CHAPTER 13

Retinal Degenerations Associated With Systemic Disease

Highlights

- Many systemic diseases can have retinal manifestations.
- A multidisciplinary approach to management is often warranted for retinal degenerations associated with systemic disease.
- Gene therapies are under investigation for many systemic diseases with retinal degenerations.

Introduction

For many of the conditions discussed in this chapter, a correct diagnosis could lead to meaningful, and in some cases life-saving, interventions. Important diagnostic and prognostic questions that arise in evaluating a patient who presents with retinal degeneration include the following:

- Is the degeneration hereditary or acquired?
- Is the condition stable or progressive?
- Can a precise diagnosis be made?

Systemic diseases with retinal degenerations are a highly heterogeneous group that often require multidisciplinary subspecialty care because of potentially severe associated morbidities and mortality. Gene therapies are under investigation for many of these diseases.

Retinal Degeneration With Systemic Involvement

Pigmentary retinopathy and retinal degenerations may be associated with a wide spectrum of genetic or acquired diseases. The term *pigmentary retinopathy* refers broadly to a panretinal disturbance of the retina and retinal pigment epithelium (RPE). Pigment deposits define most pigmentary retinopathies and typically present in the form of pigment clumps or spicules. In some diseases, there is generalized depigmentation characterized by atrophy and little or no pigment deposition. This section summarizes some important examples of these disorders (Table 13-1).

Table 13-1 Selected Systemic Diseases With Pigmentary Retinopathies

Disorder	Features
Autosomal dominant disorders	
Arteriohepatic dysplasia (Alagille syndrome)	Intrahepatic cholestatic syndrome, posterior embryotoxon, Axenfeld anomaly, congenital heart disease, flattened facies and bridge of nose, bony abnormalities, myopia, pigmentary retinopathy
Charcot-Marie-Tooth disease	Pigmentary retinopathy, degeneration of lateral horn of spinal cord, optic atrophy
Myotonic dystrophy (Steinert disease)	Muscle wasting, "Christmas tree" cataract, retinal degeneration, pattern dystrophy or reticular degeneration; ERG response subnormal
Oculodentodigital dysplasia (oculodentodigital syndrome)	Thin nose with hypoplastic alae, narrow nostrils, abnormality of fourth and fifth fingers, hypoplastic dental enamel, congenital cataract, colobomas
Olivopontocerebellar atrophy	Retinal degeneration (peripheral and/or macular), cerebellar ataxia, possible external ophthalmoplegia
Stickler syndrome arthro-ophthalmopathy)	Progressive myopia with myopic retinal degeneration, arthropathy including joint hypermobility and arthritis, midfacial hypoplasia, high arched or cleft palate, bifid uvula; retinal detachment common; ERG response subnormal
Waardenburg syndrome	Hypertelorism, wide bridge of nose, cochlear deafness, white forelock, heterochromia iridis, poliosis, pigment disturbance of RPE, choroidal vitiligo; ERG response normal to subnormal
Wagner hereditary vitreoretinal degeneration	Narrowed and sheathed retinal vessels, pigmented spots in the retinal periphery and along retinal vessels, choroidal atrophy and optic atrophy, extensive liquefaction and membranous condensation of vitreous body; subnormal ERG response; overlapping features with Stickler syndrome
Autosomal recessive disorders	
Bardet-Biedl syndrome	Pigmentary retinopathy, bull's-eye maculopathy, mild cognitive disabilities, polydactyly, obesity, hypogenitalism, renal abnormalities, progressive visual field loss; ERG response severely diminished to undetectable
Bietti crystalline dystrophy	Yellow-white crystals scattered in posterior pole, round subretinal pigment deposits, confluent loss of RPE and choriocapillaris on fluorescein angiogram, possible crystals in limbal cornea
Homocystinuria	Fine pigmentary or cystic degeneration of retina, marfanoid appearance, myopia, lens subluxation or dislocation, cardiovascular abnormalities (thromboses), glaucoma, cognitive disabilities
α-Mannosidosis	Macroglossia (enlarged tongue), flat nose, large head and ears, skeletal abnormalities, possible hepatosplenomegaly, storage material in retina; resembles severe mucopolysaccharidosis I
Mucopolysaccharidosis I (severe; Hurler syndrome)	Early corneal clouding, retinal pigmentary degeneration, coarse facies, deafness, cognitive disabilities, dwarfism, skeletal abnormalities, hepatosplenomegaly, optic atrophy; subnormal ERG response
Mucopolysaccharidosis I (attenuated; Scheie syndrome)	Coarse facies, aortic regurgitation, stiff joints, early clouding of the cornea, normal life span, normal intellect, pigmentary retinopathy
Mucopolysaccharidosis III (Sanfilippo syndrome)	Milder somatic stigmata than in severe mucopolysaccharidosis I, but severe pigmentary retinopathy

