Retinal Dystrophies: Clinical Work-Up and Selected Examples

34

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Abstract

Childhood retinal dystrophies may be isolated or represent one sign of serious systemic diseases. Because of the variety of ways they manifest themselves, retinal dystrophies may be overlooked or misdiagnosed. A thorough patient history, family history, ophthalmologic examination, ancillary testing, and complete review of systems and physical examination are imperative to detect and to accurately diagnose disease. The diagnosis can be confirmed using genetic testing in a large proportion of cases. This chapter discusses a practical approach to the diagnosis and management of patients with a suspected retinal dystrophy and provides case examples of a few disorders. The reader is also referred to the chapter on genetic counseling in this book for additional discussion and other case examples.

Keywords

Achromatopsia • Bardet-Biedl syndrome • Fundus flavimaculatus • Leber congenital amaurosis • Gene therapy • Retinal dystrophy • Rod monochromatism • Stargardt disease

Introduction

There are several situations in which a retinal dystrophy should be highly suspected in children and infants. One specific example is in the infant with nystagmus. Achromatopsia, Leber congenital amaurosis (LCA), oculocutaneous albinism, cone-rod dystrophy, bilateral severe optic nerve hypoplasia, and congenital stationary night blindness, for instance, may present in this manner. If a retinal dystrophy is suspected in such a patient, and physical findings do not rule out albinism and optic nerve hypoplasia, an electroretinogram (ERG) should be obtained. The findings on the ERG will help guide subsequent genetic testing. It is also important to differentiate between children with isolated ophthalmic disease from those in which the retinal dystrophy is only one of several manifestations of an underlying systemic disease. Various inherited conditions, such as mitochondrial disorders (e.g., Kearn-Sayre disease), ciliopathies (e.g., Bardet-Biedl syndrome (BBS), Usher syndrome), neurologic and metabolic disorders (neuronal ceroid lipofuscinosis [Batten disease], Refsum syndrome, gyrate atrophy, abetalipoproteinemia, and Cockayne syndrome), among others, are associated with a retinal dystrophy. It is imperative that these diagnoses are correctly identified, as some may be amenable to early treatment (see Fig 34.1). Here are key questions to ask the patient and guardians:

Key Questions in Medical and Vision History

1. Age of onset of signs and/or symptoms?
2. Symptoms worsening or stable (progression)?
3. Trouble navigating in dark surroundings (nyctalopia)?

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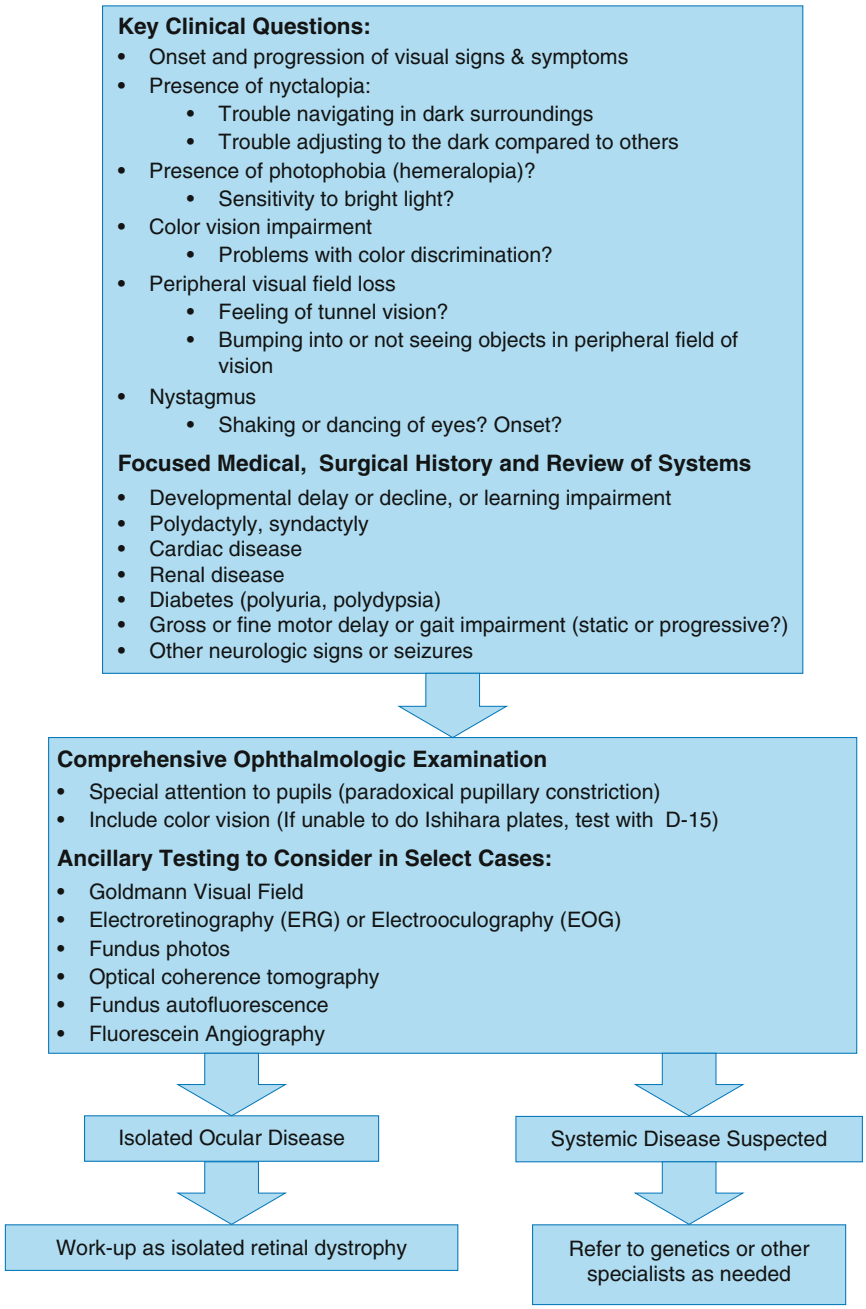

Fig. 34.1 Algorithm for the evaluation of the patient with a retinal dystrophy

4. Trouble adjusting to a darker environment (dark adaptation)?
5. Sensitivity to bright light (photodysphoria)?
6. Difficulty discriminating colors (color vision impairment)?
7. Feeling of tunnel vision (peripheral visual field loss)?
8. Shaking or abnormal movements of eyes (nystagmus)?

Focused Medical/Surgical History and ROS

1. Difficulty with schoolwork or learning (developmental delay)?
2. Loss of milestones (neurological regression)?
3. Extra/abnormal finger or toe or other malformations (polysyndactyly)?
4. Cardiac abnormality (cardiomyopathy)?
5. Kidney problems (renal disease)?
6. Polyuria or polydipsia (diabetes)?
7. Hearing loss (deafness)?
8. Problems with walking or balance (neuromuscular disease)?
9. Peculiar and very restricted diet (vitamin A deficiency)?
10. Family members with similar symptoms (family history)?

The presence of night blindness points to a rod dysfunction, while light sensitivity and difficulties discriminating colors are more suggestive of cone disorders. Peripheral visual loss is associated with LCA, cone-rod dystrophies, and retinitis pigmentosa, while central visual loss is more consistent with cone dystrophies and Stargardt disease.

