Progressive Cone/Cone-Rod Dystrophy

4

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Abbreviations

CRD	Cone-rod dystrophy
ELM	External limiting membrane
ERG	Electroretinogram
EZ	Ellipsoid zone
FAF	Fundus autofluorescence
IZ	Interdigitation zone
mfERG	Multifocal electroretinogram
OCT	Optical coherence tomography
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
SD-OCT	Spectral domain optical coherence tomography

Introduction

Progressive cone/cone-rod dystrophies (CRD) are a heterogeneous group of disorders characterized by early deterioration of visual acuity and color vision, and in some cases nystagmus. The prevalence is estimated to be 1/40,000. Patients usually present in childhood or early adult life. In later life, patients with cone dystrophies can progress to have rod dysfunction. Hence CRD may be a more appropriate terminology, to reflect widespread retinal dysfunction, with cones usually more affected than rods. When there is involvement of both cone and rod systems, it may be difficult clinically to differentiate CRD from retinitis pigmentosa (RP). Therefore, electrophysiology can be helpful, as reduction or absence of cone ERG responses, with less reduction in rod responses would indicate CRD. However, in advanced disease, both cone and rod ERG responses may become undetectable. Compared to rod-cone dystrophies, CRD are less often associated with syndromes, but CRD may be part of Bardet–Biedl syndrome and spinocerebellar ataxia type 7.

Etiopathogenesis

Autosomal dominant, recessive, and X-linked inheritance patterns have been described in CRD (Moore 1992). Many different genetic mutations have been described to cause CRD, with more being identified as technology for genetic sequencing improves (Roosing et al. 2014). Major genes include *ABCA4*, *CRX*, *GUCY2D*, and *RPGR* (Hamel 2007). CRD has been found to be associated with mutations in the gene *GUCY2D*, and cone dystrophy-3 (COD3) has been associated with mutations in GUCA1A (Payne et al. 1998; Wilkie et al. 2001). *GUCY2D* and *GUCA1A* encode the retina-specific guanylate cyclase (RETGC-1) (Kelsell et al. 1998) and its activating protein guanylate cyclase activating protein-1 (GCAP-1), respectively. GCAPs play an important role in regulating the function of RETGC-1 in a calcium-dependent manner. However, it is unclear how defects in these proteins result in degeneration which is limited to cones.

Clinical Features

Clinical features include photophobia, nystagmus, color vision defects, and visual field abnormalities. Various visual field defects have been reported, which include central scotoma, peripheral field loss, generalized loss of sensitivity, and ring scotoma (Simunovic and Moore 1998). In later stages of the disease when the rod photoreceptors are involved, night blindness may also become a prominent symptom.

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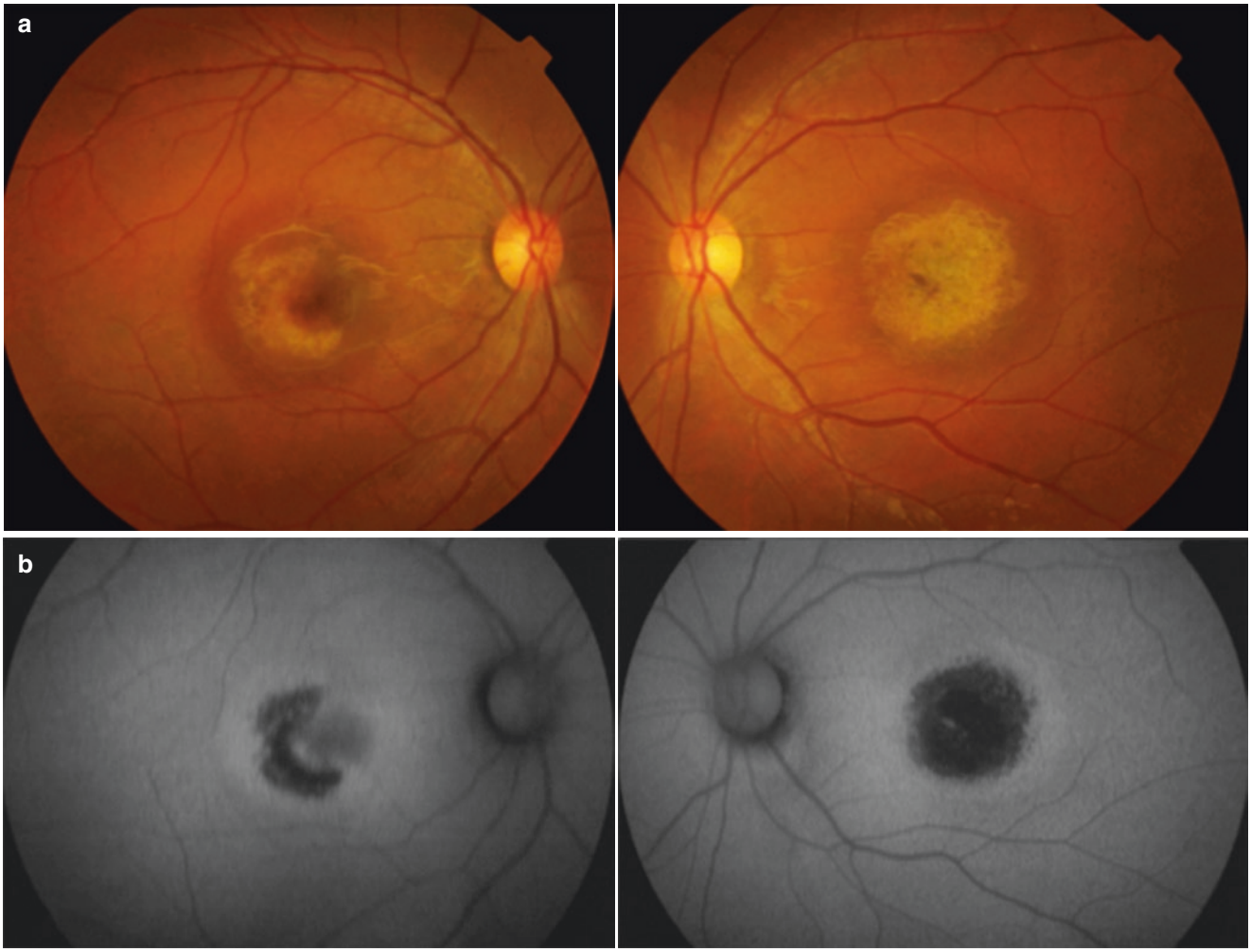