Disorder	Features
Neonatal adrenoleukodystrophy (Zellweger spectrum disorder)	Pigmentary retinopathy, optic atrophy, seizures, hypotonia, adrenal cortical atrophy, psychomotor impairment; extinguished ERG response
Neuronal ceroid lipofuscinoses (CLN; Batten disease)	Infantile (CLN1, Haltia-Santavuori): onset age 6–18 months with rapid deterioration, fine granular inclusions, bull's-eye maculopathy Late infantile (CLN2, Jansky-Bielschowsky): onset age 2–4 years, rapid CNS deterioration, curvilinear body inclusions Lake-Cavanagh: onset 4–6 years, ataxia, dementia, curvilinear and fingerprint-like inclusions Juvenile (CLN3, Batten-Spielmeyer-Vogt): onset age 6–8 years, slowly progressive, fingerprint-like inclusions, pigmentary retinopathy, bull's-eye maculopathy
Refsum disease	Elevations of phytanic acid, pigmentary retinopathy, optic atrophy, partial deafness, cerebellar ataxia, ichthyosis
Spinocerebellar degeneration	Ataxia, limb incoordination, nerve deafness, maculopathy, retinal degeneration, optic atrophy
Usher syndrome	Congenital deafness (partial or profound), pigmentary retinopathy, vestibular areflexia (type 1)
Zellweger (cerebrohepatorenal) syndrome (Zellweger spectrum disorder)	Hypotonia, high forehead and hypertelorism, hepatomegaly, deficient cerebral myelination, nystagmus, cataract, microphthalmia, retinal degeneration; undetectable ERG response
X-linked disorders	
Incontinentia pigmenti (Bloch-Sulzberger syndrome)	Skin pigmentation in lines and whorls, alopecia, dental and CNS anomalies, optic atrophy, falciform folds, cataract, nystagmus, strabismus, patchy mottling of fundi, conjunctival pigmentation
Mucopolysaccharidosis II (Hunter syndrome)	Minimal or no corneal clouding, mild clinical course; onset of signs at age 2–4 years: full lips, large and rounded cheeks, broad nose, enlarged tongue, possible cognitive disabilities, pigmentary retinopathy; subnormal ERG response; over time, voice changes from vocal cord enlargement; possible airway obstruction from airway narrowing
Pelizaeus-Merzbacher disease	Infantile progressive leukodystrophy, cerebellar ataxia, limb spasticity, cognitive impairment, possible pigmentary retinopathy with absent foveal reflex
Mitochondrial disorders	
Kearns-Sayre syndrome; maternally inherited diabetes and deafness (MIDD); mitochondrial encephalopathy, lactic acidosis, stroke like episodes (MELAS)	Chronic progressive external ophthalmoplegia, ptosis, pigmentary retinopathy and/or macular atrophy, heart block (Kearns-Sayre syndrome); normal to subnormal ERG response

CNS = central nervous system; ERG = electroretinogram; RPE = retinal pigment epithelium.

Information from Rimoin DL, Connor JM, Pyeritz RE, Korf BR, eds. *Emery and Rimoin's Principles and Practice of Medical Genetics*. 3 vols. 4th ed. Churchill Livingstone; 2002:chap 137.

Infantile-Onset to Early Childhood–Onset Syndromes

The dystrophies characterized by early onset and rapid progression of severe bilateral vision loss are collectively called *Leber congenital amaurosis (LCA)*. In any infant suspected of having poor or declining vision, LCA should be considered when a severely diminished or extinguished electroretinogram (ERG) signal is present at birth (see Chapter 12 for further discussion). When the ERG signal is diminished and the changes in vision are progressive, evaluation should include careful screening for congenital syndromes and metabolic disorders that affect the retina.

Huang CH, Yang CM, Yang CH, Hou YC, Chen TC. Leber's congenital amaurosis: current concepts of genotype-phenotype correlations. *Genes (Basel).* 2021;12(8):1261. doi:10.3390/genes 12081261.

Bardet-Biedl Syndrome

Bardet-Biedl syndrome is a genetically and clinically heterogeneous disorder of ciliary function. Many different types have been identified and have a similar constellation of findings, including pigmentary retinopathy (with or without pigment deposits), obesity, polydactyly, hypogonadism, cognitive disability, and renal abnormalities (see the section "Renal diseases"). Patients with Bardet-Biedl syndrome typically demonstrate a form of rod–cone dystrophy with variable severity, usually sine pigmento, with a bull's-eye atrophic maculopathy (Fig 13-1). These disorders are sometimes classified as autosomal recessive, but molecular studies strongly suggest that many are multigenic, with 2 or even 3 different mutations contributing to the phenotype. Increasing evidence suggests that the primary function of the proteins affected in Bardet-Biedl syndrome are to mediate and regulate microtubule-based intracellular transport processes.

