitis punctata albescens.

- Chorioretinal atrophic areas appear in the fundus periphery; initially they are isolated, small and sharply defined. These areas of atrophy can also appear around the disc, along the temporal arcades and later in the macular region (areolar atrophy).
  - *Vitreous changes* can sometimes be very discrete (cellophane aspect due to increased reflexes from the internal limiting membrane in the posterior pole), but can also present as vitreous condensation, floaters, vitreous prepapillary hamartomas, posterior vitreous detachment and pigment dust in the vitreous (Fig. 9.8).
  - *Macular alterations* are most commonly found in progressed cases and can present as increased reflexes of the vitreoretinal interface (cellophane maculopathy), cystoid macular oedema or atrophy.

In women carrier of X-linked retinitis pigmentosa, retinal pigmentary changes can be observed either as reticular lesions or as atrophic areas associated with osteoblastic pigment. Abnormal tapetal reflexes can be seen. Such reflexes can also be found in young patients affected with certain forms of X-linked cone-rod dystrophies.

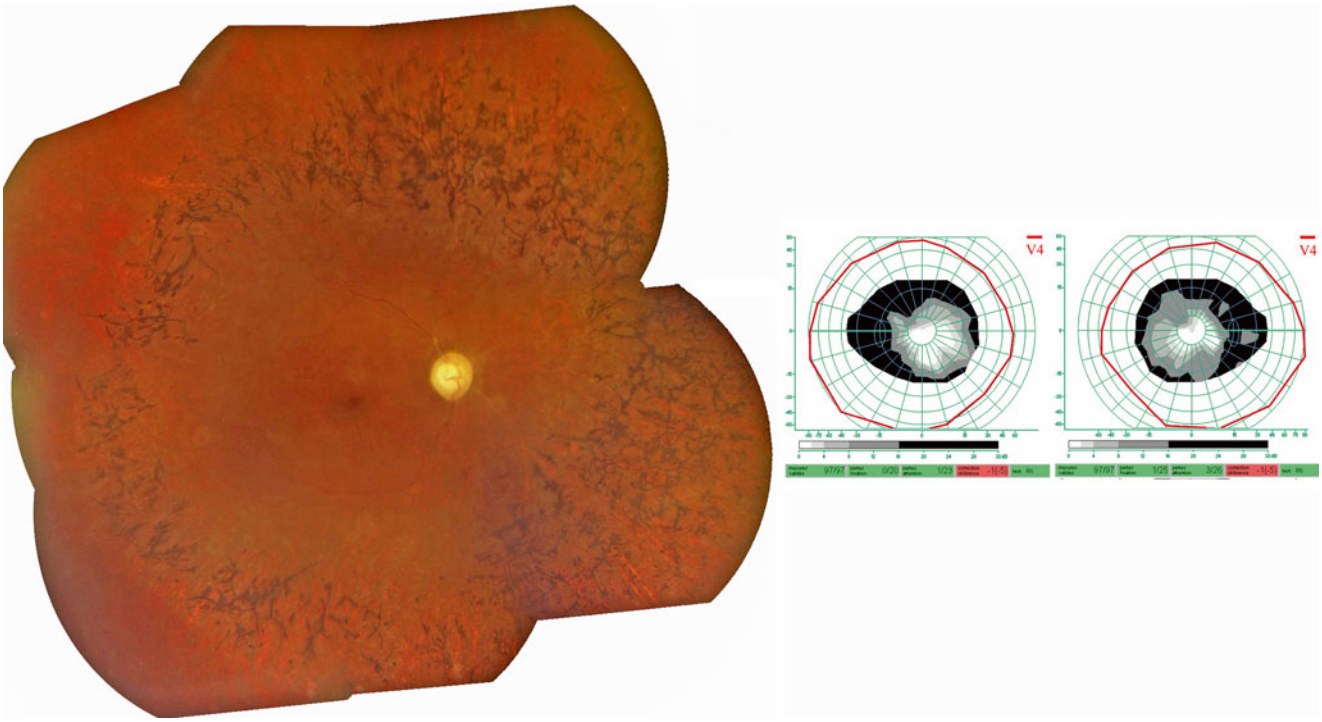

Fig. 9.9 A 32-year-old woman with sporadic retinitis pigmentosa. The dark adaptation curve is monophasic (Fig. 9.15) and the ERG not recordable

9.4.4 Investigations

9.4.4.1 Fluorescein Angiography

The diagnostic importance of fluorescein angiography has markedly been reduced since the introduction of fundus autofluorescence and optical coherence tomography. It remains useful in difficult diagnoses, in the possible detection of female carriers of X-linked RP and in the diagnosis of vascular complications of retinitis pigmentosa.

- *Depigmentation of the retinal pigment epithelium (RPE)*. This is found in the posterior pole and around the optic disc, but does not involve the macular region. It can extend slightly over the temporal arcades (Fig. 9.5). Sometimes a clear demarcation can be seen between the affected area and more healthy areas. This depigmentation is especially obvious in mitochondrial retinitis pigmentosa where an aspect similar to "fundus pulverulentus" or very small pigmented flecks and peripheral pigmentary changes can be seen.
- *Ruptures of the blood-retinal barrier* (BRB) can be observed in the periphery where the terminal part of the retinal vessels may leak fluorescein. Such a rupture of the BRB can sometimes be seen in the vicinity of the optic disc along the larger retinal vessels and be associated with cystic macular oedema, which is a common complication of retinitis pigmentosa (Fig. 9.10). This gives a typical stellar aspect on late fluorescein angiography.

9.4.4.2 Fundus Autofluorescence (FAF)

The scanning laser ophthalmoscope allows to observe the amount of lipofuscin in the retinal pigment epithelium. Lipofuscin is the principal source of autofluorescence. Hyperfluorescence corresponds to a metabolic dysfunction of the retina and hypofluorescence to atrophy of the retinal pigment epithelium. This allows a mapping of the more or less affected regions and a correlation with retinal function. In RP most commonly annular regions of hyper- or hypofluorescence are seen as well as atrophic areas scattered around the posterior pole. Hyperfluorescent rings around the macula or more in the periphery are found in almost 80 % of the cases (Fig. 9.11).

9.4.4.3 Optical Coherence Tomography

OCT allows to visualise the thinning or the disappearance of retinal layers including the photoreceptor layer in the posterior pole. Special attention should be given to the disappearance of the junction between inner and outer segment of the photoreceptors or connecting cilia. OCT also highlights cystoid macular oedema, modifications of the vitreoretinal interface and the progressive disappearance of the photoreceptors (Figs. 9.12 and 9.13). OCT may also reveal a serous detachment of the RPE.

9.4.4.4 Dark Adaptation

This test is usually performed with the Goldmann-Weekers adaptometer. In the normal subject the curve obtained after light