Ancillary tests are critical to the attainment of a clinical diagnosis. Fundus photographs, fundus autofluorescence, optical coherence tomography, ERG, and occasionally EOG and fluorescein angiography can provide very specific clues to a particular disease and assist in guiding genetic testing.

Because of the very large number of retinal dystrophies and systemic disorders associated with retinal degeneration, this chapter focuses on just a few of the more common types that are encountered in children. The reader is referred to other specialized texts for more detailed descriptions of these conditions and to the chapter on genetic counseling in this textbook.

Achromatopsia (Rod Monochromatism)

Case 1 (Table 34.1)

Table 34.1 Case 1

Clinical History	11-year-old female with a history of a retinal dystrophy, nystagmus, poor vision, severe photophobia, and relatively stable visual acuity in recent years. PMH and FH were noncontributory		
Base Exam		OD	OS
	BCVA	20/125	20/100
	Versions	Full	Full
	CRx	−2.75 + 2.25 × 100	−2.75 + 2.50 × 085
Fundus Exam		OD	OS
	Disc	Pallor	Pallor
	Macula	Mild macular pigmentary mottling	Mild macular pigmentary mottling
	Vessels	Normal	Normal
	Periphery	Limited (severe photophobia)	Limited (severe photophobia)
Previous Genetic Testing	Negative for Leber congenital amaurosis (LCA)		
Subsequent Genetic Testing	Two novel variations in the *CNGB3* gene identified		
Diagnosis	Achromatopsia		
Treatment	– Currently no effective treatment for achromatopsia – Tinted lenses may be worn to alleviate photophobia		

The patient is an 11-year-old female with a history of a retinal dystrophy, nystagmus, poor vision, and severe photophobia from very early in life. She has had a stable visual acuity of 20/100 for the last few years. She had mild bilateral optic nerve pallor and macular pigmentary mottling while the peripheral retina (Figs. 34.2, 34.3, and 34.4) appeared relatively normal. Previous genetic testing for LCA was negative. Subsequent testing for achromatopsia (*CNGA3*, *CNGB3*, *PDE6C*, and *PDE64*) revealed two novel pathogenic variations in the *CNGB3* gene, and these were deemed to cause her retinal dystrophy—diagnosis: achromatopsia.

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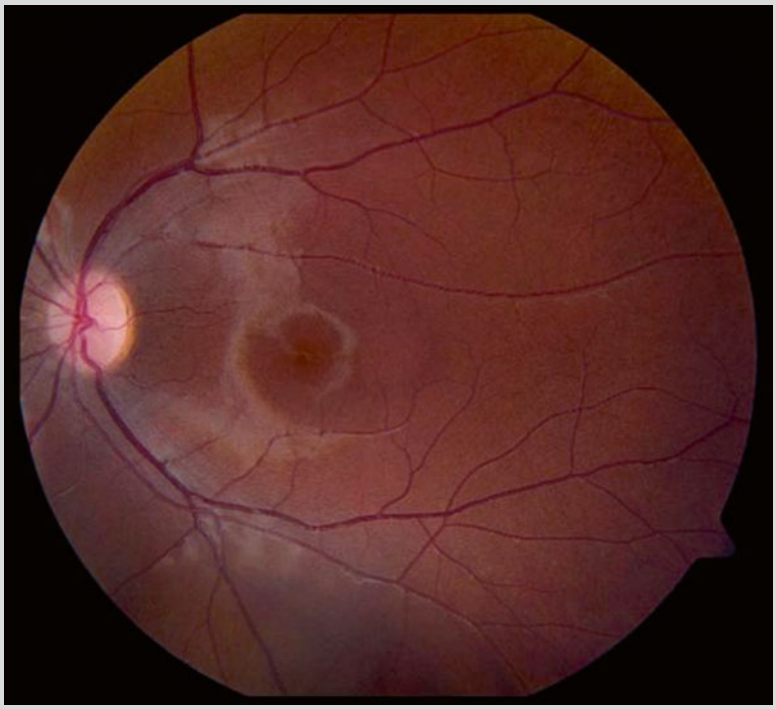

Fig. 34.2 Color fundus photo of an 11-year-old achromatopsia patient with mild optic nerve pallor and subtle macular pigmentary mottling of the left eye

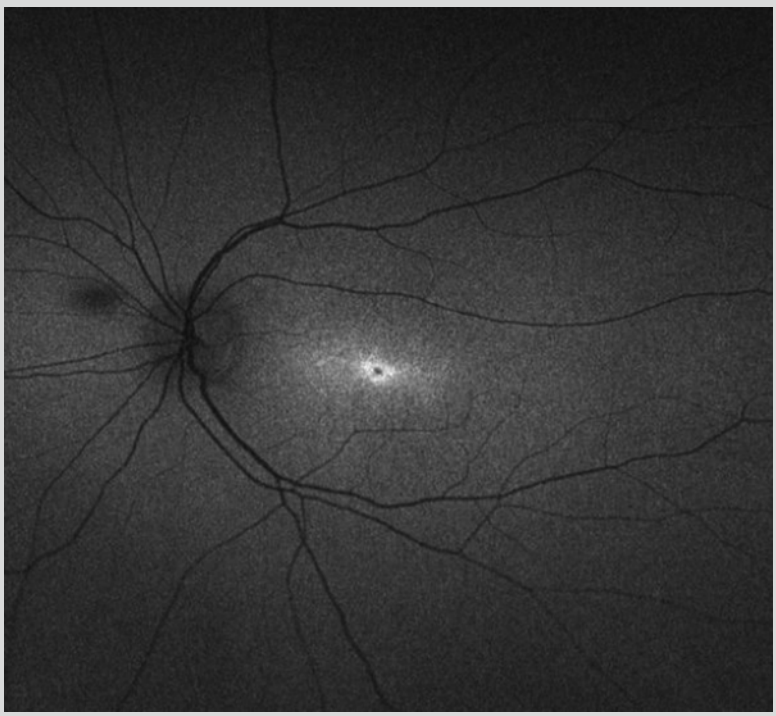

Fig. 34.3 Fundus autofluorescence (FAF) of the achromatopsia patient demonstrating increased perifoveal autofluorescence in the left eye

Comment: Achromatopsia, also known as rod monochromatism, is a nonprogressive hereditary disorder characterized by an absence of cone function with normal rod function. It has an estimated prevalence of 1 in 20,000 to 50,000 [1]. A higher prevalence (about 10 %) is seen on the island of Pingelap in the Eastern Caroline Islands of Micronesia secondary to a founder mutation in *CNGB3* [2, 3]. Poor central vision, color blindness, congenital nystagmus, and photophobia are present from birth. Although the lack of color vision is a defin-