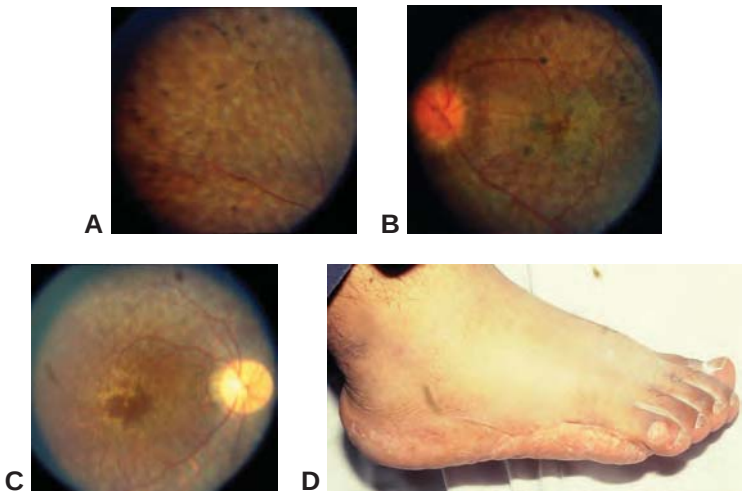

Figure 13-1 Bardet-Biedl syndrome. **A, B,** Fundus photographs show pigmentary alterations in the periphery and macula. **C,** Fundus photograph from the sibling of the patient in **A** and **B** demonstrates similar macular changes. **D,** Clinical photograph of a patient's foot with 6 toes (polydactyly). *(Courtesy of David Sarraf, MD.)*

M'hamdi O, Ouertani I, Chaabouni-Bouhamed H. Update on the genetics of Bardet-Biedl syndrome. *Mol Syndromol.* 2014;5(2):51–56.

Hearing Loss and Pigmentary Retinopathy: Usher Syndrome

Usher syndrome is the most common name used to describe the association of retinitis pigmentosa (RP) with congenital sensorineural hearing loss, whether partial or profound. The prevalence of Usher syndrome is thought to be 3 cases per 100,000 persons. There are 3 types of Usher syndrome, with types 1 and 2 being more common than type 3. Patients with type 1 have early and profound deafness, RP, and vestibular areflexia. Patients with type 2 are born with moderate to severe hearing loss and develop RP within the second decade of life but have normal vestibular function. Patients with type 3 have progressive hearing loss, RP of variable severity, and sporadic vestibular function.

All forms show autosomal recessive inheritance. Currently, 16 genetic loci have been identified as associated with Usher syndrome. The proteins encoded by these genes are part of a dynamic protein complex present in the cilia of the inner ear and in the cone outer segments of the photoreceptor cells of the retina. See Table 13-2 for other genetic conditions that may lead to pigmentary retinopathy and hearing loss.

Mathur P, Yang J. Usher syndrome: hearing loss, retinal degeneration and associated abnormalities. *Biochim Biophys Acta.* 2015;1852(3):406–420.

Neuromuscular Disorders

Pigmentary retinopathy associated with neuromuscular pathology is present in a variety of disorders (see Table 13-1). ERG abnormalities found in these neurologic disorders confirm the presence of retinopathy but are not diagnostic for any one disorder.

Although *Duchenne muscular dystrophy* does not cause a pigmentary retinopathy, it deserves mention because the ERG signal shows a negative waveform similar to that found in patients with congenital stationary night blindness—specifically, a normal a-wave but a reduced b-wave (see Chapters 3 and 12). This ERG response suggests a defective "on-response" pathway, but patients with this disorder do not have nyctalopia (night blindness). Interestingly, Duchenne muscular dystrophy is caused by mutations in the gene for dystrophin, a protein that is abundant in muscle but also found in neural synaptic regions and in the retina.

Barboni MT, Nagy BV, de Araújo Moura AL, et al. ON and OFF electroretinography and contrast sensitivity in Duchenne muscular dystrophy. *Invest Ophthalmol Vis Sci.* 2013; 54(5):3195–3204.

Table 13-2 Disorders Causing Pigmentary Retinopathy and Hearing Loss

Alport syndrome
Alström syndrome
Cockayne syndrome
Congenital rubella syndrome
Mucopolysaccharidosis I (severe; also known as *Hurler syndrome*)
Refsum disease
Spondyloepiphyseal dysplasia congenita

Diseases Affecting Other Organ Systems

Most retinopathies associated with diseases affecting other organ systems are rare and genetic. Clinicians may find the OMIM, Online Mendelian Inheritance in Man, website (www.omim.org) useful in recognizing these disorders.

Renal diseases

Several forms of congenital renal disease are ciliopathies associated with retinal degeneration. *Familial juvenile nephronophthisis* (also called *Senior-Løken syndrome, renal-retinal dysplasia*) is one of a group of diseases characterized by autosomal recessive inheritance, retinal degeneration, and childhood onset of end-stage renal disease. Individuals with *Joubert syndrome* have cerebellar malformation (a characteristic "molar tooth" deformity that can be observed on magnetic resonance imaging of the brain) and may also have associated chorioretinal coloboma. Patients with *Bardet-Biedl syndrome* (discussed earlier) commonly have urethral reflux with pyelonephritis and kidney damage, whereas patients with *Alström syndrome* may demonstrate obesity and have short stature and cardiomyopathy in addition to renal disease. *Jeune syndrome* is a retinal ciliopathy that is complicated by cystic kidney disease and asphyxiating thoracic dystrophy.

Liver disease

Patients with *arteriohepatic dysplasia* (also called *Alagille syndrome*) present with hepatorenal abnormalities, including cholestatic jaundice. Characteristic ocular findings, which include posterior embryotoxon and pigmentary retinopathy, can have a peripapillary and macular predilection.