Fig. 4.1 A 23-year-old male with cone dystrophy with decreased vision in both eyes. Visual acuity (VA) 6/15 OD and 6/45 OS. (**a**) Color fundus photographs showing retinal pigment epithelium (RPE) atrophy at the macular (left worse than right). (**b**) Corresponding fundus autofluorescence (FAF) showing hypoautofluorescence at areas of RPE atrophy

Fundus examination findings can range from a normal macula to bull's eye configuration in late disease (Roosing et al. 2014). White flecks at the level of RPE, and tapetum-like sheen have also been described (Simunovic and Moore 1998). When there is widespread retinal involvement, there can be presence of bone spicules resembling RP. Late stages of CRD may be indistinguishable from RP.

Here we showcase various forms of cone and cone rod dystrophies (Figs. 4.1, 4.2, 4.3, 4.4, 4.5, and 4.6).

Investigations

Optical coherence tomography (OCT) characteristic of cone dystrophy in the early stages may be subtle, such as loss of interdigitation zone (IZ) with or without foveal cavitation. There is a less distinct border in the periphery between the EZ and the ELM with lower intensity and thinning of the EZ band. At the macula, the EZ band can show irregular foveal loss or segmental foveal loss. Another pattern of OCT abnormality that has been observed in cone dystrophy is central foveal thickening with irregular perifoveal loss of the EZ band. In the later stages, the ELM and EZ may be completely lost at the macular region but preserved in the peripheral regions of the fundus. There is also generalized thinning of the RPE layer. Overall, cone and cone-rod dystrophy show characteristic changes on OCT that affects predominantly the macula area in the early stages and correlates with the level of visual impairment.

Fundus autofluorescence (FAF) findings in cone/cone-rod dystrophy can be variable and may depend on the stage of disease. A ring of hyperautofluorescence surrounded by an area of macula RPE atrophy has been described (Robson et al. 2010) (Fig. 4.4b).