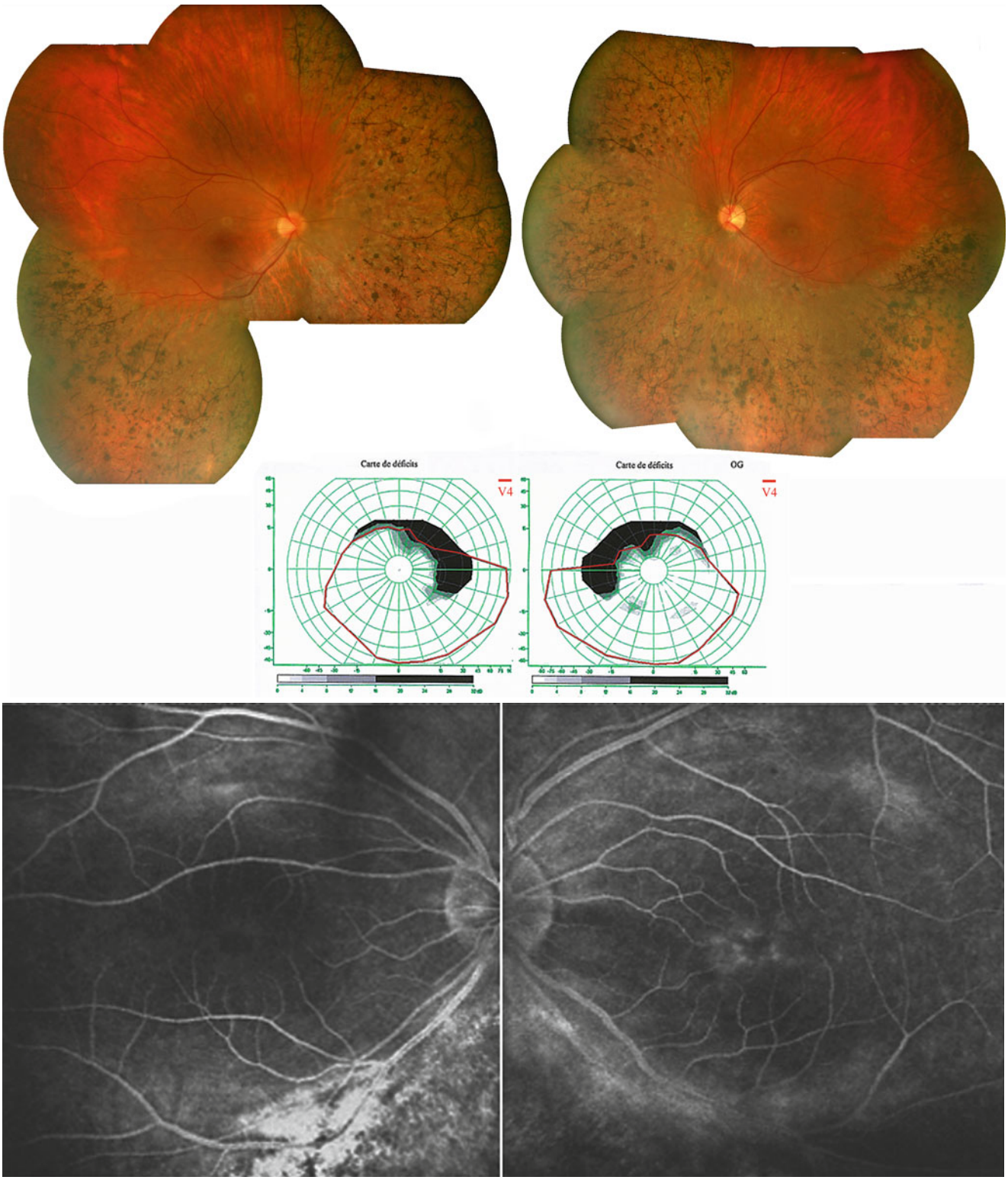

Fig. 9.10 A 38-year-old female patient. The diagnosis of retinal dystrophy was made 15 years earlier. VA 10/10 OD and 9/10 OS. The superotemporal field defects correspond to the affected areas on ophthalmoscopy. Rupture of the blood-retinal barrier and cystoid macular oedema

adaptation is biphasic. The first short and rapidly declining segment corresponds to the adaptation of the cones and lasts about 3–6 min, and a slower second slope gradually reaches a parallel with the time axis. The junction between the cone and the rod adaptation is called point alpha. The final threshold is usually reached after 20 min and may slightly vary with age.

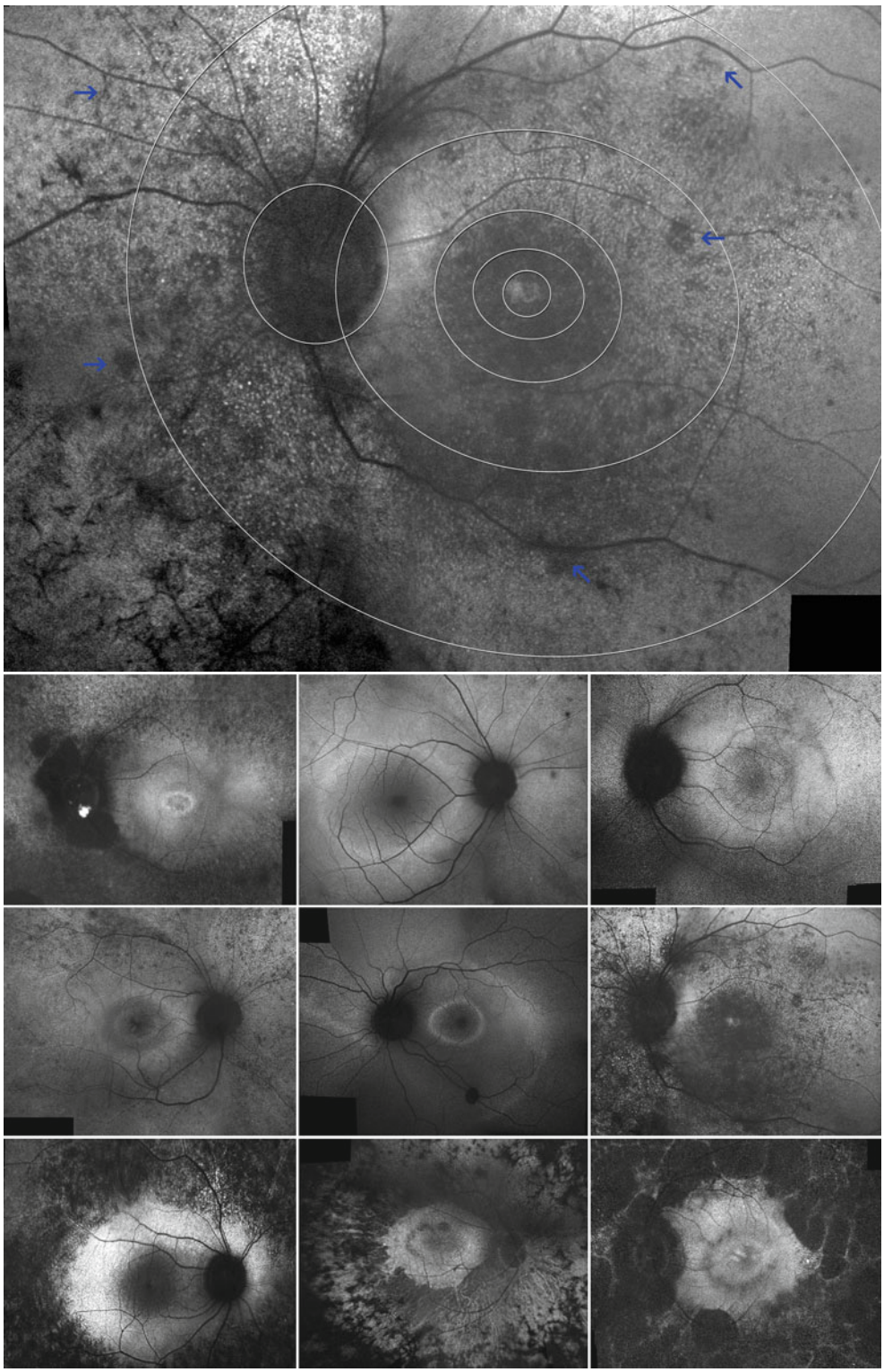

Fig. 9.11 Various autofluorescent aspects in RP. The top picture is that of a 50-year-old man with slowly progressive retinitis pigmentosa and still 10/10 visual acuity in both eyes. The different rings outline areas of hypo- and hyperfluorescence. The hyperfluorescent dots could possibly correspond to lipofuscin deposits which often precede osteoblastic pigments in RP. The dark areas of hypofluorescence (*blue arrows*) correspond to areas where the retinal pigment epithelium has lost its normal autofluorescence. The peripapillary hypofluorescence sometimes extends further. The other pictures represent different stages of the disease

Monophasic curves can be found when the rods are primarily affected. A prolonged cone adaptation results in a displacement of the alpha point to the right.

In classic retinitis pigmentosa the recovery of rod sensitivity is abnormally delayed; the curve is prolonged and the normal threshold is reached very late or not at all. The curve tends to be monophasic and the curve is elevated (Figs. 9.9, 9.14 and 9.15).