Gastrointestinal tract disease

Familial adenomatous polyposis (*FAP;* also known as *Gardner syndrome*) is associated with pigmented lesions that are similar to those found in congenital hypertrophy of the RPE. However, the lesions in FAP are ovoid, more variegated than the classic isolated lesions of congenital hypertrophy of the RPE, and typically multiple and bilateral. The presence of more than 4 widely spaced, small (<0.5–disc diameter) lesions per eye and bilateral involvement suggest FAP. Note that congenital grouped pigmentation (bear tracks) is not associated with FAP (Fig 13-2). Caused by mutations in the adenomatous polyposis gene *(APC),* FAP has an autosomal dominant inheritance pattern with incomplete expression. The pigmented retinal lesions are an important marker for identifying family members at risk for colonic polyps, which have a high malignant potential (see BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors*).

Nusliha A, Dalpatadu U, Amarasinghe B, Chandrasinghe PC, Deen KI. Congenital hypertrophy of retinal pigment epithelium (CHRPE) in patients with familial adenomatous polyposis (FAP): a polyposis registry experience. *BMC Res Notes*. 2014;7:734.

Dermatologic diseases

Ichthyosis, comprising abnormal scaling, dryness, and tightness of the skin, may be found in conjunction with the pigmentary retinopathy of Refsum disease and the crystalline maculopathy of Sjögren-Larsson syndrome (Fig 13-3). *Incontinentia pigmenti (Bloch-Sulzberger syndrome)* is a rare X-linked disorder that presents only in females; the syndrome is lethal

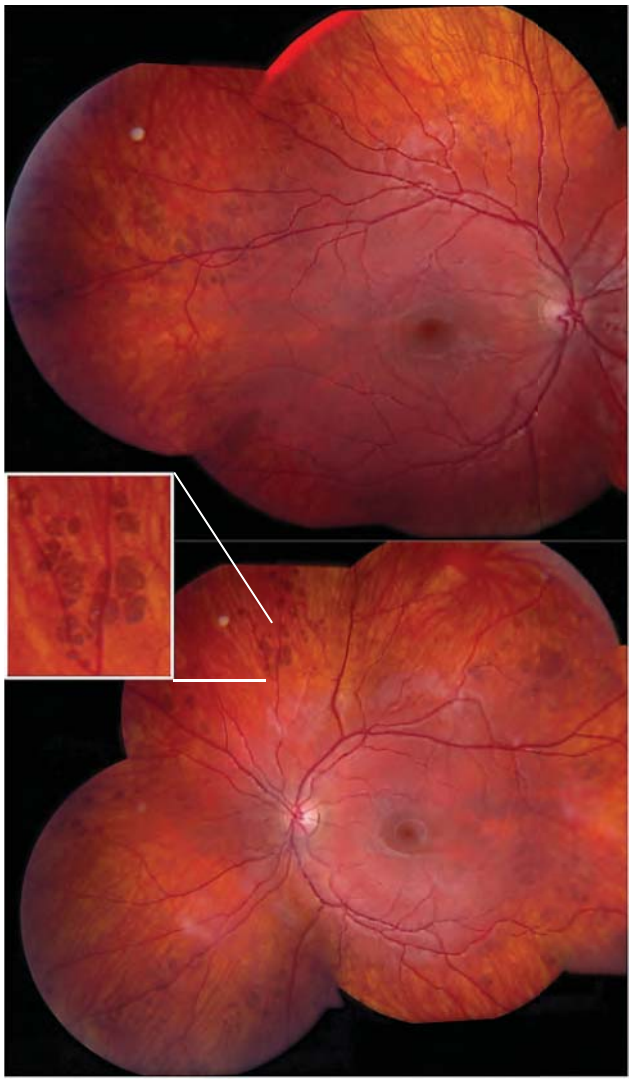

Figure 13-2 Bilateral, extensive bear tracks in congenital hypertrophy of the retinal pigment epithelium (CHRPE). *Inset* shows a magnified cluster, highlighting the sharp borders and location deep to the retina (under the retinal vessels), consistent with localization at the level of the RPE. In contrast, pigmented lesions in familial adenomatous polyposis are more widely spaced, larger, and typically ovoid compared to the bear track lesions in this fundus photograph. *(Courtesy of Anthony B. Daniels, MD, MSc.)*

in utero to males. It is characterized by streaky skin lesions and abnormalities of the teeth and central nervous system (CNS). Ocular involvement occurs in approximately 35%–77% of affected females and includes pigmentary abnormalities as well as peripheral retinal nonperfusion and neovascularization that may cause traction and cicatricial retinal detachment (see also BCSC Section 6, *Pediatric Ophthalmology and Strabismus*). *Pseudoxanthoma elasticum* is associated with a "plucked chicken" skin appearance, peripapillary angioid streaks, and a peau d'orange fundus appearance (see Chapter 4).