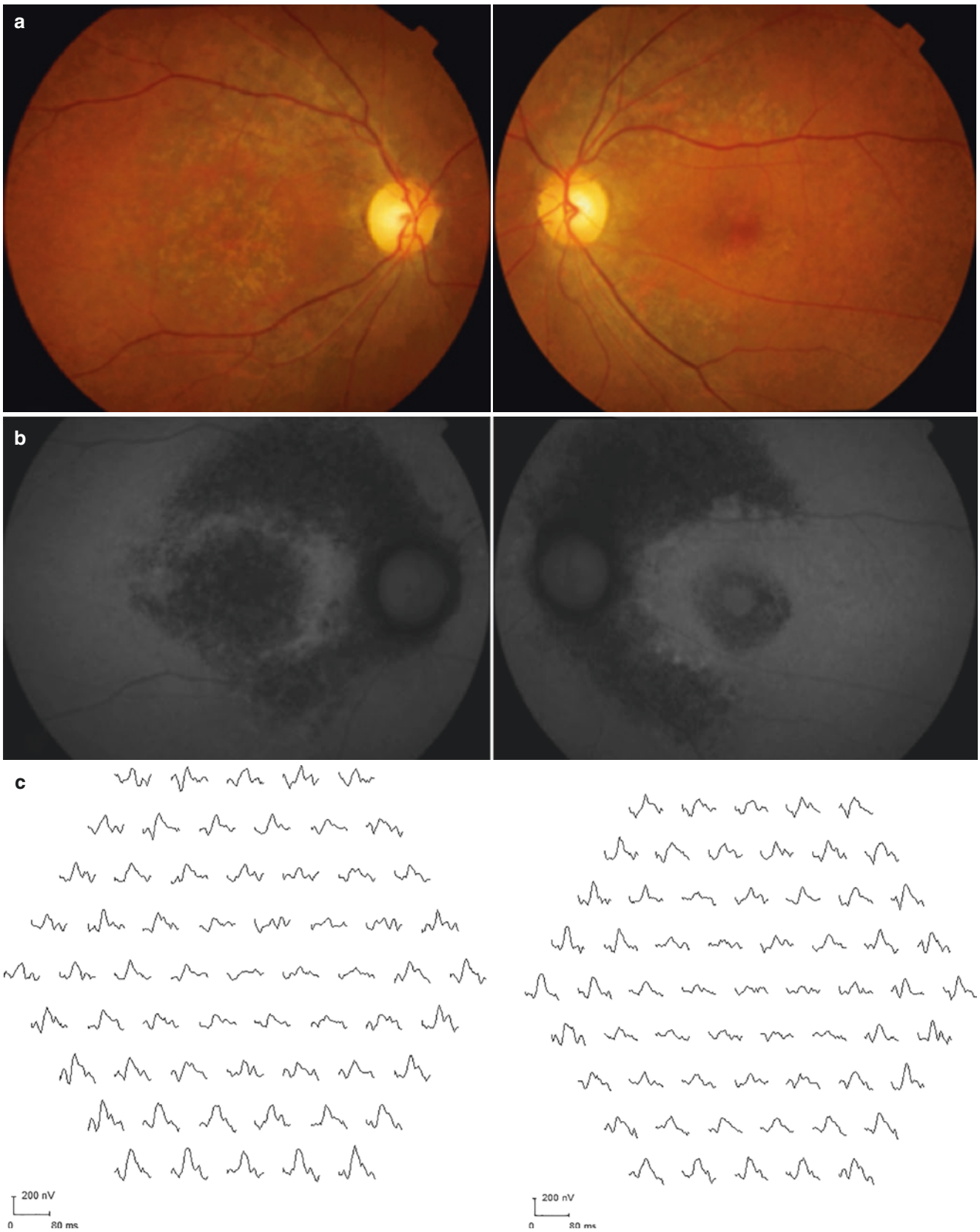

Fig. 4.2 A 68-year-old female with cone-rod dystrophy with right eye blur vision for 2 years. VA count fingers OD 6/12 OS. (**a**) Color fundus photographs showing RPE mottling at the macula, with associated RPE disturbance in the mid periphery. (**b**) FAF showing hypoautofluorescent areas in the macula and beyond the macula region, suggesting more widespread RPE dysfunction (right worse than left). (**c**) Multifocal electroretinogram (mfERG) showing reduced and delayed responses in the central 2–3 rings in both eyes. OD (picture on left), OS (picture of right)