9.4.4.5 Electroretinography (Fig. 9.16)

Karpe was the first to show the severe ERG changes in retinitis pigmentosa [23]. The ERG is affected early in life, and

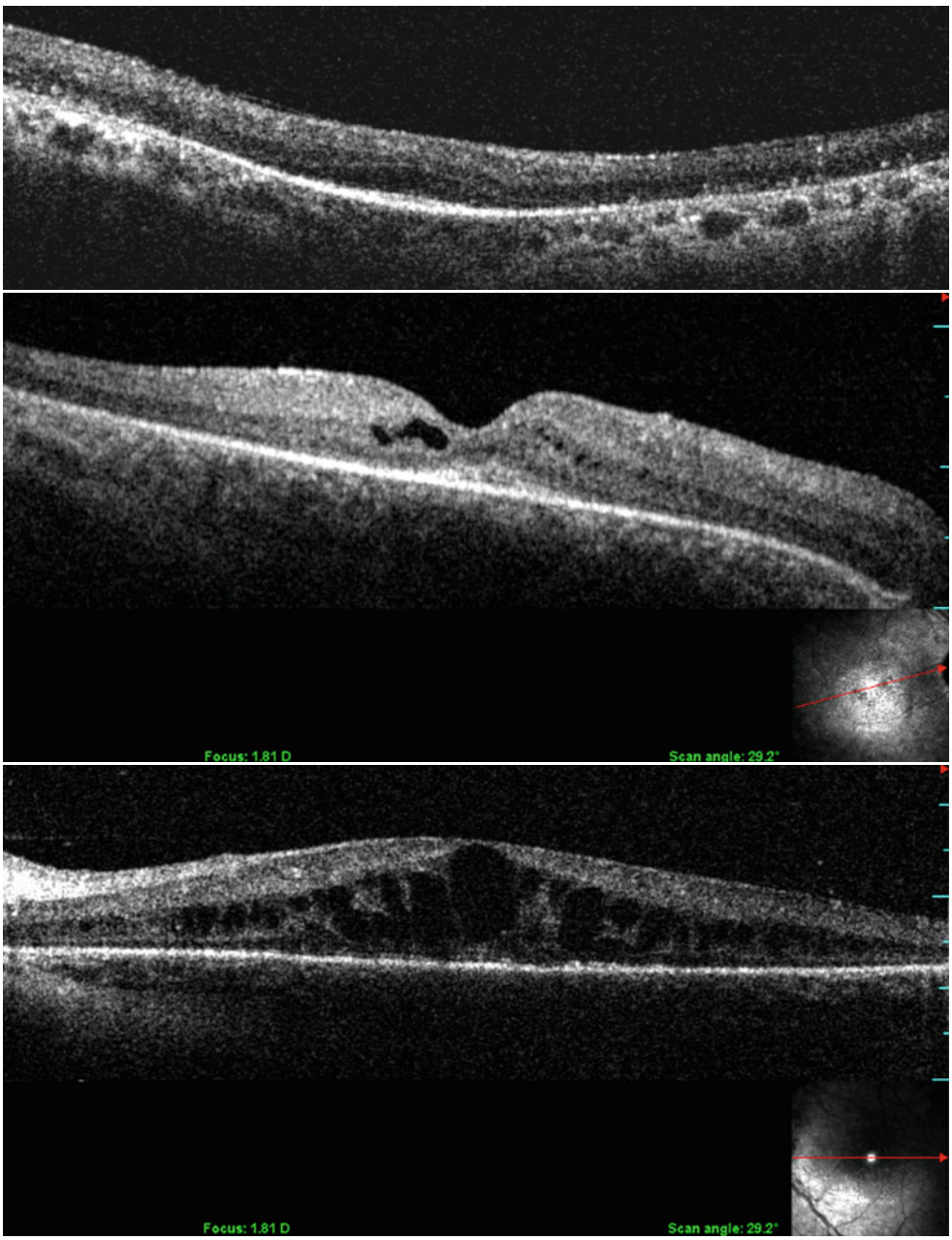

Fig. 9.12 Cystoid macular oedema in retinitis pigmentosa patients. A. Disappearance of the foveal depression and localised neuroretinal detachment. B. Residual intraretinal vacuoles. C. Cystoid macular oedema and marked retinal thickening

according to Berson, individuals older than 6 years of age with normal ERGs have not been reported to develop typical retinitis pigmentosa at a later time [3]. The responses obtained after dark adaptation in general relate to the rod function and those in photopic conditions to cone function. A poor photopic response allows an early differentiation of rod-cone from cone-rod dystrophies. ERG is also essential for the diagnosis of atypical forms without pigments from congenital haemeralopia and to detect female carriers of X-linked forms.

- In the early stages of the disease, the photopic responses of the ERG may present a normal morphology or be slightly modified in amplitude and delayed in their timing.
- The scotopic involvement is more marked. The amplitudes may be reduced by one third or more already at the first examination; later when the disease progresses, the amplitude further diminishes and eventually disappears. Once the scotopic responses have disappeared, the photopic responses may still be detectable although their amplitude is reduced.
- With progression of the disease, no ERG is detected, although central visual acuity may still be excellent. Berson et al. noticed that on average patients lost 16–18 % of the amplitude of the responses per year [2].

Various types of ERG changes have been described, although this does not necessarily help in the diagnosis or prognosis of retinitis pigmentosa [13, 17]. The amplitude of the ERG has been correlated to the size and the sensitivity of the remaining visual field. Sectorial RPs have obviously