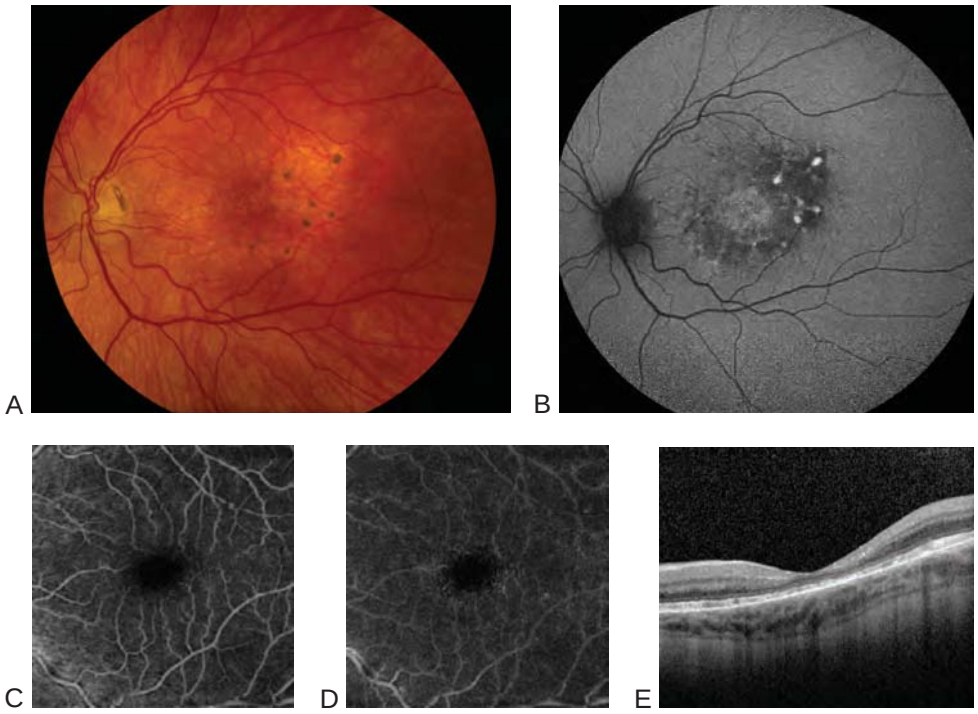

Figure 13-3 Images from a patient with late-stage Sjögren-Larsson syndrome. **A,** Fundus images demonstrate RPE changes and atrophy with lipofuscin deposits in the macula. **B,** Fundus autofluorescence reveals hyperautofluorescence of lipofuscin deposits. **C, D,** Increased flow voids, vessel dilation, and decreased capillary density in the superficial and deep retinal capillary plexuses are displayed with optical coherence tomography (OCT) angiography. **E,** Spectral-domain OCT (SD-OCT) shows hyperreflective dots in the inner retina and RPE and disruption of the ellipsoid zone. *(Courtesy of Jaclyn L. Kovach, MD.)*

Swinney CC, Han DP, Karth PA. Incontinentia pigmenti: a comprehensive review and update. *Ophthalmic Surg Lasers Imaging Retina.* 2015;46(6):650–657.

Dental disease

Amelogenesis imperfecta is a genetic disease that causes abnormalities in dentition development resulting from defective enamel production. When associated with a cone–rod dystrophy, this condition is referred to as *Jalili syndrome* and has a wide range of clinical retinal manifestations, including macular coloboma and pigmentary retinopathy.

Paraneoplastic and Autoimmune Retinopathies

Occasionally, retinal degeneration is a complication of cancer resulting from a paraneoplastic immunologic mechanism. The 2 main paraneoplastic retinopathy syndromes are *cancer-associated retinopathy* (*CAR;* Fig 13-4) and *melanoma-associated retinopathy (MAR).* Patients with these syndromes can have normal-appearing fundi. The characteristic ERG findings in MAR are a preserved dark-adapted a-wave followed by a strikingly

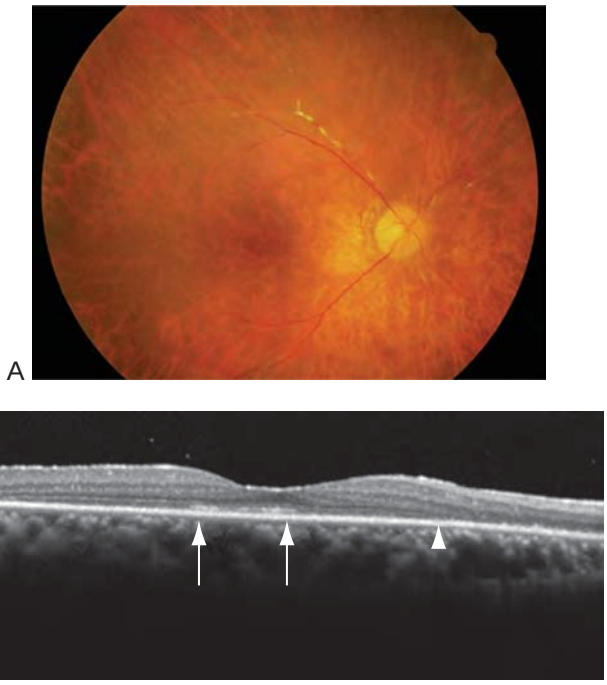

Figure 13-4 Cancer-associated retinopathy (CAR). **A,** Fundus photograph of CAR in a patient with ovarian carcinoma. Note the severe vascular attenuation without obvious pigmentary alterations. **B,** Fourier-domain cross-sectional OCT of an eye with CAR that shows disruption *(arrowheads)* of the outer nuclear layer and external limiting membrane as well as decreases in reflectivity of the inner segment ellipsoid zone *(arrows)*. *(Part A courtesy of John R. Heckenlively, MD; part B modified from Mesiwala NK, Shemonski N, Sandrian MG, et al. Retinal imaging with en face and cross-sectional optical coherence tomography delineates outer retinal changes in cancer-associated retinopathy secondary to Merkel cell carcinoma.* J Ophthalmic Inflamm Infect. *2015;5(1):53. https://doi.org/10.1186/s12348-015-0053-0)*