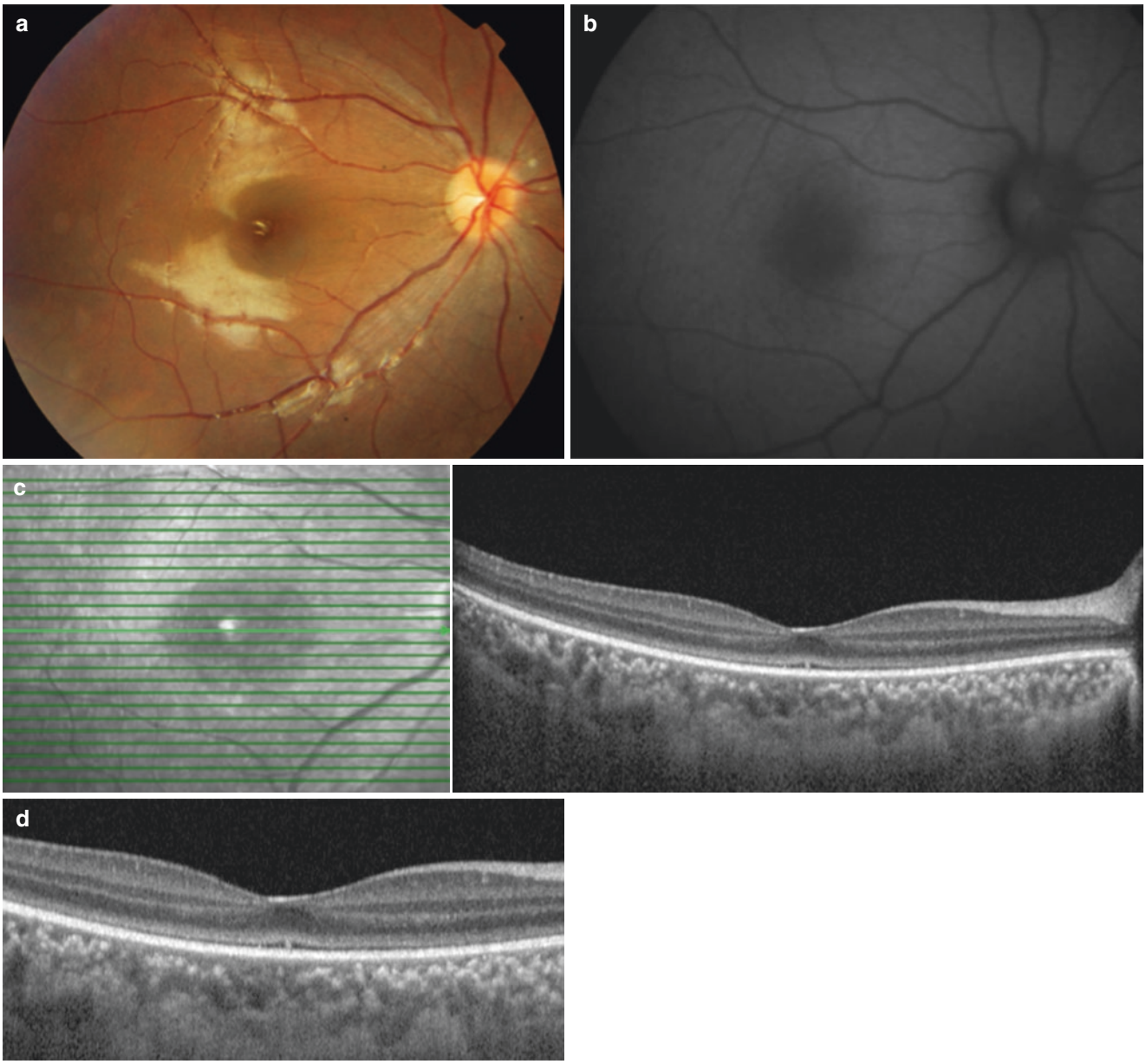

Fig. 4.3 A 12-year-old male with early cone dystrophy who presented with dyschromatopsia and visual acuity of 6/24 OU. (**a**) Color fundus photograph showing relatively normal macula with normal fovea reflex. (**b**) Normal FAF. (**c**) Spectral domain optical coherence tomography (SD-OCT) shows loss of interdigitation zone (IZ) between the cone outer segments and apical processes of the RPE along the whole span of cut but more marked in the foveal region and foveal cavitation. A less distinct border in the periphery between the ellipsoid zone (EZ) and the external limiting membrane with lower intensity and thinning of the EZ band is also observed. (**d**) Magnified view of (**c**)