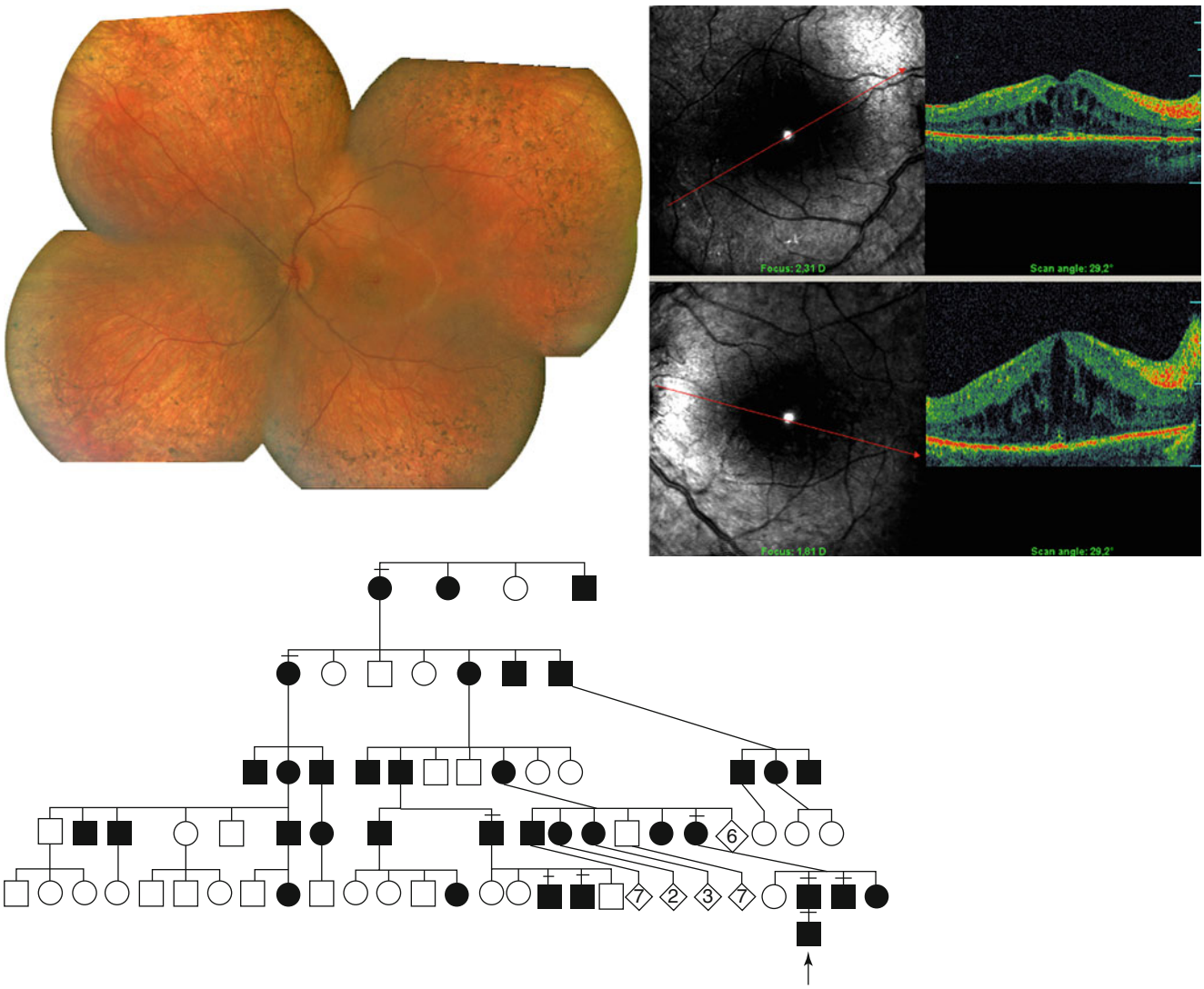

Fig. 9.13 A 10-year-old child with autosomal dominant retinitis pigmentosa. Visual acuity is 4/10 RE and 3/10 LE. The ERG is markedly disturbed. Cystoid macular oedema has been detected in several family members and is here extremely marked

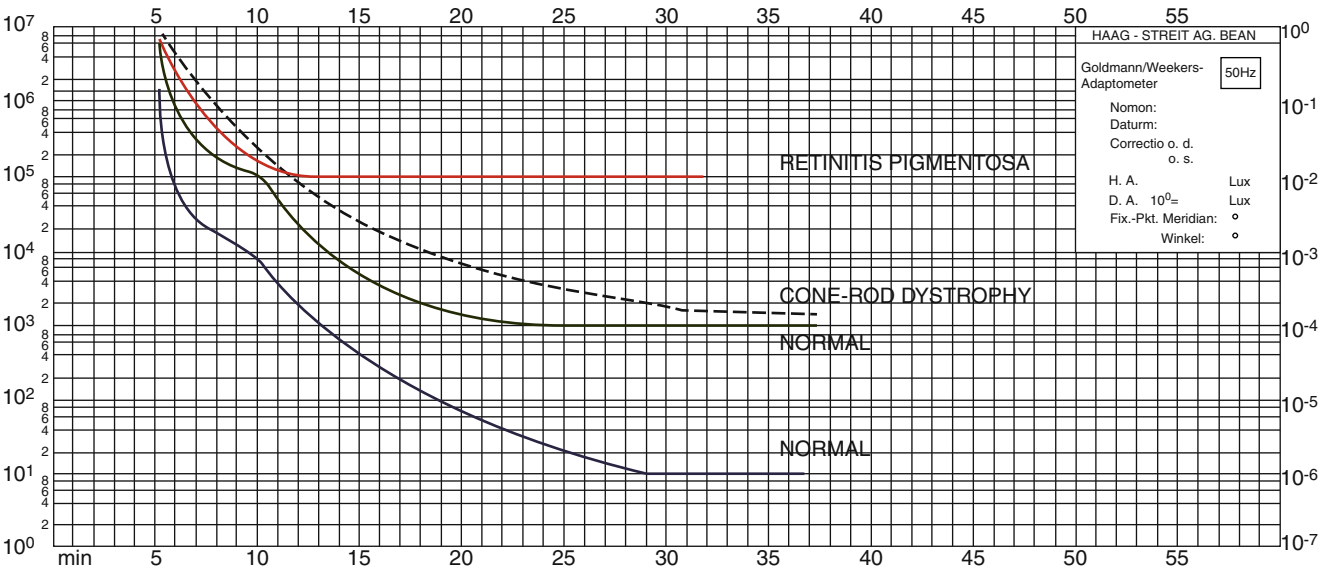

Fig. 9.14 Goldmann-Weekers adaptometry. The top curve corresponds to a retinitis pigmentosa patient

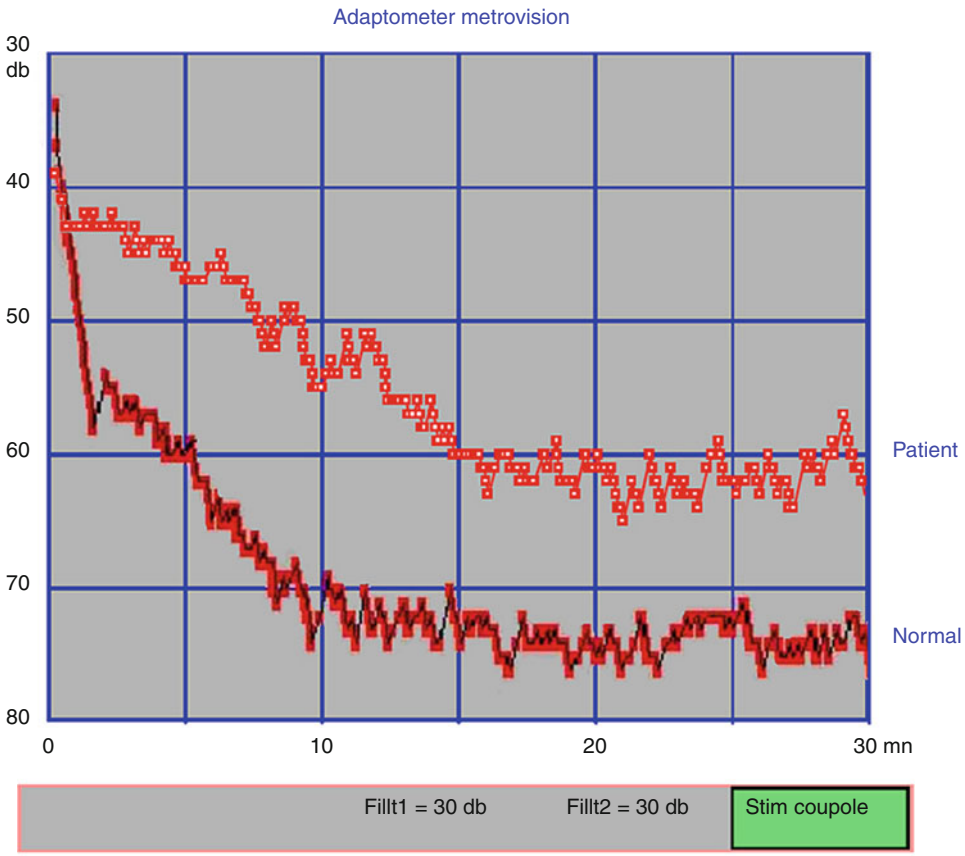

Fig. 9.15 Adaptometry with the ophthalmic monitor. The light red curve which is monophasic and does not show an alpha point corresponds to the patient in Fig. 9.10

far better ERG responses. In X-linked RP, characterised by a more rapid progression, the ERG is often extinguished before the age of 20 years. RP2 is associated with early involvement of the cones. On the other hand, in some forms of autosomal dominant RP, the diagnosis is made only late in life, and the progression is much slower so that an ERG response can still be recorded till the age of 50 years.

9.4.4.6 Multifocal Electroretinography

This examination maps the electrical responses of about 20° of the central retina. This area is usually the last affected in RP, and multifocal ERG does not allow an early diagnosis of the disease.

9.4.4.7 Electro-oculography (EOG)

The EOG is always modified in RP and follows the evolution of the ERG although the EOG is less sensitive. It does not have the diagnostic and prognostic value of the ERG.

9.4.5 Evolution

As there is still no effective treatment, the progression is unavoidable. The evolution may vary for the same affected gene or the same mutation within a same family. The more severe cases become apparent earlier in life [35]. Juvenile and X-linked forms have a worse prognosis than late onset cases. Luckily for most cases the evolution is very slow and will take between 30 and 40 years. Sometimes one has to wait for 3–5 years to be able to measure the progression of the disease. According to a study by Grover et al. on retinitis pigmentosa, patients aged 45 years or older, 52 % had 20/40 or better vision in at least one eye, 25 % had 20/200 or worse vision and 0.5 % had no light perception [14].

