Cohen Syndrome

22

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Synonyms
Hypotonia, Obesity, Prominent incisors, Pepper syndrome, Norio syndrome, Mirhosseini-Holmes-Walton syndrome [13].

Cohen syndrome comprises multiple congenital anomalies with mental retardation, hypotonia, obesity, facial dysmorphism with protruding teeth, benign neutropenia and chorioretinal dystrophy. It has an autosomal recessive pattern of inheritance with variable expression [3] and was first described in a brother and sister in 1973 [2]. The affected gene, *COH1*, maps to 8q22 and encodes the VPS13B vacuolar protein involved in vesicular transportation [1, 18, 19].

22.1 Clinical Features

22.1.1 Presentation

The typical features of the disease are not present at birth. There is early mental retardation. The patient remains of short stature with a small head and although microcephaly is not always present in the newborn, it becomes more obvious with age.

22.1.2 Ophthalmic Features

The earliest ocular manifestations are microphthalmos, early onset strabismus and high myopia. The diagnosis of retinal dystrophy is made at a later age although the ERG is affected early in life [1]. There may be microcornea, possibly associated with microphthalmos (Fig. 22.1). Cataract may be present (Fig. 22.2).

Fundus changes appear in the first years of life. The retina becomes depigmented and the relatively dark foveo-macular region contrasts with the depigmented posterior pole. Atrophy of the retinal pigment epithelium around the macula

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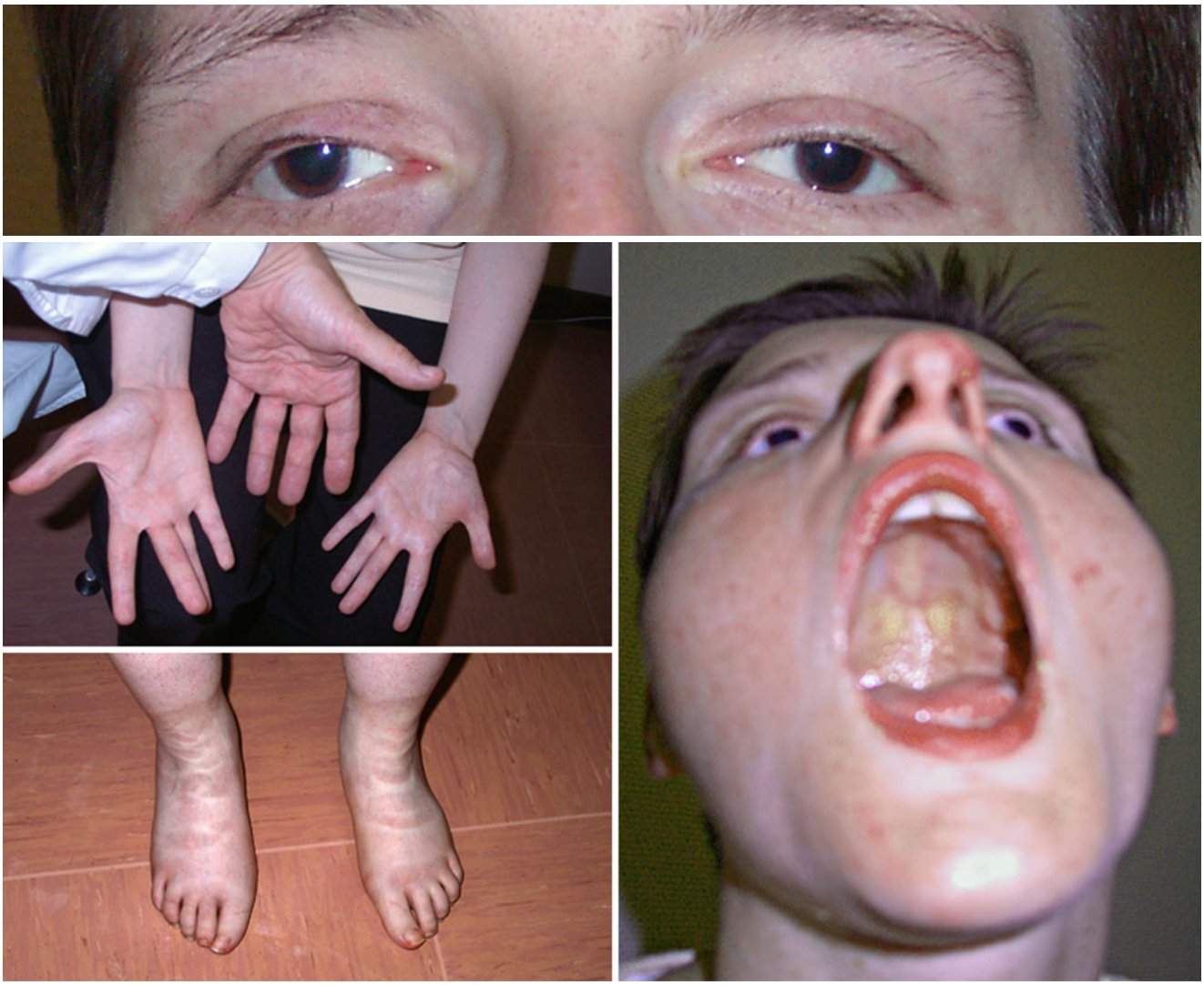