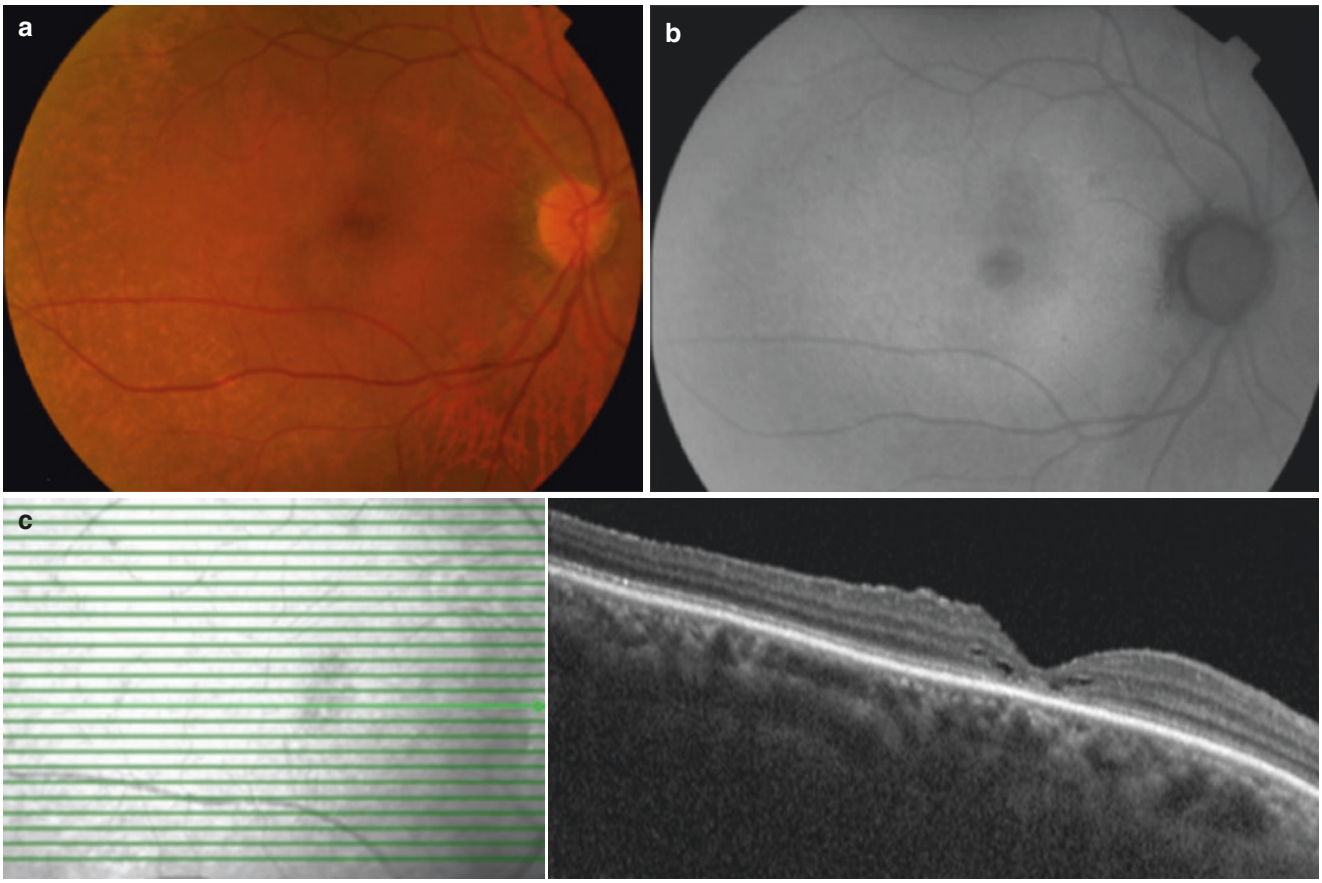

Fig. 4.4 A 67-year-old female with cone dystrophy with poor vision for many years. VA 6/120 OD, 6/90 OS. (**a**) Color fundus photograph showing subtle mottling at the macula. This patient also has age-related peripheral drusen. (**b**) FAF showing abnormal hyperautofluorescence in the parafoveal area, with a wider ring of hypoautofluorescence in the macula region. (**c**) SD-OCT of right macula showing RPE atrophy, loss of ellipsoid zone, and degenerative cysts