The visual field becomes gradually more narrow. The annular scotoma, initially situated between 20 and 30, enlarges towards the periphery and towards the centre. The peripheral isopter disappears first nasally leaving often for a long time a temporal crescent, and eventually the fields become tubular.

The central visual acuity depends on the preservation of the central island, which is the last portion of the field to disappear. However, an earlier loss of central vision is possible in cases of associated macular lesions (cystoid macular oedema, epiretinal membranes).

9.4.6 Complications

9.4.6.1 Cystoid Macular Oedema

Cystoid macular oedema has frequently been described in retinitis pigmentosa; it may be found in all genetic forms and

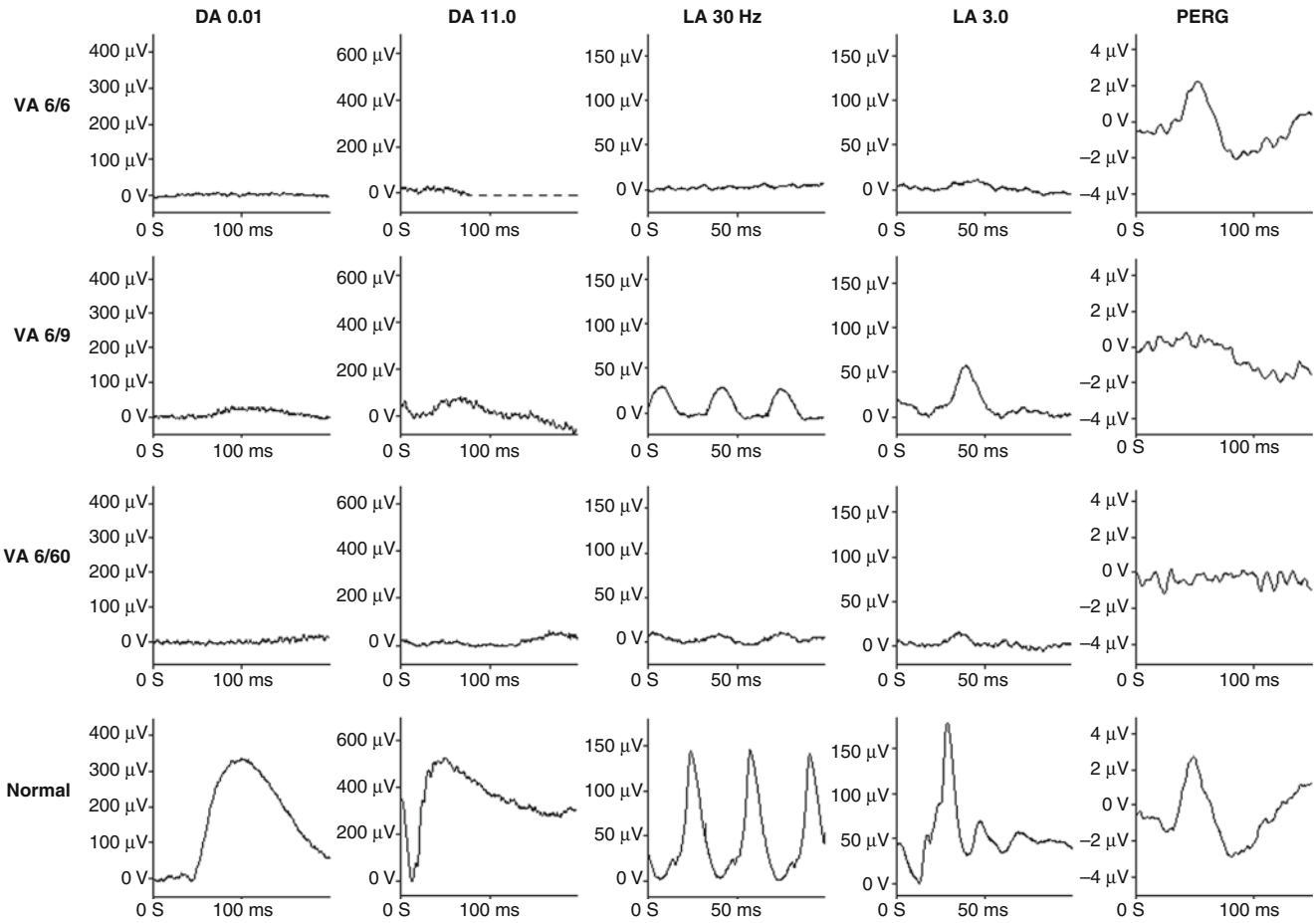

Fig. 9.16 ERG Typical findings in three patients with retinitis pigmentosa RP and rod-cone dystrophy all show markedly abnormal ERGs with the rod system being more affected than the cone system. The rod-specific ERG is undetectable in the patients with 6/6 and 6/60 visual acuity (*VA*) and markedly subnormal in the patient with 6/9 VA. Those findings indicate loss of rod system sensitivity. The profound reduction in bright flash dark-adapted ERG (*DA 11.0*) a-wave amplitudes establishes the abnormality to be at the level of the photoreceptor. There is severe cone system abnormality in the 6/6 patient, with only residual cone single-flash ERG function (*LA 3.0*). The patients with 6/9 and 6/60 show clearly detectable cone ERGs with profound amplitude reduction and the marked delay characteristically seen in generalised cone dysfunction as part of a generalised photoreceptor degeneration. The PERG is normal in the 6/6 patient, despite almost extinguished full-field ERGs, indicating sparing of the macula. The 6/9 patient shows much better overall ERGs, but the PERG is markedly reduced even though visual acuity is only mildly affected, indicating marked macular involvement. In the 6/60 patient, there is severe macular involvement demonstrated both by an undetectable PERG and the level of VA reduction. The findings demonstrate the complementary nature of pattern and full-field ERGs in the characterisation of patients with generalised retinal dysfunction that may or may not involve the macula

usually affects both eyes. According to Fetkenhour et al. , up to 70 % of RP patients present some degree of CMO [10]. Inflammatory signs are frequently observed in the vitreous of RP patients. With time some coalescence of the intraretinal cysts may be observed, giving the aspect of a lamellar hole. This is however quite exceptional.

The diagnosis of CMO is actually most easily made with OCT (Figs. 9.12, 9.13 and 9.17).

Different treatment modalities have been proposed, even grid photocoagulation of the macula. Such a treatment is however not recommended as it will further reduce the central visual field. A favourable response can be obtained in early cases with acetazolamide. The chronic use of acetazolamide may provoke a rebound phenomenon as observed with OCT [1]. The alternative is steroid treatment and even intravitreal triamcinolone injections, which may induce a temporary reabsorption of the intraretinal fluid, but with recurrence of CMO after a few months.

9.4.6.2 Hamartomas

An astrocytic hamartoma is characteristic of Bourneville tuberous sclerosis but can also be found in neurofibromatosis. Isolated lesions in otherwise healthy individuals are not exceptional. Robertson described six cases of retinitis pigmentosa associated with hamartomas of the optic disc [38]. These lesions were relatively large, irregular and mulberry – like masses present at the optic disc and adjacent retina. New masses were observed, while others in the retina [7, 31, 36] were transformed from barely translucent lesions to more discrete pearly masses (Fig. 9.18).