reduced b-wave, resulting in an electronegative ERG, which is similar to the ERG findings in congenital stationary night blindness. Patients with MAR usually present with acquired nyctalopia and shimmering photopsias. In CAR, the ERG shows decreased or extinguished a- and b-waves.

A third entity, *autoimmune retinopathy,* refers to an acquired, presumed immunologically mediated, retinal degeneration that resembles paraneoplastic retinopathy but there is no identifiable systemic malignancy. See BCSC Section 9, *Uveitis and Ocular Inflammation*, for more on this retinopathy, CAR, and MAR.

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a paraneoplastic syndrome characterized by multiple melanocytic lesions of the choroid that may be associated with rapidly progressive posterior subcapsular cataract, iris and ciliary body cysts, and exudative retinal detachment. BDUMP has been associated with various systemic malignancies (see Chapter 9). *Acute exudative polymorphous vitelliform maculopathy,* which is characterized by multiple waxing and waning subretinal vitelliform lesions, has been reported in association with metastatic cutaneous melanoma and other systemic malignancies.

Fox AR, Gordon LK, Heckenlively JR, et al. Consensus on the diagnosis and management of nonparaneoplastic autoimmune retinopathy using a modified Delphi approach. *Am J Ophthalmol.* 2016;168:183–190.

Grange L, Dalal M, Nussenblatt RB, Sen HN. Autoimmune retinopathy. *Am J Ophthalmol.* 2014;157(2):266–272.

Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: evaluation and management. *Surv Ophthalmol.* 2013;58(5):430–458.

Metabolic Diseases

When patients with retinal degeneration are being evaluated, it is important to consider metabolic diseases, as some of these disorders are potentially lethal and others have severe morbidities. Disorders such as abetalipoproteinemia and Refsum disease are among the differential diagnostic concerns for RP even though the retinopathy associated with these diseases can be granular and atypical. See BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* which covers many of the entities discussed in the following subsections, including albinism.

Albinism

In albinism, the synthesis of melanin is reduced or absent. When the reduction in melanin biosynthesis affects the eyes, skin, and hair follicles, the disease is called *oculocutaneous albinism (OCA).* There are several different types, which are usually inherited in an autosomal recessive pattern. If the skin and hair appear normally pigmented and only ocular pigmentation is affected, the condition is called *ocular albinism.* Ocular albinism typically has an X-linked inheritance pattern. Female carriers of X-linked ocular albinism may show partial iris transillumination and fundus pigment mosaicism.

Regardless of the type of albinism, ocular involvement generally conforms to 1 of 2 clinical patterns: (1) congenitally subnormal visual acuity (typically 20/100–20/400) and nystagmus; or (2) normal or minimally reduced visual acuity without nystagmus. The first pattern is true albinism; the second has been termed *albinoidism* because of its milder visual consequences. Both patterns share the clinical features of photophobia, iris transillumination, and hypopigmented fundi (Fig 13-5A). They differ according to whether or not the fovea develops normally; in true albinism, the fovea is hypoplastic, with no foveal pit or reflex and no evident luteal pigment (Fig 13-5B, C). The gold standard for diagnosis of true albinism is the finding of characteristic abnormalities of the flash and pattern visual evoked potentials (VEP): in albinism, stimulation of 1 eye results in an asymmetric occipital response, which is due to the greater number of decussating fibers in individuals with this disorder and contrasts with the symmetric VEP in persons without albinism.

OCA has 2 forms that are potentially lethal. The first, Chédiak-Higashi syndrome, is characterized by albinism, neutropenia, and an extreme susceptibility to infections, as well as other complications such as bleeding (caused by deficient platelets). The second, Hermansky-Pudlak syndrome, is characterized by a platelet defect that causes easy bruising and bleeding. In the United States, most patients with Hermansky-Pudlak syndrome are of Puerto Rican descent.