Fig. 22.1 Same patient as Fig. 22.3, antimongolian slant of the eyelids, microcornea, decentration of the pupils, narrow hands with long fingers, small narrow feet with clinodactyly, high palate and maxillary hypoplasia

gives a bull's eye appearance (Fig. 22.3) [14]. In the periphery the RPE changes are first seen as atypical pigment clusters, later as osteoblastic pigments mainly situated along the retinal vessels (Fig. 22.4).

22.1.3 Extra-ocular Features

In addition to the mental retardation and microcephaly, there is truncal obesity. Characteristic facial dysmorphism becomes obvious after the age of 5–6 years. Most typical are an antimongoloid slant of the eyelids, poorly folded ears sometimes lacking the lobulus, prominent superior incisors, maxillary hypoplasia, short philtrum which does not cover the incisors and high nasal bridge (Fig. 22.5). The hands are small and narrow, sometimes with anomalies of the fingers (camptodactyly, syndactyly), short metacarpals or metatarsals and joint hypermobility [8]. Adult patients have a cheerful disposition and may have autistic features [6].

22.1.4 Investigations

ERGs show features of a generalised retinal dystrophy with a rod-cone pattern of dysfunction.

Fluorescein angiography highlights the global depigmentation with sparing of the macula. With time islands of hypofluorescence correspond to areas of chorioretinal atrophy with loss of pigment epithelium and choriocapillaris (Fig. 22.7).