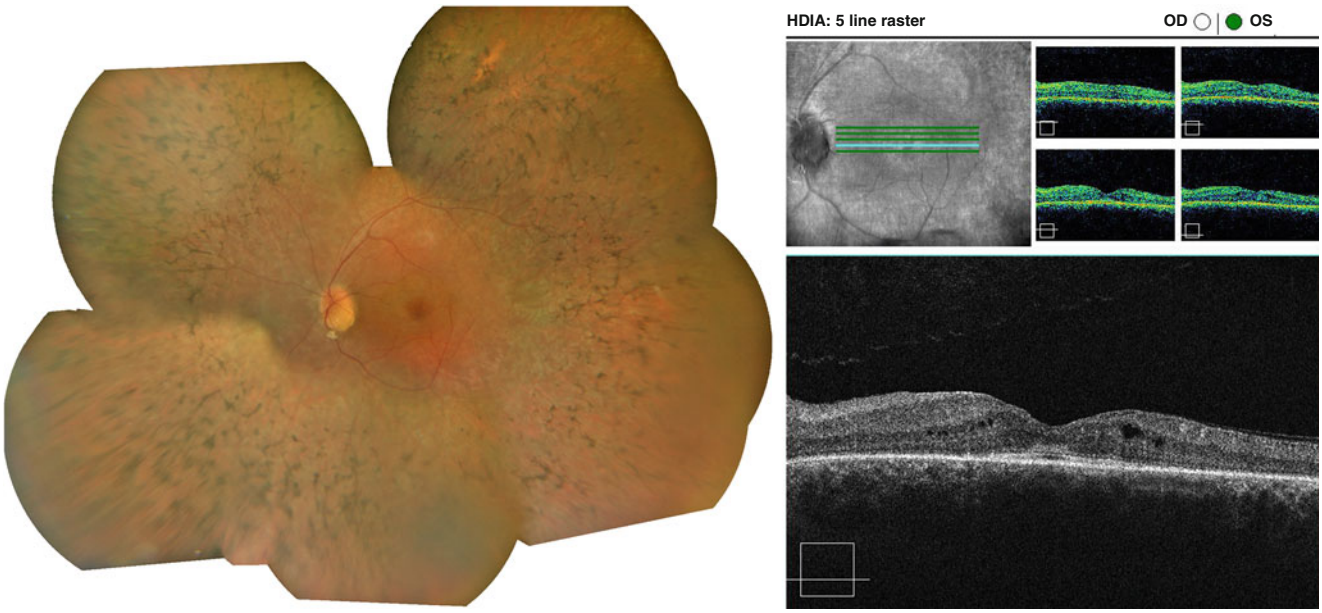

Fig. 9.17 Father of the child in Fig. 9.13. Visual acuity 4/10 ODS. Residual cystoid macular oedema and parapillary "hamartoma"

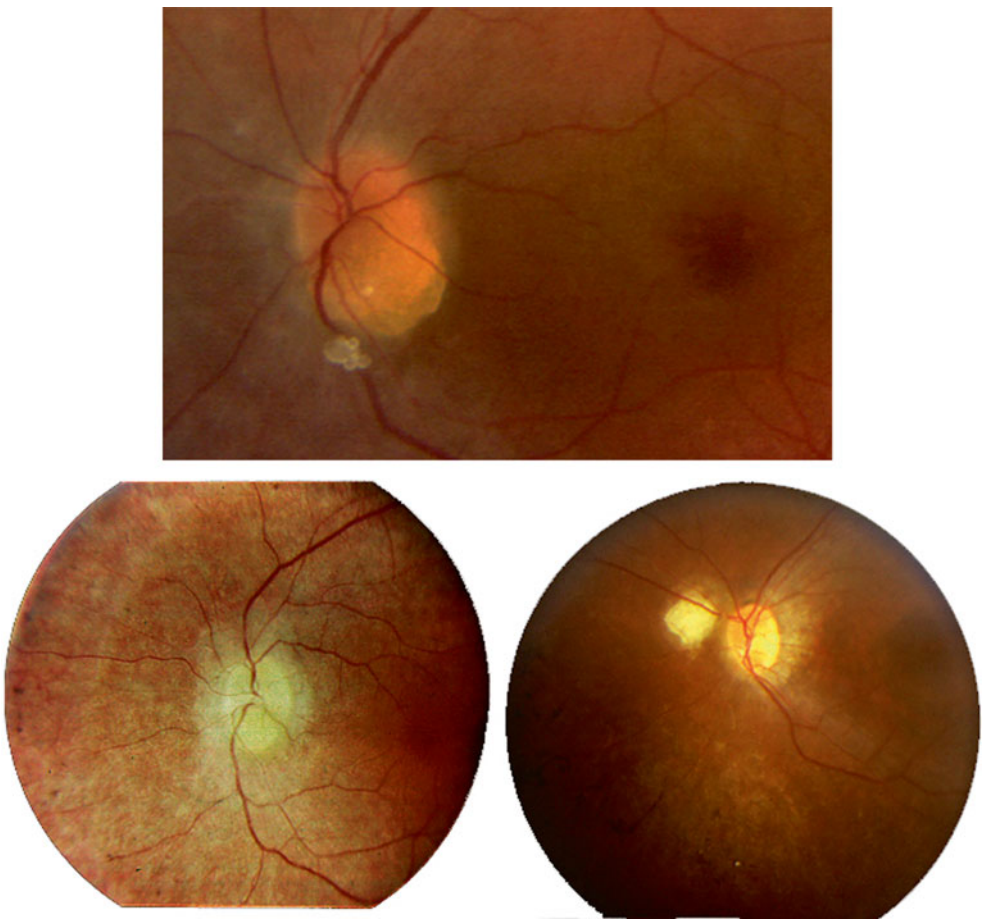

Fig. 9.18 Three different patients with retinal dystrophy and peripapillary "hamartoma"

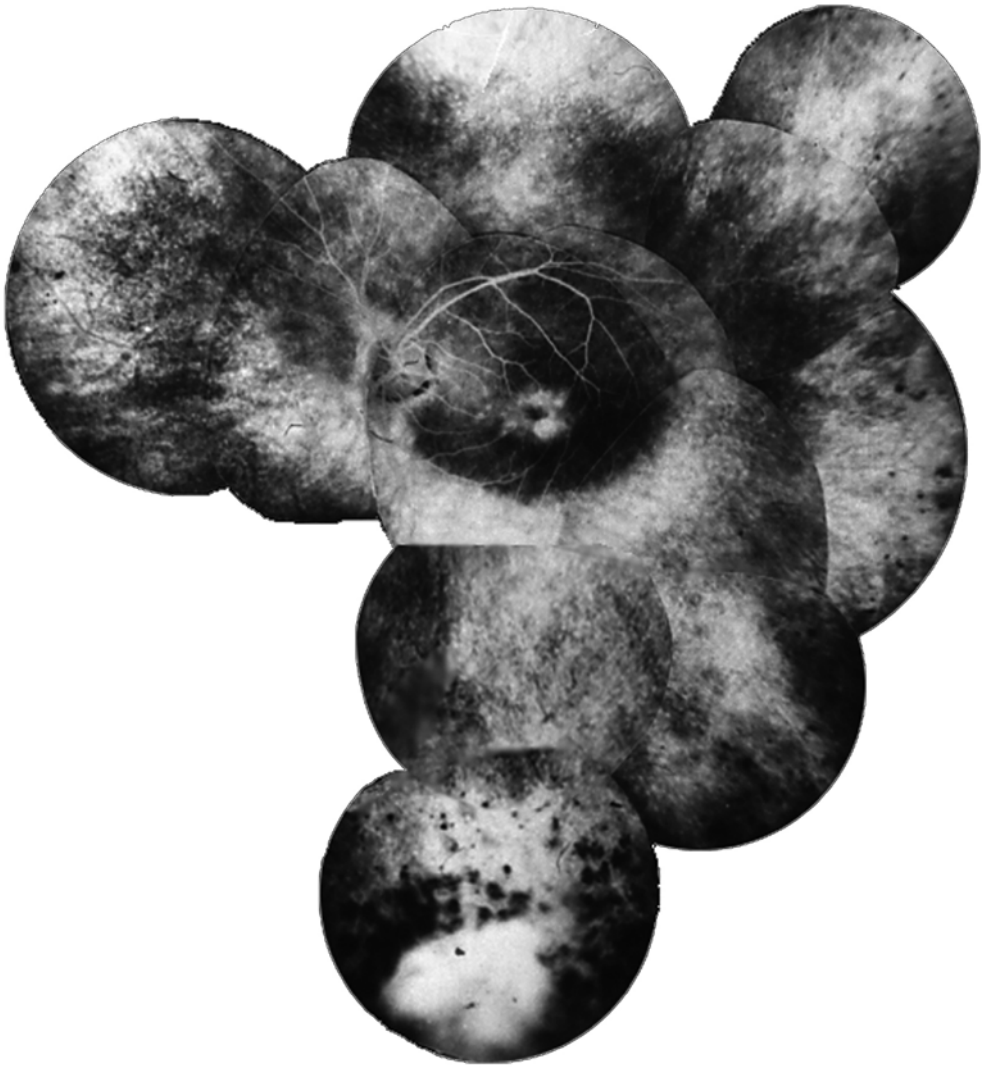

Fig. 9.19 Coats-like syndrome in a 50-year-old man. The right eye was lost by exudative detachment and neovascular glaucoma. Cystoid macular oedema and telangiectasis in the inferior periphery (partially surrounded by laser scars)