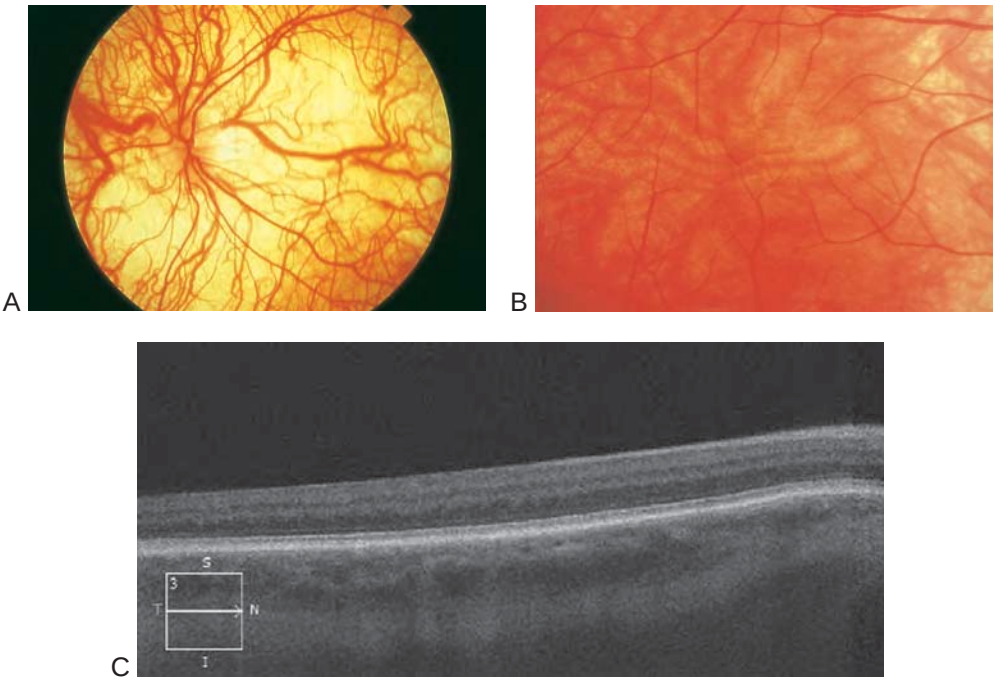

Figure 13-5 Albinism. **A,** Fundus photograph shows generalized fundus hypopigmentation. **B,** High-magnification fundus photograph shows foveal hypoplasia. No foveal reflex or luteal pigment is evident. **C,** SD-OCT image shows the lack of a foveal pit. Eccentric fixation was also present, resulting in superior decentration of the scans. *(Parts A and B courtesy of Carl D. Regillo, MD; part C courtesy of David Browning, MD.)*

King RA, Jackson IJ, Oetting WS. Human albinism and mouse models. In: Wright AF, Jay B, eds. *Molecular Genetics of Inherited Eye Disorders.* Harwood Academic; 1994:89–122.

Metabolic Diseases With Central Nervous System Abnormalities

The following subsections discuss some of the major inherited metabolic diseases known to affect the CNS and retina (see Table 13-1). See BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* for a list of the ocular findings in inborn errors of metabolism.

Neuronal ceroid lipofuscinoses

The neuronal ceroid lipofuscinoses (NCLs) are a group of autosomal recessive diseases caused by the accumulation of waxy lipopigments (eg, ceroid and lipofuscin) within the lysosomes of neurons and other cells. These disorders usually become evident in early childhood and are characterized by progressive dementia, seizures, vision loss associated with a pigmentary retinopathy in early-onset cases, and variable life expectancy. A diagnosis can be made with genetic testing, in addition to a peripheral blood smear or biopsy and electron microscopy of conjunctival or other tissues, which can reveal the characteristic curvilinear, fingerprint-like or granular inclusions. The infantile and juvenile types

of NCLs are associated with pigmentary retinopathies (see Table 13-1). Ocular findings in infantile NCL include optic atrophy; macular pigmentary changes including bull's-eye atrophic maculopathy, mottling of the fundus periphery, and retinal vascular attenuation; and reduced or absent ERG signals (Fig 13-6). The 2 adult forms of NCL do not have ocular manifestations.

Haltia M. The neuronal ceroid-lipofuscinoses: from past to present. *Biochim Biophys Acta.* 2006;1762(10):850–856.

Abetalipoproteinemia and vitamin A deficiency

Abetalipoproteinemia is an autosomal recessive disorder in which apolipoprotein B is not synthesized, which causes fat malabsorption, resulting in deficiency of fat-soluble vitamins and retinal and spinocerebellar degeneration. Supplementation with vitamins A and E is needed to prevent or ameliorate the retinal degeneration. The most common form of vitamin A deficiency retinopathy occurs in patients who have undergone gastric bypass surgery for obesity or small-bowel resection for Crohn disease. These patients have malabsorption of fat-soluble vitamins and may develop a blind loop syndrome, in which an overgrowth of bacteria consumes vitamin A. Patients experience nyctalopia, and if the condition remains untreated, they eventually demonstrate vision loss and diffuse, drusen-like spots similar to those observed in retinitis punctata albescens.