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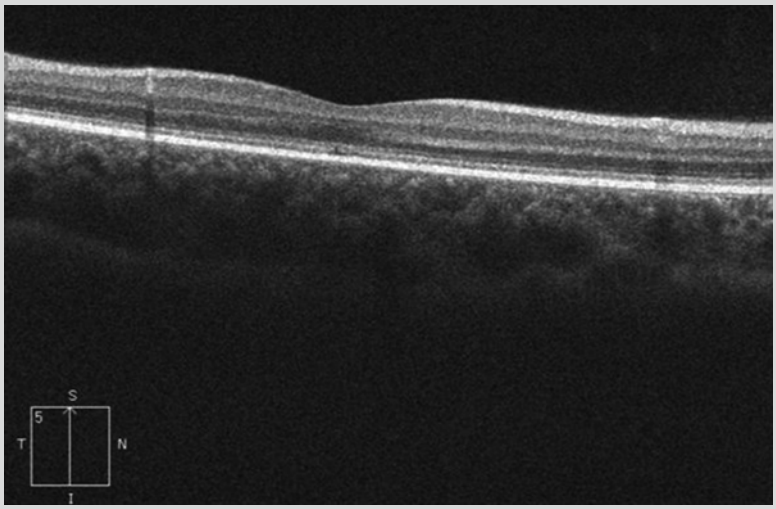

Fig. 34.4 SD-OCT of the achromatopsia patient showing subtle disruption of the IS/OS junction within the fovea and a shallow foveal depression

ing feature, variable degrees of abnormal color perception may be observed in some patients as they age [1]. As a result, achromatopsia can be categorized as complete/typical (no color perception) or, less commonly, incomplete/atypical (some degree of abnormal color perception) [1]. In the complete form visual acuity is usually <20/200, while in the incomplete form the visual acuity may be better (in the range of 20/80) [2, 3]. A "bull's eye" maculopathy or granular macular pigmentation is usually present. However, the macula can appear entirely normal. Hyperopia is a common feature of the complete form in which extrafoveal cones are reduced in number, while a normal number of cones with abnormal morphology are found in the fovea [1].

The photopic ERG is usually non-recordable in achromatopsia, while the scotopic ERG is normal, but may eventually become subnormal. On dark adaptation testing, the cone segment is abnormal and may even be absent while the rods exhibit normal function. Visual field testing may reveal central scotomas, but peripheral visual fields remain intact. Foveal hypoplasia, inner/outer segment loss, RPE disruption, and an optically empty foveal cavity are characteristic findings on optical coherence tomography (SD-OCT) [2–4]. The fluorescein angiogram may be normal or reveal window defects in areas of pigmentary change.

Achromatopsia is typically inherited in an autosomal recessive fashion and linked to five genes including *CNGA3*/*ACHM3*, *CNGB3*/*ACHM3*, *GNAT2*/*ACHM4*, *PDE6C*/*ACHM5*/*COD4*, and *PDE6H* (Table 34.2). *CNGB3* is the most commonly (50 %) involved gene [2, 3]. Mutations in *CNGA3* account for about 30 % of all cases of achromatopsia and slightly higher than that in patients of European descent (40 %) [2, 3].

Table 34.2 Genetic types of achromatopsia [1–5]

Gene	Locus	Mutation frequency (%)	Gene product
CNGA3/ACHM2	2q11.2	30	Alpha subunit of cone cGMP-gated cation channel
CNGB3/ACHM3	8q21.3	50	Beta subunit of cone cGMP-gated cation channel
GNAT2/ACHM4	1p13.3	<2	Alpha subunit of cone transducin
PDE6C/ACHM5/COD4	10q23.33	<2	Alpha subunit of cone-specific phosphodiesterase
PDE6H	12p12.3	0.3	Gamma subunit of cone photoreceptor cyclic guanosine monophosphate phosphodiesterase

There is currently no effective treatment for achromatopsia. Tinted spectacle or contact lenses may be worn to alleviate the intense photophobia [2, 3]. In patients with complete achromatopsia, red filter lenses are thought to offer the most amount of alleviation. Red filters reduce photophobia by allowing the passage of long-wavelength light, which is less stimulatory to rods, while blocking short-wavelength light. In patients with residual cone function, red tinting may interfere with color discrimination by blocking light within the visible spectrum. Consequently, reddish-brown lenses are preferred for patients with incomplete achromatopsia [6].

Bardet-Biedl Syndrome

Case 2 (Table 34.3)

Table 34.3 Case 2

Clinical History	15-year-old female with a history of a retinal dystrophy, poor vision, obesity, hyperlipidemia, renal disease, polydactyly, and retrognathia. PMH was noncontributory. She has a family history of "blindness" in a second cousin		
Base Exam		OD	OS
	BCVA	20/60	20/60
	Versions	Full	Full
	Alignment	LXT 4 (at distance)	
	CRx	−0.75 + 1.75 × 085	−2.75 + 2.00 × 095
Fundus Exam		OD	OS
	Disc	Normal	Normal
	Macula	Pigmentary mottling	Pigmentary mottling
	Vessels	Mild attenuation	Mild attenuation
	Periphery	Pigmentary mottling	Pigmentary mottling
Genetic Testing	Two heterozygous sequence variants in *BBS1* identified		
Diagnosis	Bardet-Biedl syndrome (BBS)		
Treatment	Currently no effective treatment for BBS		

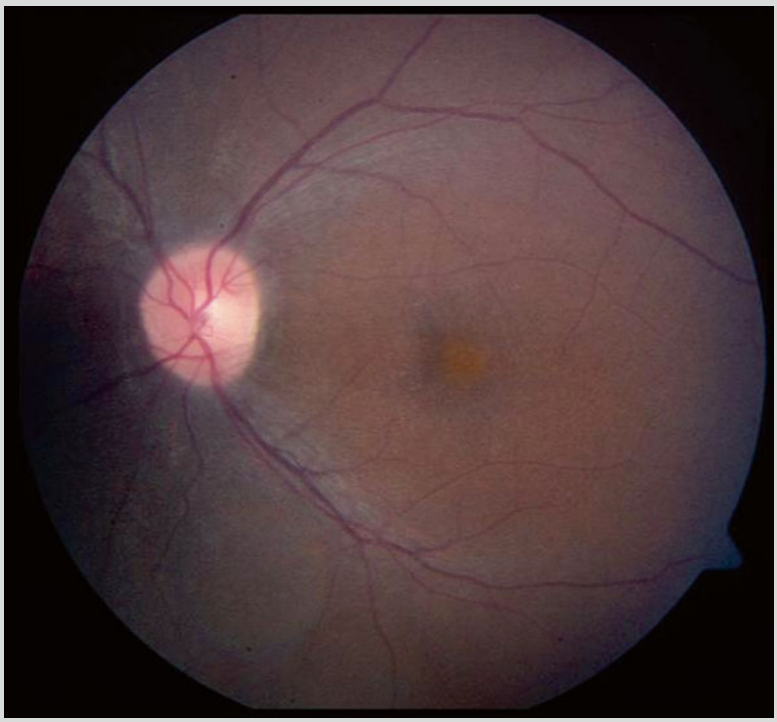

Fig. 34.5 Color fundus photo of a 15-year-old Bardet-Biedl syndrome (BBS) patient with diffuse retinal pigmentary mottling, which is most prominent within the fovea, and mild vascular attenuation of the left eye. No significant optic nerve pallor is present

The patient is a 15-year-old female with a history of a retinal dystrophy, reduced visual acuity, obesity, hyperlipidemia, renal disease, polydactyly, and retrognathia. Her fundus examination revealed bilateral diffuse retinal pigmentary mottling and mild vascular attenuation, but no significant optic nerve pallor (Figs. 34.5, 34.6, and 34.7). Genetic testing confirmed the clinical diagnosis of BBS, and she was found to have two heterozygous pathogenic sequence variations in *BBS1*.