9.4.6.3 Coats Syndrome and Retinitis Pigmentosa

In 1956 Zamorani described first the association of Coats-like lesions and retinitis pigmentosa [45]. The association is relatively rare but may be found in all genetic forms of RP [8]. In most cases the diagnosis of retinitis pigmentosa was made long before the vascular lesions were detected. Cystoid macular oedema is almost always present. A characteristic finding is the sometimes very impressive inflammatory reaction of the vitreous. The Coats-like lesions are situated in the inferior periphery (Figs. 9.19 and 9.20). The lesion may consist of clusters of new formed vessels surrounded by some haemorrhages and lipoid exudates. In more progressed cases, subretinal exudation is present, and the lesion acquires a pseudotumoural aspect covered by dilated vessels, telangiectasis and neovascularisation. The retinal exudation may be extremely marked and progress up to the posterior pole. Spontaneous disappearance of the exudates has been documented.

Although some eyes may stabilise or even show spontaneous regression of the exudates, untreated eyes tend to progress to exudative detachment, recurrent vitreous haemorrhages or even neovascular glaucoma. Direct photocoagulation of the lesions has been attempted with varying results. Probably a more efficient and also safer approach is ab externo cryocoagulation if necessary after release of subretinal fluid in cases of associated exudative detachment.

9.4.7 Histopathology

The earliest pathological changes are the displacement and later loss of the nuclei from the outer nuclear layer [12]. The rod outer segments shorten which eventually leads to

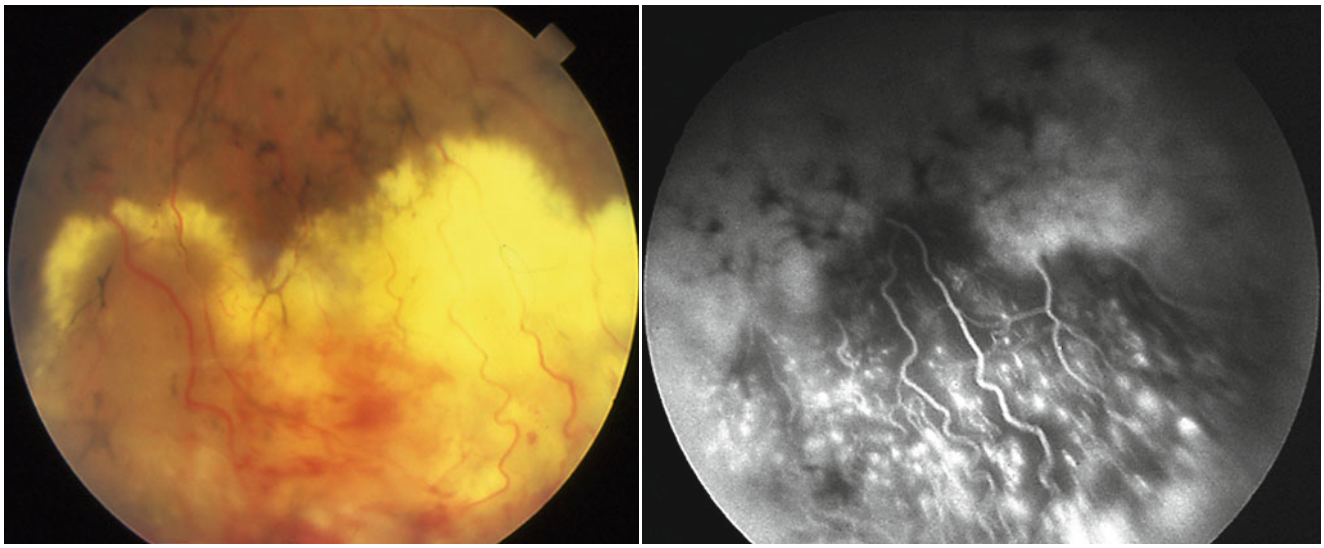

Fig. 9.20 Woman of 26 years of age with a diagnosis of retinitis pigmentosa since childhood. Visual acuity 2/10 ODS. Cystoid macular oedema and pseudotumoural exudative lesion in the inferior periphery

cell loss [29]. This occurs initially in the midperiphery. Rods around the macula and near the ora serrata survive longest. In the case of rhodopsin mutation, it has been suggested that photoreceptor cell death is the consequence of the accumulation of mutant rhodopsin in the endoplasmic reticulum and in the Golgi apparatus, interfering with their function [30]. The peripheral rods sprout anomalous neurites which bypass bipolar and horizontal synapses and become associated with the Müller cells. Cone degeneration, depending on the genetic form of the disease, may occur early or late. The process is similar to that of the rods, although neurite sprouting is less marked than in rods. Rod degeneration could play a deleterious role in the survival of cones.

Retinal pigment epithelial cells migrate into the retina, mainly around the retinal blood vessels, but also as bone spiculae characteristic of the disease. Due to the migration of the RPE cells, the subretinal space shrinks and eventually disappears. Proliferating glial cells and fibres are found.

The Müller cells undergo reactive gliosis, and the degenerated photoreceptors are replaced by thickened Müller cell processes which form a fibrous layer which seals off the underlying choroid.

Although the internal nuclear layer and the ganglion cell layer were considered to be less involved, a considerable reduction in ganglion cell numbers has been noticed [40].

Marc et al. [26] extensively studied neural remodelling in retinal degeneration. This includes neuronal cell death, neuronal and glial migration, elaboration of new neurites and synapses, rewiring of retinal circuits, glial hypertrophy and development of a glial membrane that isolates the remnant retina from the surviving RPE and choroid [26].

A typical feature of retinitis pigmentosa is the marked attenuation of the retinal blood vessels. This may result from decreased oxygen consumption, related to photoreceptor cell loss and thus increased oxygen tension in the inner retina. A prominent layer of extracellular matrix can be found between the retinal pigment epithelium and the endothelial cells of venules and capillaries. This may even occlude the retinal vessels. Vascular endothelial cells in the vicinity of migrated RPE cells may develop fenestrations and thus explain the fluorescein angiographic features of leaking vessels.

The areas of choriocapillaris in the vicinity of large zones of RPE destruction undergo destruction, although large portions of the choriocapillaris may remain intact even under degenerated retina.

The pallor of the optic disc, which is clinically striking, is possibly related to ganglion cell loss. It may however also be the consequence of extensive gliosis [28].

9.4.8 Differential Diagnosis (Table 9.2)

Rod-cone dystrophies must first be differentiated from other retinal dystrophies which may be:

Table 9.2 Differential diagnosis

Stationary	Fundus albipunctatus cum hemeralopia	
	Congenital stationary night blindness (CSNB)	
	Achromatopsia	
	Blue cone monochromatism	
	Grouped pigmentation of the retina	
Progressive	Cone and cone rod dystrophies	
	Choroidopathies	Krill choriocapillaris atrophy
		Choroideremia
		Atrophia gyrata
		L-ORD dystrophy
		Bietti crystalline dystrophy
		Sorsby pseudo inflammatory dystrophy
		Progressive bifocal chorioretinal dystrophy
	Syndromic retinitis pigmentosa	
		Bardet Biedl syndrome
		Usher syndrome
		Refsum syndrome
		Allagile syndrome
		Alstrom syndrome
		Bassen-Kornzweig syndrome
		Cockayne syndrome
		Flynn Aird syndrome
		Hallervorden Spatz syndrome
		Jeune syndrome
		Kearns Sayre syndrome
		Mucopolysaccharidoses
		Senior-Loken syndrome
		Neuroceroid lipofuscinosis (Batten disease)

Rod-cone dystrophies have to be differentiated as well from acquired retinal degeneration mimicking retinitis pigmentosa (Table 9.3).