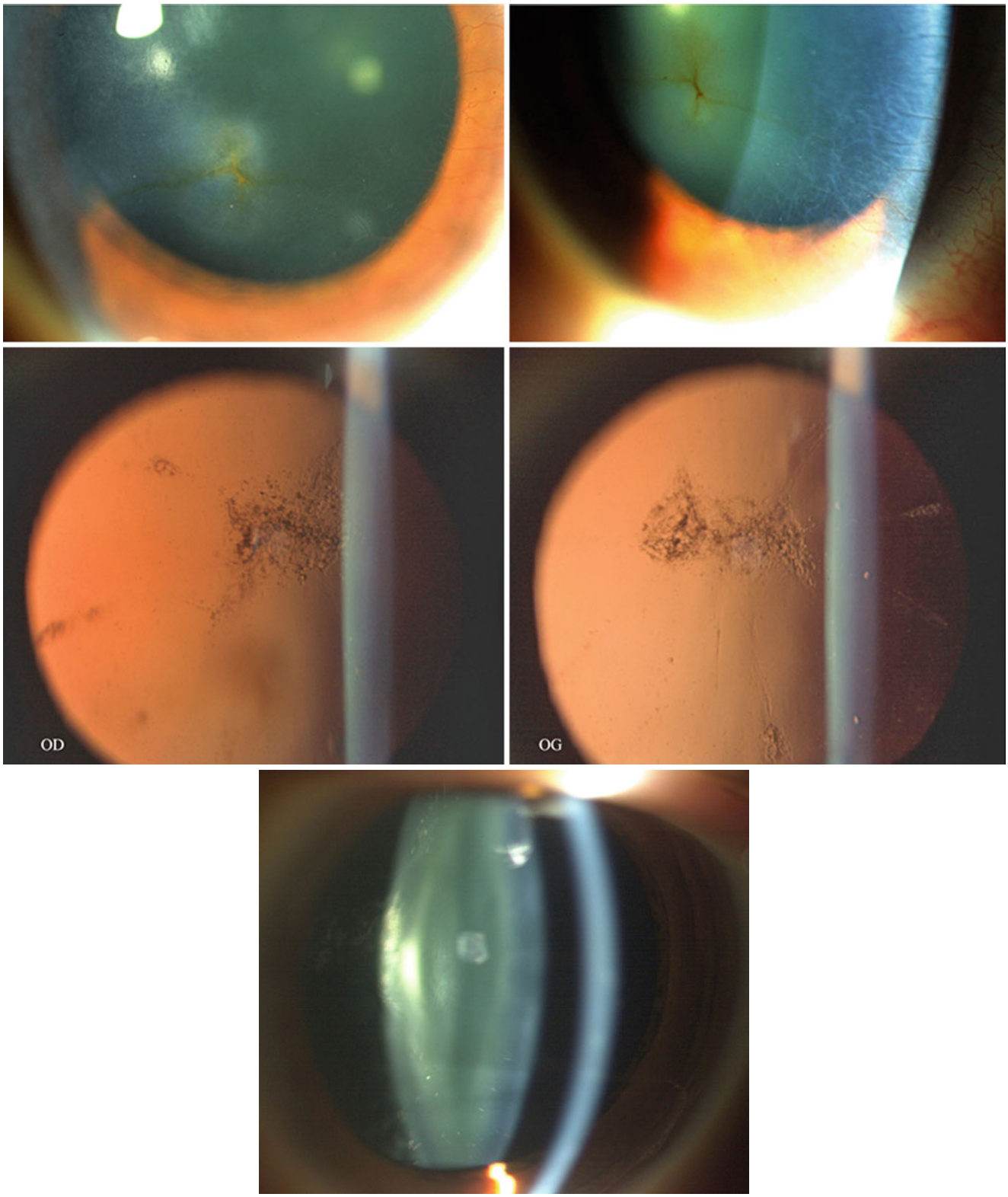

Fig. 22.2 *Top pictures*: corneal scar and empty new vessels in the corneal periphery. *Middle pictures*: subcapsular posterior cataract and increased visibility of the lens sutures. *Bottom picture*: nuclear sclerosis and fine white opacities. *OD* right eye, *OG* left eye

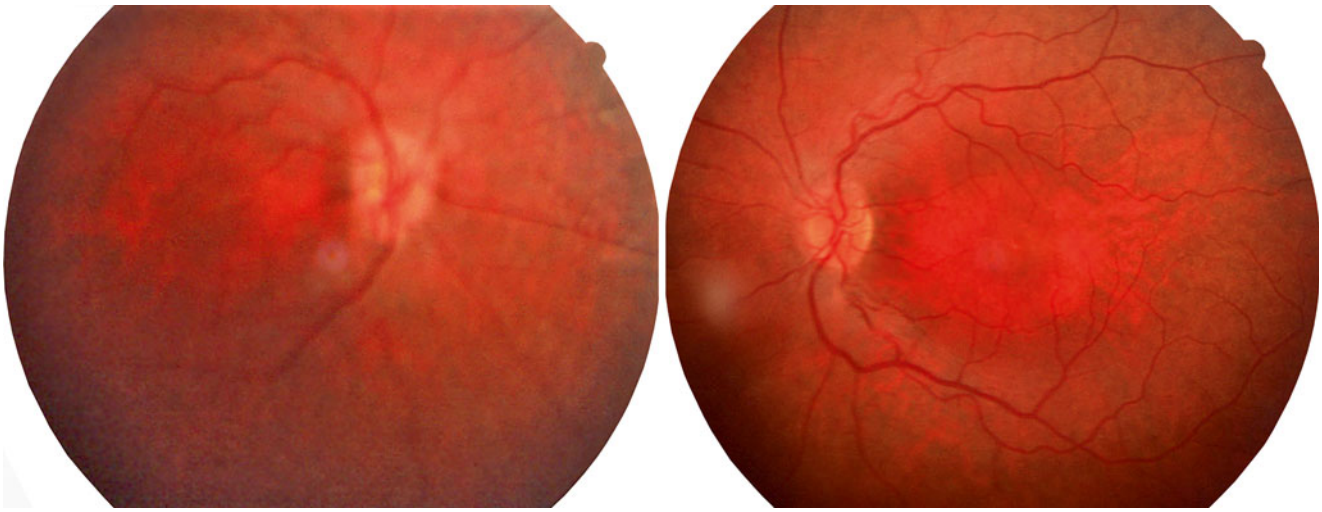

Fig. 22.3 A 22-year-old female patient with marked psychomotor retardation, truncal obesity, divergent squint, rotatory nystagmus, microphthalmos, extinguished ERG and ocular fundus typical for retinitis pigmentosa. The macula is surrounded by marked depigmentation