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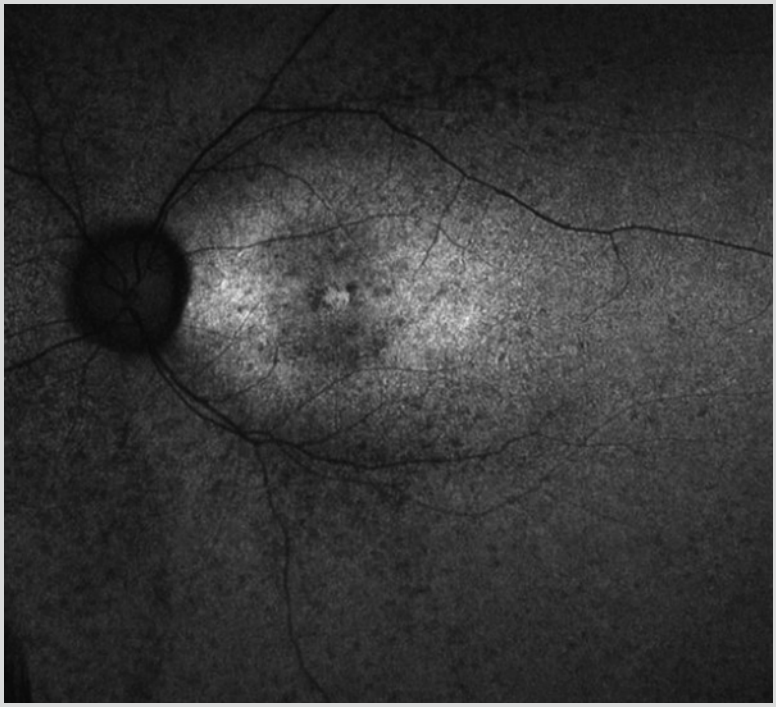

Fig. 34.6 FAF of the BBS patient reveals increased foveal autofluorescence surrounded by an inner perifoveal ring of decreased autofluorescence and an outer perifoveal of increased autofluorescence in the left eye. In addition, there is generalized mottling of both increased and decreased autofluorescence within the macula that extends beyond the arcades into the mid-periphery

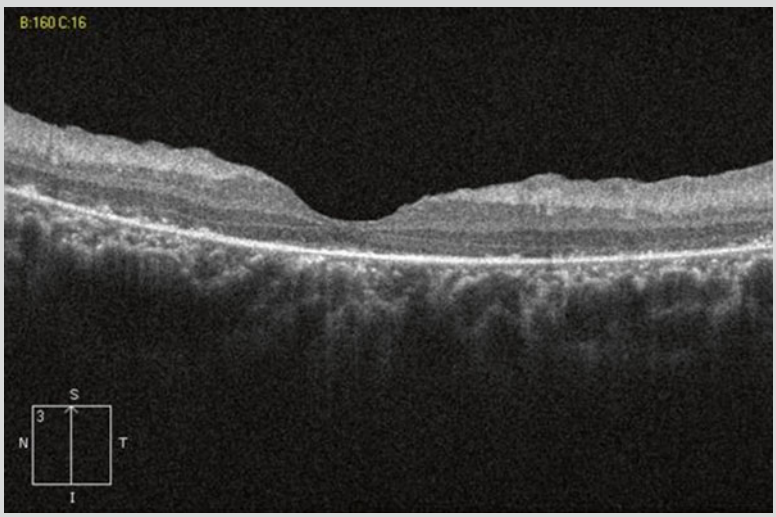

Fig. 34.7 SD-OCT of the BBS patient shows abnormal foveal contour and gross perifoveal retinal thickening. There is severe distortion of the outer retina, including disruption of the IS/OS junction and hyperreflective deposits at the level of the RPE

Comment: BBS has a worldwide prevalence of 1 in 100,000. It is more common among the Bedouin of Kuwait, occurring in 1 in 13,500 individuals. A similarly high prevalence is seen in Newfoundland [2, 3, 7]. The salient clinical characteristics of BSS are retinal degeneration, postaxial polydactyly, learning difficulties, and renal/genital tract abnormalities [8].

The clinical diagnosis of BBS requires the presence of 4 of 6 major criteria or 3 of 6 major criteria plus 2 of 11 minor criteria [9] (Table 34.4).

More than 80 % of patients with BBS have a pigmentary retinopathy with early macular involvement [7]. Parents usually notice night blindness around 8 years of age, although onset of visual impairment is variable [9]. A salt-and-pepper-like retinopathy or one with frank bone spicules may also be observed. Polydactyly and syndactyly are present in 75 % and 14 % of BBS patients, respectively. Early in the disease course of BBS minimal pigmentary changes may be observed in the setting of "normal" vision. However, severe vision loss occurs in almost all patients by 30 years of age, with more than 90 % having a vision of 20/200 or less by this age [7]. Severe color abnormalities and profoundly constricted visual fields also occur. Nystagmus is rarely (5 %) observed in BBS patients but could be an early sign of the disorder. Anosmia, resulting from the involvement of the ciliated

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Table 34.4 Clinical diagnostic criteria for BBS [9].

Major criteria (frequency, %)	Minor criteria (frequency, %)
Rod-cone or cone-rod dystrophy (90–100)	Speech delay (54–81)
Obesity (72–92)	Developmental delay (50–91)
Polydactyly (63–81)	Brachydactyly, syndactyly (46–100)
Genital anomalies (59–98)	Dental anomalies (51)
Learning difficulties (50–61)	Ataxia/poor coordination (40–86)
Renal abnormalities (20–53)	Diabetes mellitus (6–48)
	Anosmia/hyposmia (60)
	Cardiopathy (10)
	Deafness (11, 12)
	Congenital heart disease (7)

Table 34.5 Genetic types of BBS and their protein products

Type	Locus	Gene	Gene product
1	11q13.2	*BBS1*	BBS1 protein
2	16q12.2	*BBS2*	BBS2 protein
3	3q11.2	*BBS3/ARL6*	GTPase
4	15q24.1	*BBS4*	BBS4 protein
5	2q31.1	*BBS5*	Flagellar apparatus-basal body protein DKFZp7621194
6	20p12.2	*BBS6/MKKS*	Part of chaperonin complex/BBSome assembly
7	4q27	*BBS7*	BBS7 protein
8	14q31.3	*BBS8/TTC8*	Tetratricopeptide repeat domain 8
9	7p14.3	*BBS9/PTHB1*	Parathyroid hormone-responsive B1 protein
10	12q21.2	*BBS10*	BBS10 (C12ord58) chaperonin
11	9q33.1	*BBS11/TRIM32*	E3 ubiquitin ligase
12	4q27	*BBS12*	BBS12 protein
13	17q22	*BBS13/MKS1*	Meckel syndrome type 1 protein
14	12q21.32	*BBS14/CEP290/NPHP6*	Centrosomal protein 290 kDa
15	2p15	*BBS15/WDPCP*	Protein involved in regulation of septin localization and ciliogenesis
16	1q43	*BBS16/SDCCAG8*	Serologically defined colon cancer antigen 8
17	3p21.31	*BBS17/LZTFL1*	Leucine zipper transcription factor-like 1
18	10q25.2	*BBS18/BBIP1*	BBSome protein
	3q11.2	*ARL6*	ADP-ribosylation factor-like 6
	9q34.3	*INPP5E*	Inositol polyphosphate-5-phosphatase E
	20p12.2	*MKKS*[a]	McKusick-Kaufman syndrome protein

[a]Mutations in MKKS also cause McKusick-Kaufman syndrome with hydrometrocolpos, polydactyly, and cardiac defects [7]. BBS proteins assist microtubule-related transport and cellular organization processes

olfactory epithelia, may also be present in BBS [7]. The ERG is non-recordable or significantly reduced with elevated dark adaptation thresholds [7].