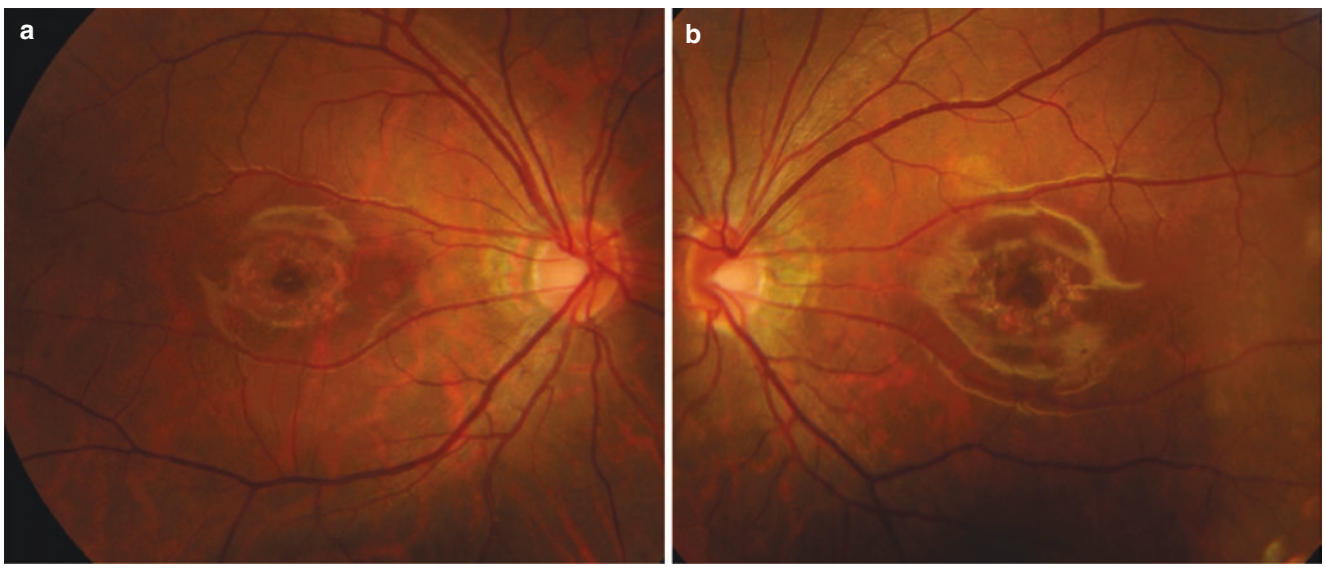

Fig. 4.5 A 20-year-old male with bilateral central blurring of vision. VA 6/21 OU. (**a**, **b**) Bull's eye maculopathy is seen in both eyes. Peripheral retina was unremarkable. However, ERG showed both rod and cone dysfunction, suggesting a *cone-rod dystrophy*. (**c**, **d**) FAF shows a central ring of iso-autofluorescence, surrounded by a ring of hypoautofluorescence, then a peripheral ring of hyperautofluorescence, typical of bull's eye lesion. (**e**, **f**) SD-OCT showing EZ disruption corresponding to area of hypoautofluorescence. There is hypertransmission of light into the choroid in areas of atrophy

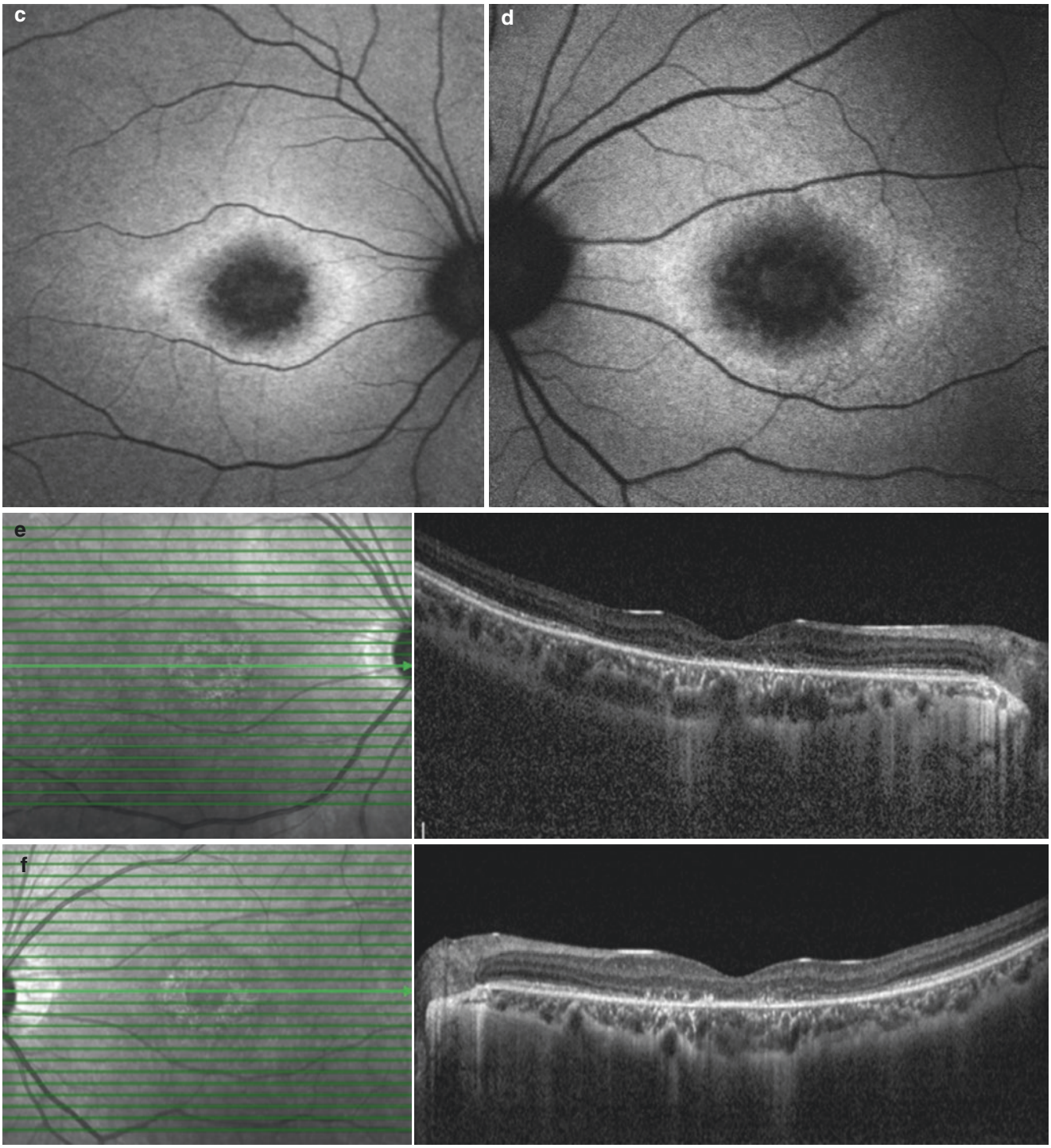

Fig. 4.5 (continued)