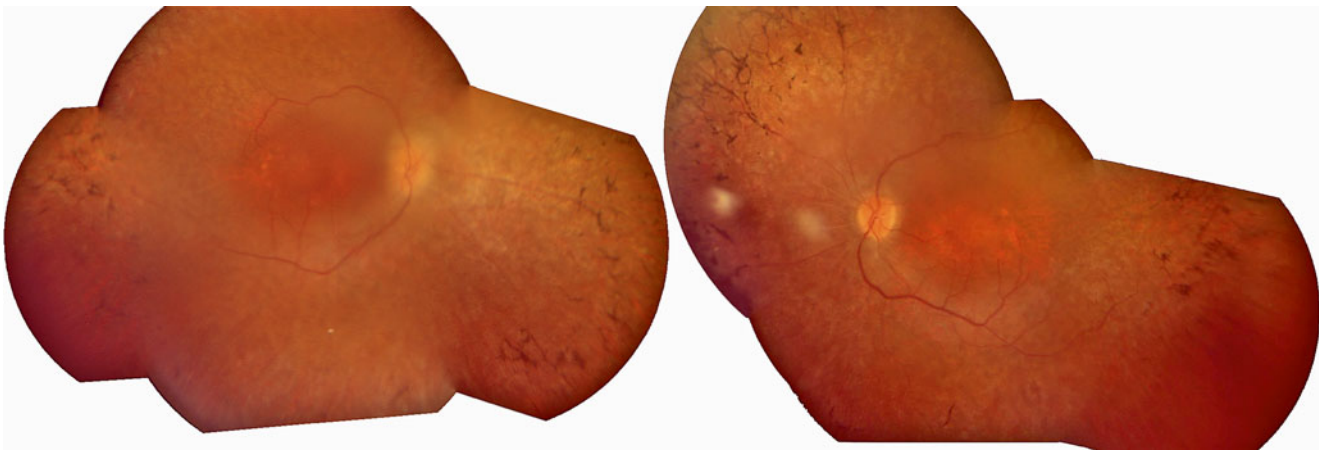

Fig. 22.4 Same patient as Figs. 22.1, 22.3 and 22.5 at the age of 36 years. Classic aspect of retinitis pigmentosa with relative absence of pigmentation of the posterior pole, narrowing of the retinal vessels and waxy aspect of the optic discs

22.1.5 Classic and Atypical Forms

The disease is highly variable, but since the discovery of the *COH1* gene, it is possible to diagnose borderline cases. Microcephaly may not be present, and exceptionally macrocephaly has been described [15]. High myopia is not always present. In exceptional cases no retinopathy was found [7, 12]; a normal ERG is mandatory to confirm the absence of retinopathy. In a recent study of patients in school age with mutation of the *COH1* gene, some did not have neutropenia, microcephaly or chorioretinal dystrophy [5].

22.1.6 Diagnosis and Differential Diagnosis

The diagnosis may be difficult in the first 3 or 4 years of life until the facial dysmorphism becomes apparent. The retina will initially have a normal appearance. The diagnosis is based on the clinical aspect (see Table 22.1) and can be confirmed genetically. Cohen-like cases can be considered in the absence of *COH1* gene mutation or if there is no chorioretinal dystrophy. The facial and physical characteristics are reminiscent of Prader-Willi syndrome, which however has autosomal dominant inheritance [4]. Cohen syndrome must be differentiated from Bardet-Biedl syndrome, which is