Even in the presence of a typical retinal dystrophy, one has to consider the possibility of systemic involvement. This necessitates a thorough investigation of the personal and the family history; genetic investigations; examination of other family members, to look for hidden or not obvious disorders such as deafness; possible previous surgery for hexadactyly, skeletal, kidney or skin anomalies; and dysmorphisms. This is certainly the case in young children who may still not have developed systemic signs and symptoms. A neuro-paediatric examination is recommended.

Some complementary tests are sometimes needed for difficult or atypical cases:

- Serum phytanic acid when other neurologic abnormalities are present
- Plasma ornithine levels when a diagnosis of gyrate atrophy has to be considered
- Electromyography and ECG in suspected Kearns-Sayre syndrome
- Lipid profile with possible protein electrophoresis in patients with suspected abetalipoproteinaemia
- Antiretinal antibodies, particularly antirecoverin and anti-enolase antibodies, in paraneoplastic processes such as cancer-associated retinopathy (CAR) or melanoma-associated retinopathy (MAR).
- Venereal Disease Research Laboratory (VDRL) test and fluorescent treponemal antibody absorption (FTA-ABS) test, to rule out previous syphilis

Table 9.3 Acquired conditions mimicking retinitis pigmentosa

Unilateral	
Choroidal vascular occlusion (Fig. 9.21)	
Trauma	
Infectious	DUSN (diffuse unilateral subacute neuroretinitis)
Inflammatory	Vogt-Koyanagi-Harada, AZOOR Resolution of uveal effusion or of retinal detachment
Tumoral	leucaemic infiltrates, non-Hodgkin lymphoma
Bilateral	
Infectious	Syphilis Rubella embryopathy CMV retinitis
Toxic	Phenothiazine Chloroquine
Paraneoplastic processes	Cancer associated retinopathy Melanoma associated retinopathy
Nutritional	Avitaminosis A

Summary for the Clinician

- Retinitis pigmentosa is a term which is still used today. In this chapter mainly rod-cone dystrophies are considered.
- Rod-cone dystrophy is a genetic disorder with variable mode of inheritance. More than 50 defective genes have been identified but still more remain to be discovered.
- The first symptom is loss of night vision.
- Central visual acuity may be preserved till late in the disease process, unless complications occur.
- The visual field is always affected. The progression of the visual field defects is however very variable from case to case even in a same family.
- The fundus is characterised by narrowing of the retinal vessels, pallor of the optic disc and retinal pigment changes, of which the bone spiculae are the most obvious. They may appear initially in the midperiphery, often around the blood vessels.
- Ruptures of the blood-retinal barrier are commonly seen.
- The ERG is the key for an early diagnosis. Both photopic and scotopic responses are affected, and eventually the ERG will become extinguished.
- The most common complication is cystoid macular oedema, which is actually best diagnosed with OCT.
- Acquired peripheral angiomatosis (adult Coats disease) is far less frequent than CMO in retinitis pigmentosa but may lead, if untreated, to exudative retinal detachment and neovascular glaucoma.
- Rod-cone dystrophies must be differentiated from other chorioretinal dystrophies but also from a number of acquired diseases which may mimic retinitis pigmentosa.
- Especially in children, one has to consider syndromic cases. A child with suspicion of retinitis pigmentosa must be evaluated as well by a neuron-paediatrician.
- Genetic counselling is mandatory.

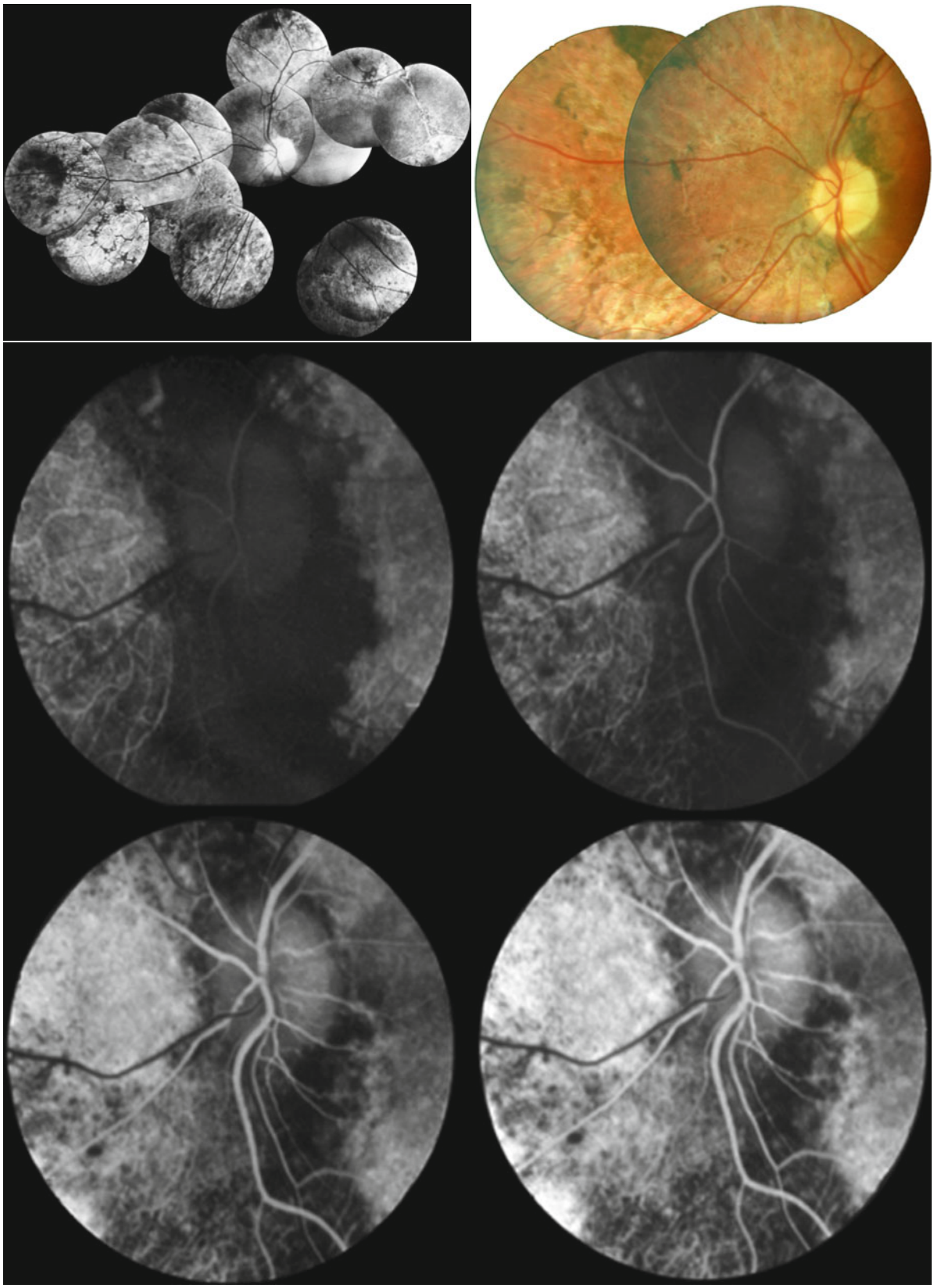

Fig. 9.21 This 30-year-old woman had undergone general anaesthesia for placenta accreta. This was complicated by heavy blood loss due to transient coagulation disturbances. When she woke up from the anaesthesia, she noticed blindness of her left eye. This was diagnosed as occlusion of the central retinal artery. When she was examined at the Ghent University Eye department 1 year later, her right eye was completely normal. The vision of the left eye was reduced to hand movements. The peripheral field was complete, but a dense and extensive annular scotoma was present. That eye presented an aspect of unilateral retinitis pigmentosa with chorioretinal atrophy and pigment epithelial disturbances and on fluorescein angiography a marked peripapillary watershed zone. Both photopic and scotopic ERG amplitudes were less than 25 % of the normal in the left eye and normal in the right eye. This case is illustrative of a massive choroidal infarction

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