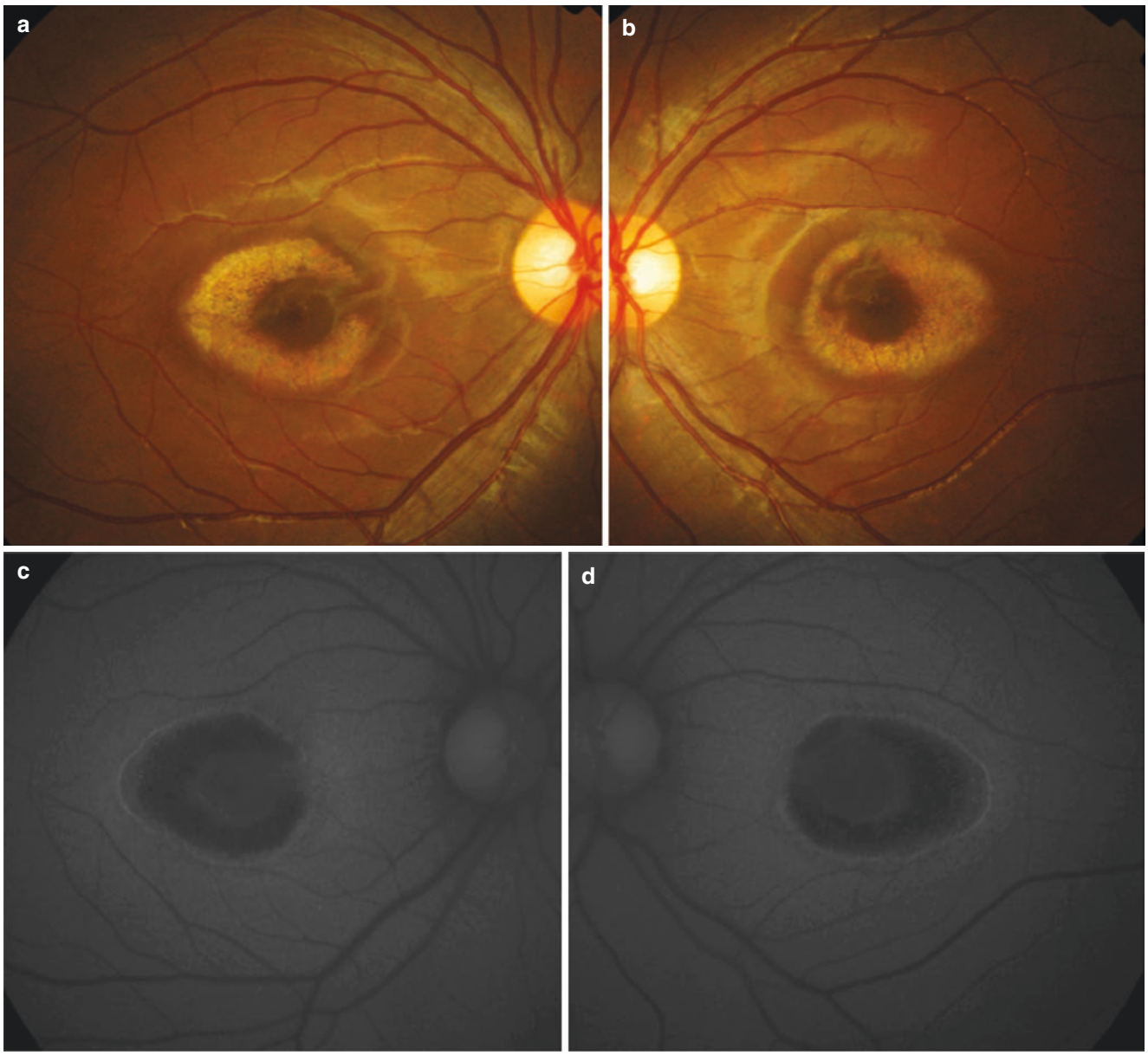

Fig. 4.6 A 12-year-old female with relatively good VA of 6/12 in the right eye and 6/9 in the left eye. (**a**, **b**) Bull's eye maculopathy is also seen in both eyes. Full field ERG was normal, but mfERG was reduced in the central two rings but not delayed. As global cone function is intact, a diagnosis of *benign concentric annular macular dystrophy* was made. (**c**, **d**) FAF shows a central ring of iso-autofluorescence, surrounded by a ring of hypoautofluorescence, then a peripheral ring of hyperautofluorescence, typical of bull's eye lesion. (**e**, **f**) SD-OCT showing EZ disruption corresponding to area of hypoautofluorescence. There is hypertransmission of light into the choroid in areas of atrophy