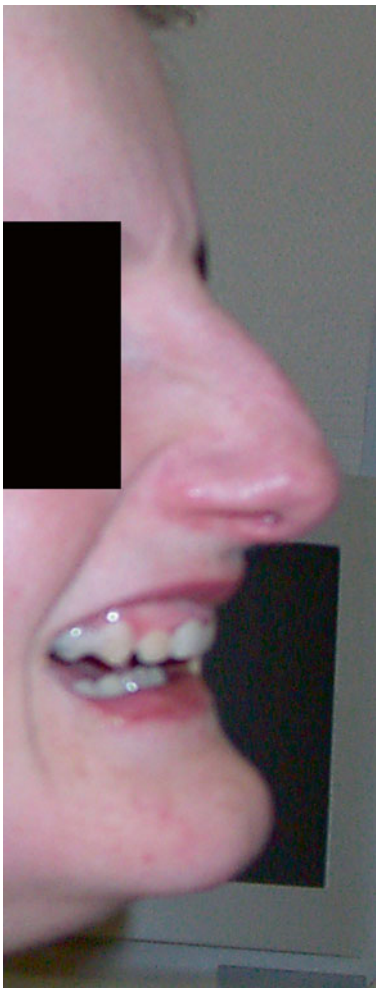

Fig. 22.5 Same patient as Figs. 22.1 and 22.3, prominent root of the nose, prominent upper incisors, short philtrum, retrognathism, micrognathia, thick hair and angioma planum in the occipital region

Table 22.1 The eight criteria according to Kolehmainen et al. [11]

Developmental delay
Microcephaly
Typical Cohen syndrome facial gestalt
Truncal obesity with slender extremities
Overly sociable behaviour
Joint hypermobility
High myopia and/or retinal dystrophy
Neutropenia

associated with finger anomalies, in particular polydactyly and renal disease. Rubinstein-Taybi syndrome is characterised by a macular dystrophy, broad thumbs and toes, nanism, a marked forehead, a prominent nose and vertebral and sternal anomalies.

22.1.7 Evolution

The ocular condition progresses slowly and patients keep central vision until at least the second decade (Fig. 22.6). Vision may be influenced by nystagmus, amblyopia (due to squint) and high myopia. A subcapsular posterior cataract appears relatively early. The maculopathy leads to legal blindness, but the age at blindness is variable, 20–30 years in English cases [1] and after the age of 50 years in Finnish patients [9].

22.1.8 Histology

An eye of a 19-year-old patient with Cohen syndrome has been subject to histological examination [16]. There was a totally detached retina, a shrunken vitreous body and, in the retro retinal space, a yellowish rubbery material. The different layers of the retina showed degenerative alterations with several xanthomata and hyperpigmented cells. Vessels were rare. In the retroretinal space diffuse bleedings, partly embedded in homogeneously eosinophilic material, were present.

22.2 Genetics/Inheritance

Cohen syndrome has an autosomal recessive inheritance with variable expression [3]. The affected gene, *COH1*, maps to 8q22 and encodes a transmembrane protein of 4.022 amino acids with a presumed role in vesicle-mediated sorting and intracellular protein transport [10]. Slightly more than 70 different mutations have been identified [17]. If the patient does not present five of the eight major signs it should be considered as Cohen-like syndrome [11] (Table 22.1).

Cohen syndrome is extremely rare with less than 150 cases reported.

Summary for the Clinician

- Cohen syndrome is an autosomal recessive condition.
- The COH1 gene, which is responsible for the disease, codes for a transmembranal protein which plays a role in the selection and intracellular transport of proteins in vesicles.
- The disease is characterised by mental retardation, short stature and diverse physical anomalies.
- The expression of the disease is variable. Retinal dystrophy may be absent.
- When present the retinal dystrophy starts early in life and its presence may help in the diagnosis.