All BBS types are inherited in an autosomal recessive fashion. Table 34.5 lists the BBS genes and the functions of some of the proteins they encode for.

There is currently no effective treatment for BBS. Early low vision evaluation with implementation of specific interventions can ease adaptations and guide IEP in the school setting (see chapter on Low Vision).

Leber Congenital Amaurosis

Case 3 (Table 34.6)

Table 34.6 Case 3

Clinical History	8-year-old female with a history of a retinal dystrophy. PMH and FH were noncontributory.		
Base Exam		OD	OS
	BCVA	20/60-2	20/200
	Versions	Full	Full
	Alignment	Small X(T)	
	WRx	+3.00 + 2.50x095	+2.75 + 2.75x085
Fundus Exam		OD	OS
	Macula	Pigmentary mottling	Pigmentary mottling
	Vessels	Vascular attenuation with PPRPE	Vascular attenuation with PPRPE
	Periphery	Pigmentary mottling	Pigmentary mottling
Genetic Testing	Two heterozygous variations in the *CRB1* gene identified		
Diagnosis	Leber congenital amaurosis (LCA)		
Treatment	– An effective treatment for LCA has not yet been established – A gene therapy trial is currently under way for patients with LCA harboring mutations in *RPE65*		

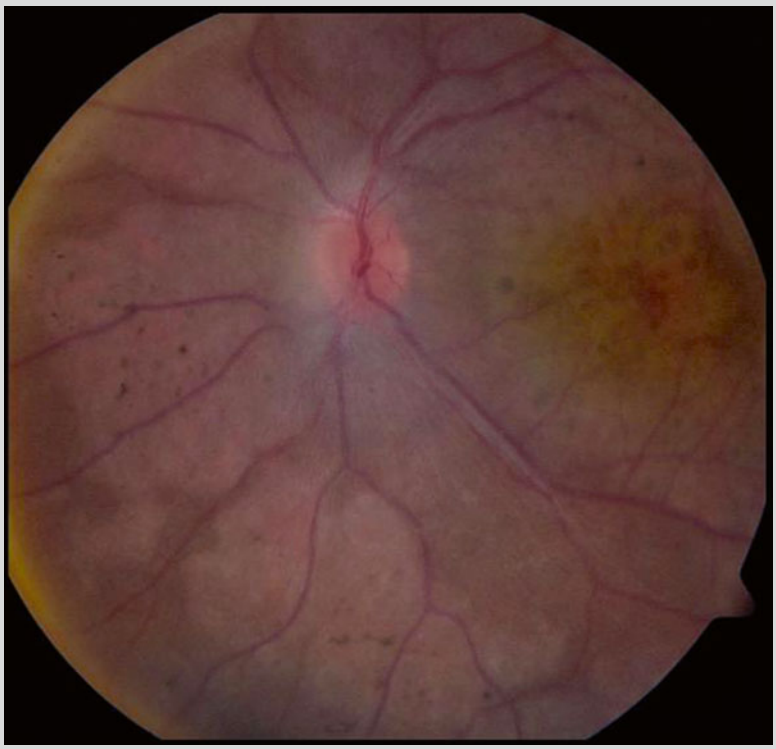

Fig. 34.8 Color fundus photo of an 8-year-old Leber congenital amaurosis (LCA) patient with RPE atrophy and pigmentary mottling within the macula and extending along the retinal vessels of the left eye. Vascular attenuation is also present

The patient is an 8-year-old female with a history of a retinal dystrophy and poor visual acuity (20/60-2 OD and 20/200 OS). On dilated ophthalmoscopy there was bilateral pigmentary mottling in the posterior pole with preservation of the para-arteriolar retinal pigment epithelium (PPRPE) and vascular attenuation (Figs. 34.8, 34.9, and 34.10). Genetic testing was significant for two heterozygous mutations in the *CRB1* gene that were determined to be disease-causing sequence variations, confirming the clinical diagnosis of LCA.

Comment: LCA refers to a group of hereditary retinal disorders with onset in early childhood or at birth. ERG reveals non-recordable photopic and scotopic waveforms in the great majority of cases. Patients typically have nystagmus, severe-to-profound visual impairment, poorly reactive pupils, nyctalopia, or photophobia (50 %). LCA has a prevalence of 1 in 30,000 to 80,000 people. Visual acuity ranges from 20/200 to CF, and rarely LP or NLP, but could be better in some cases, and may depend on the underlying genetic defect. The fundus changes in LCA

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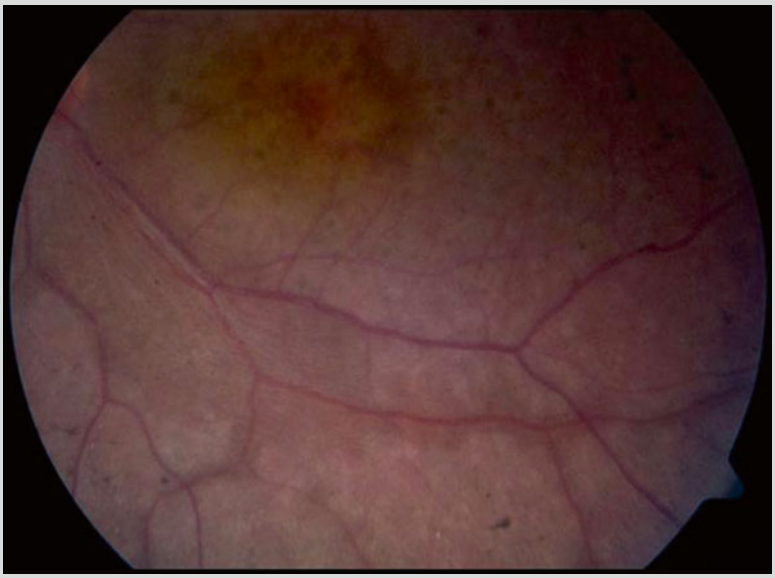

Fig. 34.9 Color fundus photo of the LCA patient highlighting preservation of the para-arteriolar retinal pigment epithelium (PPRPE), which is characteristic of mutations in *CRB1*, along the inferior arcade of the left eye