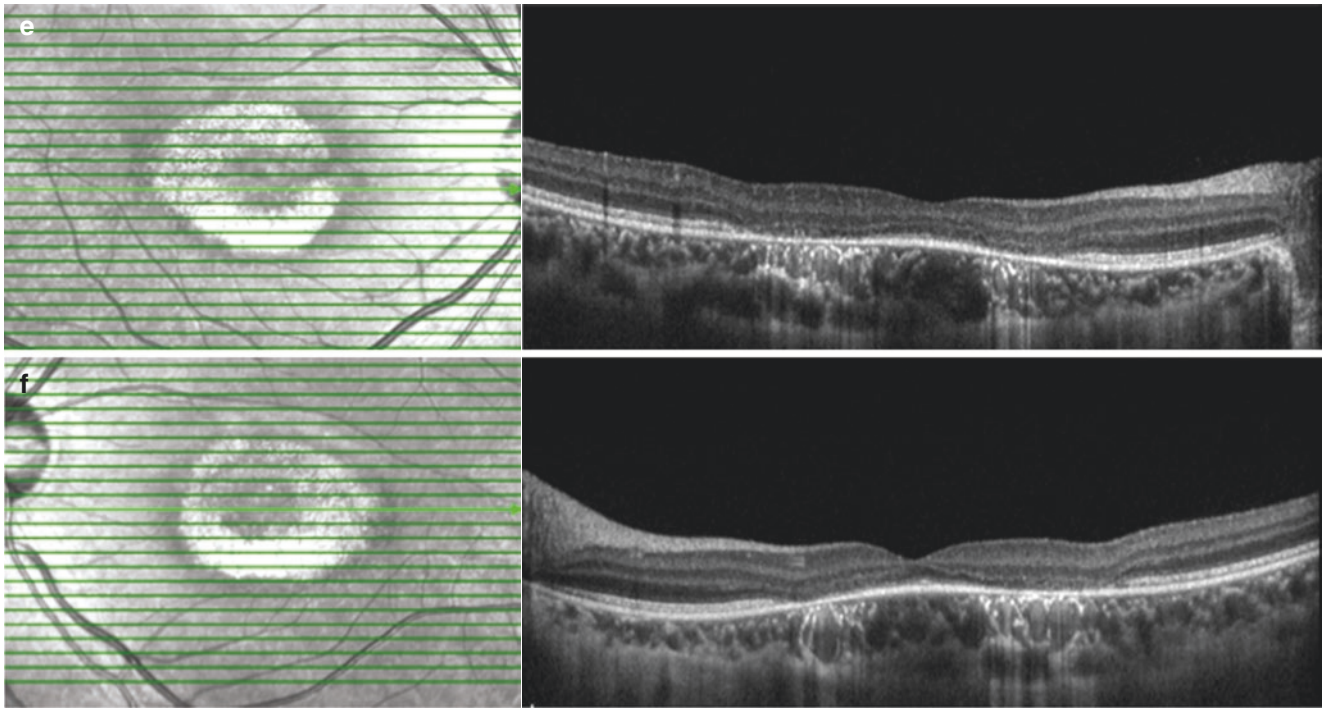

Fig. 4.6 (continued)

Fluorescein angiography may show hyperfluorescence at the macula due to RPE atrophy. However, this finding is not specific to cone/cone-rod dystrophy.

Macular dysfunction can be detected using multifocal electroretinogram (ERG), which can also document the areas of dysfunction topographically. Full-field ERG typically shows poor photopic and 30 Hz flicker responses, with relatively preserved scotopic (rod-derived) responses. Variable disturbance in rod responses may also be seen in later stages (Roosing et al. 2014). ERG is particularly informative as they may be abnormal before distinguishable clinical signs appear. For patients with Bull's eye maculopathy (as in Figs. 4.5 and 4.6), ERG is able to distinguish cone dystrophy from macular dystrophy.

Management and Prognosis

A holistic treatment approach is recommended for patients with cone and CRD. Management is generally conservative and use low vision aids when appropriate. Genetic testing to characterize the mode of inheritance is important for genetic counseling. Current research has been focusing on identifying the genetic basis of cone dystrophies, with the hope that in the future gene therapy might be possible (Roosing et al. 2014).

The clinical course of CRD is more severe than RP, leading to early legal blindness and disability.

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