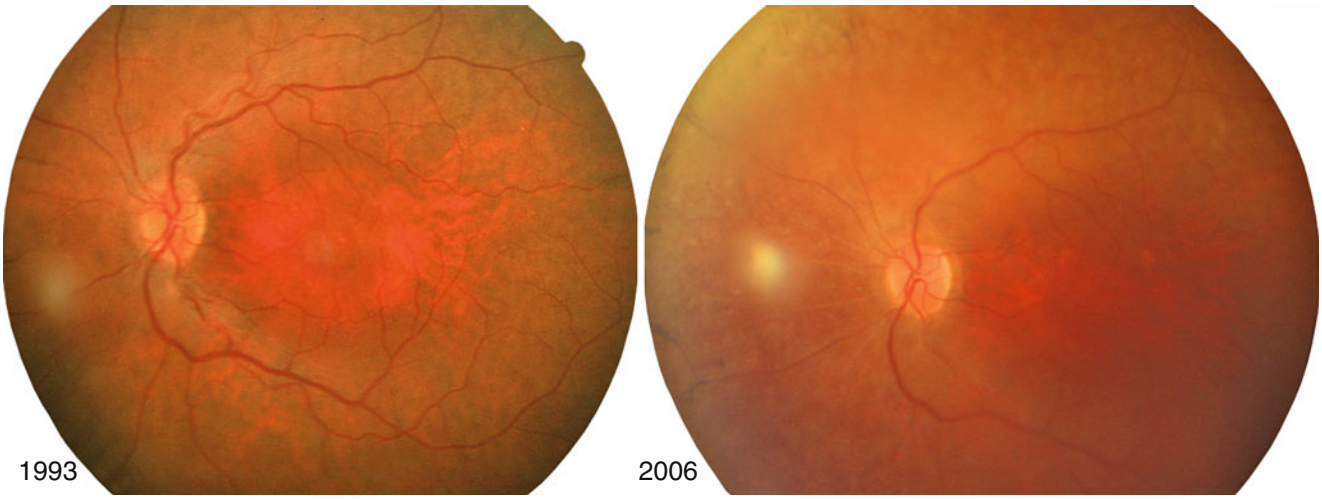

Fig. 22.6 Evolution of the fundus lesions in the posterior pole over a period of 13 years

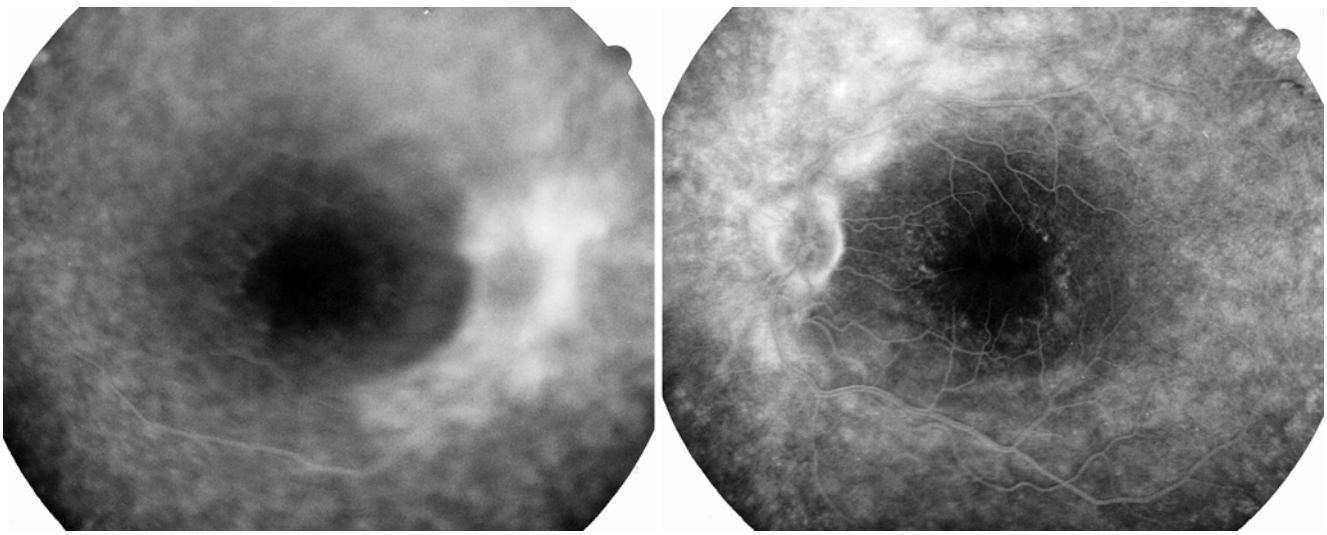

Fig. 22.7 Rupture of the blood-retinal barrier, visible in the vicinity of the optic disc along the vessels in the posterior pole

- There is no known treatment either for the syndrome or for the associated retinopathy.
- The retinopathy is of the rod-cone type and leads to blindness between the ages of 30 and 50 years.

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