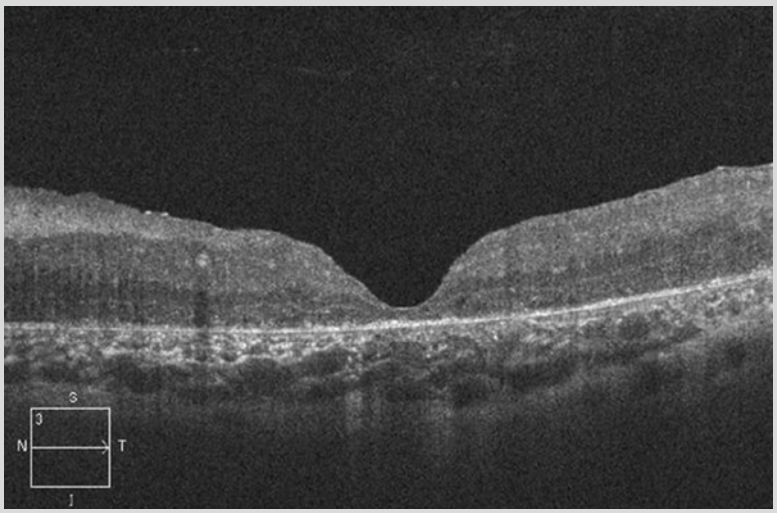

Fig. 34.10 SD-OCT of the LCA patient shows a grossly abnormal foveal contour with retinal thinning within the fovea and adjacent perifoveal thickening. There is apparent loss of the outer retina, including the photoreceptors and IS/OS junction

are quite variable. For example, the retina may appear normal early in life and in patients with *GUCY2D* mutations. A "salt-and-pepper" retinopathy, progressive retinal pigment epithelial granularity, vascular attenuation, optic nerve atrophy, pseudopapilledema, tapetal sheen, yellow flecks, nummular pigmentation, macular colobomas, chorioretinal atrophy, choroidal sclerosis, choroidal atrophy, PPRPE, preretinal fibrosis, Coats-like reaction, or a retinitis pigmentosa-like appearance have all been described. The fundus appearance may guide molecular diagnosis. For example, PPRPE is associated with mutations in *CRB1*, as in the case presented above [10]. LCA is also associated with high hyperopia in a significant proportion of patients, the oculodigital sign of Franceschetti, keratoconus, and posterior subcapsular cataracts. The presence of developmental delay, deafness, seizures, skeletal abnormalities, and renal/muscular abnormalities in some patients should prompt the search for an underlying systemic disease such as a ciliopathy.

Classically, the ERG is non-recordable before the age of one. In addition, visual fields are severely constricted. Outer nuclear layer, outer segment, and photoreceptor loss with resultant retinal thinning are observed on OCT [11]. Intraretinal cystoid spaces may also be detected on OCT in association with mutations in *CRB1* (Fig. 34.11) [12], and may respond to treatment with topical dorzolamide. Fundus autofluorescence shows a variety of patterns that depend on the underlying genetic defect and the stage of the disease [13, 14].

LCA is most commonly inherited in an autosomal recessive fashion with a high degree of phenotypic and genotypic variability (Table 34.7). Rarely, heterozygous

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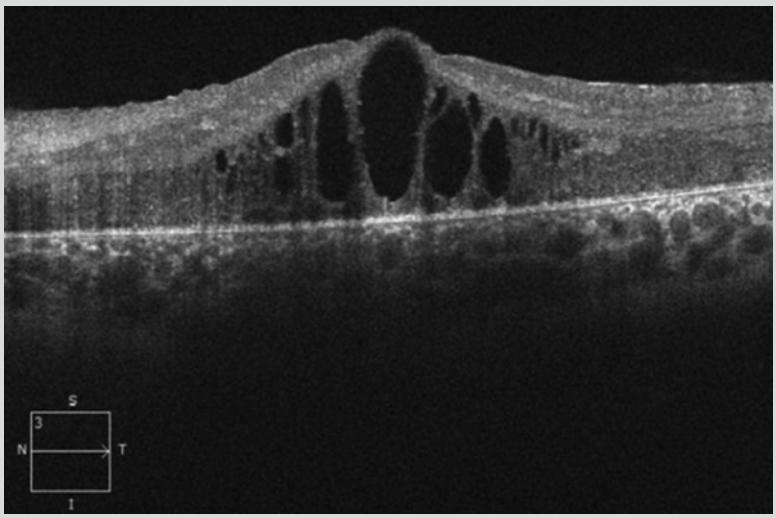

Fig. 34.11 SD-OCT exhibiting intraretinal cystoid spaces within the fovea of another LCA patient with mutations in *CRB1*

Table 34.7 Summary of the different genetic types of LCA (adapted from Table 34.1, pg. 492, of the Genetic Diseases of the Eye [2, 3])

Symbol	Locus	Gene	Mutation frequency (%)	Gene product	Clinical findings
LCA 1	17p13.1	*GUCY2D*	11.7	Retinal guanylate cyclase	Very poor vision, normal-appearing fundus, severe photophobia
LCA 2	1p31.3-p31.2	*RPE65*	6	Retinoid isomerase	Nyctalopia, transient vision improvement, relatively good vision early in life
LCA 3	14q31.3	*SPATA7*	Unknown	Unknown (possible ciliary transport)	Poor vision, retinal atrophy, attenuated vessels
LCA 4	17p13.1	*AILP1*	5.3	Rod PDE chaperone	Very progressive phenotype with atrophic maculopathy, keratoconus, cataracts, optic disc pallor, poor vision, nyctalopia
LCA 5	6q14.1	*LCA5*	1.8	Lebercilin (10), expressed in cilia	Coloboma-like macula, ciliary defect, transient improvements in vision reported
LCA 6	14q11.2	*RPGRIP1*	4.2	Protein transport	Severe vision loss, initially normal retinal appearance, progress to pigmentary retinopathy
LCA 7	19q13.33	*CRX*	1	Photoreceptor development	Severe vision loss, infantile nystagmus, some dominant cases
LCA 8	1q31.3	*CRB1*	9.9	Muller cell-photoreceptor interaction	PPRPE, Coats-like response, thickened and disorganized retina on OCT
LCA 9	1p36.22	*NMNAT1*	Unknown	Unknown	Adenylyltransferase activity
LCA 10	12q21.32	*CEP290*	15	Protein transport	Most common in patients with European descent; extremely poor vision in most, olfactory disturbances
LCA 11	7q32.1	*IMPDH1*	8.3	Guanine synthesis	Rare, diffuse RPE mottling, no pigmentary deposits
LCA 12	1q32.3	*RD3*	0.1	GUCY2D chaperone	Poor vision, atrophic macular lesion, rare
LCA 13	14q23.3	*RDH12*	2.7	All trans retinol in photoreceptor, in retinoid cycle	Rapid loss of vision, rapidly progressive maculopathy, fundus pigmentary fishnet or reticular pattern, prominent macular luteal pigment, Coats-like response
LCA 14	4q32.1	*LRAT*	0.5	Retinyl esters in retinoid cycle	Clinically like juvenile RP, similar appearance to *RPE65*
LCA 15	6p21.31	*TULP1*		Photoreceptor ciliary transport (tubby-like protein 1) (12)	Slow decline in vision, onset of VF defect around age 2, nyctalopia, yellow perifoveal annular ring, more likely to have juvenile-onset RP

(continued)

Table 34.7 (continued)

Symbol	Locus	Gene	Mutation frequency (%)	Gene product	Clinical findings
LCA 16	2q37.1	*KCNJ13*		Inwardly rectifying potassium channel Kir7.1 (12)	
LCA 17	8q22.1	*GDF6*		Member of the transforming growth factor-beta (TGFB1) superfamily	
	3q	*IQCB1*		IQ motif-containing protein B1 (12)	Lobular pattern of hypo- and hyperpigmentation outside the retinal arcades, associated with renal disease (14)
	11q13	*CABP4*		Calcium-binding protein 4 (12, 13)	Photophobia, minimal fundus changes, some have decreased foveal reflex (13)
	14q22.3	*OTX2*		Orthodenticle homolog 2 (12)	Poor vision, nyctalopia, fine, granular RPE pigmentation (15)
	1p36.22	*NMNAT1*		Nicotinamide nucleotide adenylyltransferase 1 (12)	Severe vision loss, macular coloboma (15)
		MERTK1			

mutations in the *CRX* and *IMPDH1* genes result in autosomal dominant inheritance [2, 3].

An effective treatment for LCA has not yet been established, but gene therapy trials are under way and nearing the end for patients with mutations in *RPE65*. Adeno-associated viral (AAV) vectors carrying *RPE65* DNA have been successfully utilized to deliver normal copies of the RPE65 gene in laboratory animals and in early phases of human gene therapy trials [15]. Ongoing clinical trials for gene replacement or other types of therapy in LCA can be found at http://clinicaltrials.gov.

Stargardt Disease

Case 4 (Table 34.8)

Table 34.8 Case 4

Clinical History	11-year-old male with a history of a retinal dystrophy and poor vision since early childhood. PMH and FH were noncontributory.		
Base Exam		OD	OS
	BCVA	20/200	20/250
	Versions	Full	Full
Fundus Exam		OD	OS
	Disc	Mild temporal ON pallor	Mild temporal ON pallor
	Macula	Large area of foveal atrophy with diffuse white fleck-like lesions in the posterior pole	
	Vessels	Normal	Normal
	Periphery	Extension of fleck-like lesions into the mid-periphery	
Genetic Testing	Two heterozygous mutations in the *ABCA4* gene identified		
Diagnosis	Stargardt disease		
Treatment	– No current treatment for Stargardt disease – Avoidance of vitamin A supplementation is recommended in order to reduce lipofuscin accumulation – Patients with the *ELOVL4* mutation may benefit from DHA supplementation		

(continued)

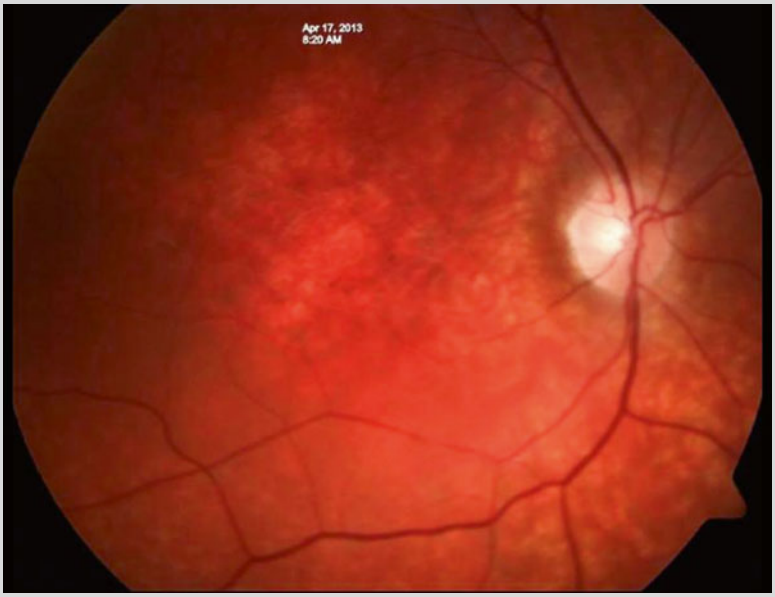

Fig. 34.12 Color fundus photo of a 14-year-old Stargardt disease patient with multiple fleck-like lesions scattered throughout the posterior pole, macular atrophy, and mild temporal optic nerve pallor of the right eye

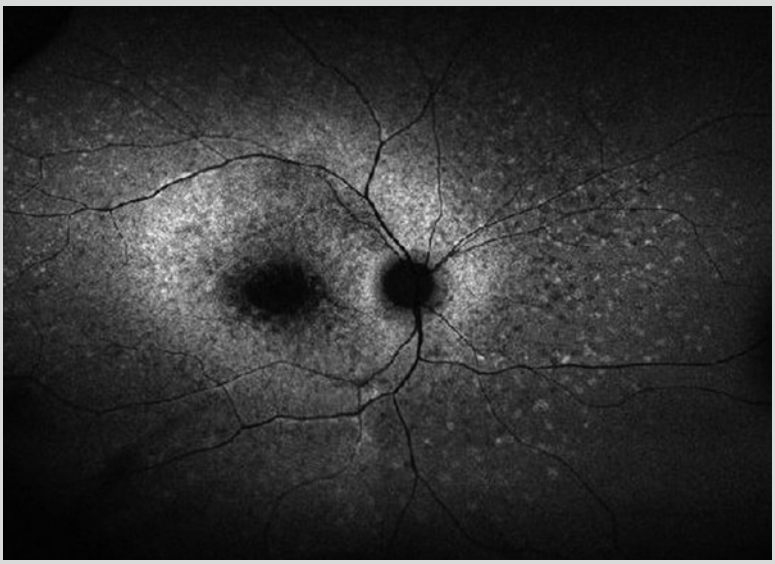

Fig. 34.13 FAF of the Stargardt disease patient displaying decreased foveal autofluorescence surrounded by generalized perifoveal increased autofluorescence that extends peripapillary in the left eye. There is also diffuse mottled increased and decreased autofluorescence present throughout the posterior pole

The patient is a 14-year-old male with a history of a retinal dystrophy and poor vision since early childhood. His most recent visual acuity was 20/200 OD and 20/250 OS. On dilated fundus examination multiple fleck-like lesions were seen scattered throughout the posterior pole and mid-periphery of both eyes. In addition, a large area of atrophy was present in the fovea bilaterally. Mild temporal optic nerve pallor was also noted (Figs. 34.12, 34.13, and 34.14). Genetic testing confirmed the clinically suspected diagnosis of Stargardt disease. Two heterozygous mutations in the *ABCA4* gene were identified.

Comment: Stargardt disease is the most common juvenile hereditary macular dystrophy with a prevalence of 1 in 10,000 [16, 17]. The age of onset can range from 5 years to 80 years of age, with a majority of patients presenting within the first two decades of life without gender predilection [2, 3]. In addition to variability in onset of disease, the clinical presentation and course of progression are vastly heterogeneous. Patients usually present with decreased central vision and in some cases the fundus can appear normal. The degree of central vision loss may be out of proportion to the macular changes, resulting in the dismissal of many cases as having functional vision loss. Fluorescein angiography or fundus autofluorescence imaging will reveal changes in the retina of such individuals and clinch the diagnosis. Characteristically,

(continued)

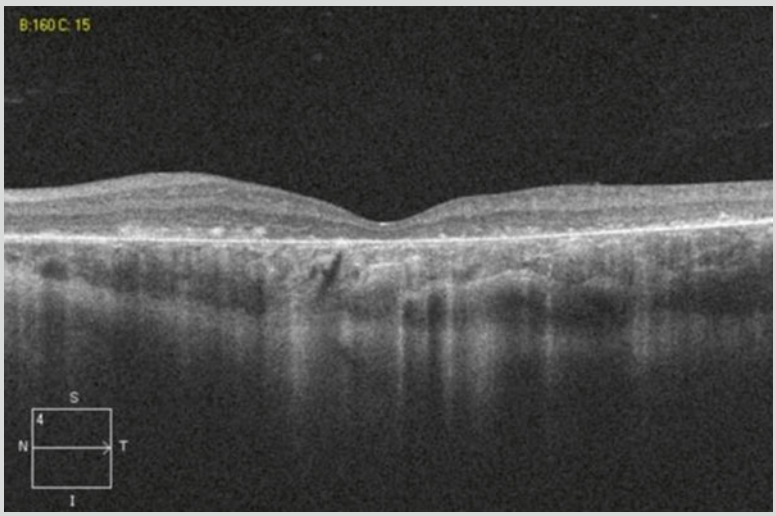

Fig. 34.14 SD-OCT of the Stargardt disease patient shows diffuse thinning and distortion of the fovea. There are distinctive hyperreflective deposits at the level of the inner RPE and outer retina

yellow pisciform flecks are scattered throughout the posterior pole. These lesions are "fish-tail" shaped and at the level of the retinal pigment epithelium (RPE). The flecks represent groups of enlarged RPE cells packed with a granular substance, which is thought to be lipofuscin [2, 3]. A disease spectrum exists, ranging from fundus flavimaculatus, occurring without a macular dystrophy in adulthood, to Stargardt disease, which presents in late childhood/adolescence. The current preferred terminology for all cases is Stargardt disease. Some patients have a bull's eye maculopathy with a "beaten bronze" appearance. Peripheral pigmentary changes may develop with age, and will lead to what has been called cone-rod dystrophy. Mild-to-moderate color vision abnormalities may develop as the disease progresses, and some patients may complain of increasing difficulties with night vision. Ancillary testing with retinal imaging, visual field, and electroretinography (ERG) may aid in the diagnosis and characterization of the retinal phenotype (Table 34.9).

Peripheral visual fields are normal in early stages. With time, a relative central scotoma, that often becomes absolute, may develop [17]. Fundus imaging with fluorescein angiography, fundus autofluorescence, and SD-OCT can be helpful in the diagnosis of Stargardt disease (Table 34.9).

The classic dark or "silent" choroid sign on fluorescein angiography is secondary to blockage of choroidal fluorescence by RPE that is packed with lipofuscin and occurs in 62–86 % of patients [2, 3, 17]. The flecks demonstrate early blockage and late hyperfluorescent staining. Other findings include window defects in areas of the macular atrophy and other hyperfluorescent spots that are not associated with the clinical flecks. On FAF, areas of decreased autofluorescence (AF) correlate with RPE loss. Yellowish flecks, on the other hand, correspond to areas of increased AF [16]. The macula may contain mottled areas of decreased AF or it can appear normal with a relatively preserved autofluorescence signal [16]. Photoreceptor loss, corresponding to atrophic macular areas with decreased foveal thickness, is seen on OCT [19]. A better visual prognosis is observed in the presence of an intact photoreceptor layer (preserved ellipsoid zone) in the setting of inner retinal atrophy. The retinal flecks correspond to hyperreflective deposits in the inner RPE and the outer nuclear layer on OCT. The ERG can be normal; however a significant number of patients or more may have photopic abnormalities. In patients with a cone-rod dystrophy phenotype, the scotopic ERG is also

Table 34.9 Ancillary tests in Stargardt disease [2, 3, 16–18]

Visual Field	– Normal early – Relative central scotoma, that often becomes absolute, may develop
FA	– Classic dark or "silent" choroid sign secondary to blockage by lipofuscin (62–86 % of patients) – Flecks demonstrate early blockage and late hyperfluorescence – Hyperfluorescent spots that are not associated with the clinical flecks – Window defects in areas of macular atrophy
FAF	– Increased and decreased AF corresponding to flecks and RPE loss, respectively – Macula may appear normal or contain mottled areas of decreased AF
OCT	– Photoreceptor loss (corresponds to macular atrophy with decreased foveal thickness) – Flecks appear as hyperreflective deposits at the level of the inner RPE or outer retina
ERG	– Can be normal – 1/3 have photopic abnormalities – Abnormal scotopic response in cone-rod dystrophy phenotype – Multifocal ERG subnormal within the macula
EOG	– Abnormal in up to 75 %

(continued)

Table 34.10 Genetic types of Stargardt disease [2, 3, 16]

Type	Gene	Locus	Inheritance	Gene product
STGD1	*ABCA4*	1p22.1	Autosomal recessive	Retina-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCR)
STGD3	*ELOVL4*	6q14.1	Autosomal dominant	Photoreceptor-specific component of polyunsaturated fatty acid elongation system
STGD4	*PROM1*	4p	Autosomal dominant	Pentaspan transmembrane glycoprotein, prominin-1

abnormal. The multifocal ERG is subnormal within the macula in all patients. The EOG is abnormal in up to 75 % of cases.

Stargardt disease is inherited predominantly in an autosomal recessive mode, but an autosomal dominant subset exists [2, 3]. Recessive Stargardt disease is caused by mutations in the *ABCA4* gene on chromosome 1p21-p22. Retina-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCR), which is encoded by *ABCA4* [16], is present in the rod and cone outer segment rims. ABCR is responsible for the extracellular transport of all-trans-retinol produced in light-exposed photoreceptor outer segments. Mutations in the *ELOVL4* (elongation of a very-long-chain fatty acid-like 4) gene on chromosome 6q14 cause autosomal dominant Stargardt disease. *ELOVL4* encodes a photoreceptor-specific component of the polyunsaturated fatty acid elongation system (Table 34.10).

The visual prognosis is quite variable. Half of the patients have vision in the range of 20/200–20/400, while 25 % of patients maintain a visual acuity of 20/40 or better in at least one eye [2, 3]. However, a certain subset, especially those patients with onset of symptoms in the first decade of life, may develop profound vision loss [18]. A significant proportion of patients labeled as having recessive cone-rod dystrophy have mutations in *ABCA4,* the gene responsible for Stargardt disease, again demonstrating the phenotypic variability. Prognostic factors related to poorer visual outcome include earlier disease onset, larger number [>/= 2] of identifiable mutations in *ABCA4* [18], and specific select genotypes. The autosomal dominant form is often less severe.

There is currently no effective treatment for Stargardt disease. Some studies in murine model of Stargardt disease suggest that vitamin A supplementation may contribute to lipofuscin accumulation. As a result, we instruct patients to avoid vitamin A supplementation. In the autosomal dominant form, there is also an inverse relationship between functional ELOVL4 activity and docosahexaenoic acid (DHA) levels in red blood cell lipids. Evidence exists that DHA may slow the progression of photoreceptor and RPE cell death. Therefore, patients harboring the *ELOVL4* mutation could potentially benefit from DHA supplementation. Gene therapy trials for Stargardt disease are under way and can be found at http://clinicaltrials.gov.

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