Zellweger spectrum disorders

Zellweger spectrum refers to a group of related peroxisomal disorders that are mostly autosomal recessive diseases and are caused by the dysfunction or absence of peroxisomes or peroxisomal enzymes, which leads to defective oxidation and accumulation of very-long-chain fatty acids. *Zellweger syndrome* is the most severe of the disorders in the spectrum. Severe infantile-onset retinal degeneration is associated with hypotonia, psychomotor

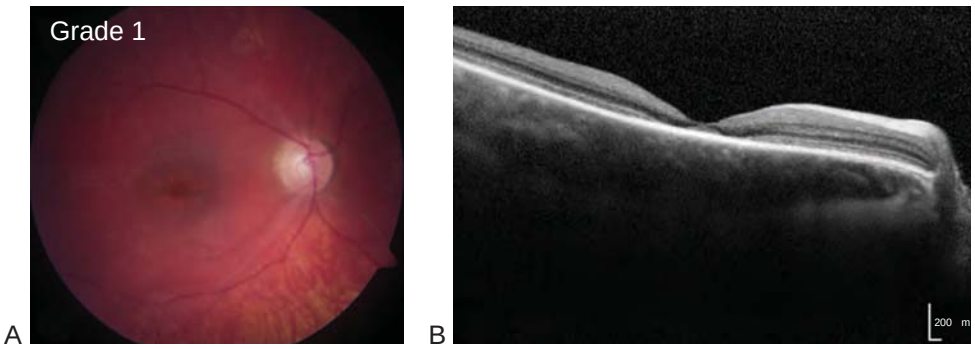

Figure 13-6 **A,** Fundus photograph from a patient with neuronal ceroid lipofuscinosis (Batten disease; *CLN3*, juvenile onset) shows bull's eye maculopathy, an early manifestation of the disease. **B,** SD-OCT shows foveal atrophy in a "flying saucer" pattern. *(Reproduced from Dulz S, Atiskova Y, Wibbeler E, et al. An ophthalmic rating scale to assess ocular involvement in juvenile CLN3 disease.* Am J Ophthalmol. *2020;220:64–71. Copyright 2020, with permission from Elsevier.)*

impairment, seizures, characteristic facies, renal cysts, and hepatic interstitial fibrosis. Death usually occurs in infancy. Patients with *neonatal adrenoleukodystrophy,* the intermediate form in the spectrum, also present in infancy but generally survive until the age of 7–10 years (Fig 13-7). Similar but less severe findings are present in *infantile Refsum disease,* which is characterized by pigmentary retinopathy with reduced or extinguished ERG signals, cerebellar ataxia, polyneuropathy, anosmia, hearing loss, and cardiomyopathy. Diagnosis is made by demonstrating elevated plasma levels of phytanic acid or reduced phytanic acid oxidase activity in cultured fibroblasts. Dietary restriction of phytanic acid precursors may slow or stabilize the neuropathy but typically not the retinal degeneration.

Mucopolysaccharidoses

The systemic *mucopolysaccharidoses (MPSs)* are caused by inherited defects in catabolic lysosomal enzymes that degrade the glycosaminoglycans dermatan sulfate, keratan sulfate, and heparan sulfate. The MPSs are transmitted as autosomal recessive traits except for type II, which is an X-linked recessive disorder (see Table 13-1).

Only those MPSs in which heparan sulfate is stored are associated with retinal dystrophy. These include severe MPS I (also known as *Hurler syndrome*) and attenuated MPS I (*Hurler-Scheie* and *Scheie syndromes*), the clinical features of which include coarse facies, cognitive disabilities (severe MPS I only), corneal clouding, and retinal degeneration. The retinal pigmentary changes may be subtle, but the ERG response is subnormal. MPS II (Hunter syndrome) also features pigmentary retinopathy but corneal clouding, if present, is only mild; patients have coarse facies and short stature and may show cognitive disabilities. In MPS type III (Sanfilippo syndrome), somatic stigmata are mild, but pigmentary retinopathy is severe.

Figure 13-7 Neonatal adrenoleukodystrophy (Zellweger spectrum disorder). Fundus photograph shows retinal arteriolar attenuation, diffuse pigmentary alterations, and mild optic atrophy. *(Courtesy of Mark W. Johnson, MD.)*

Other lysosomal metabolic disorders

Tay-Sachs disease (GM_2 gangliosidosis type I), caused by a mutation in the hexosaminidase subunit alpha gene *(HEXA),* is the most common ganglioside storage disease, with an incidence of 1 in 320,000 births in the United States. Glycolipid accumulation in the brain and retina causes cognitive disability and blindness, respectively, and death generally occurs between the ages of 2 and 5 years. Ganglion cells surrounding the fovea become filled with ganglioside, and areas with such cells appear grayish or white, in contrast with the fovea, which lacks these cells, causing a cherry-red spot (Fig 13-8).

The chronic nonneuronopathic adult form of *Gaucher disease* does not have cerebral involvement. This disease is characterized by large accumulations of glucosylceramide in the liver, spleen, lymph nodes, skin, and bone marrow. Some patients have a cherry-red spot; others show whitish superficial lesions in the midperiphery of the fundus. Spectral-domain optical coherence tomography analysis demonstrates multiple characteristic hyperreflective lesions located along the retinal surface.

The various types of *Niemann-Pick disease (NPD)* are caused by the absence of different sphingomyelinase isoenzymes and resultant accumulation of sphingomyelin in the liver, spleen, lung, brain, and other organs. In NPD type A (acute neuronopathic), a cherry-red spot is present in approximately 50% of cases. NPD type B (chronic), also known as *sea-blue histiocyte syndrome,* is the mildest, and there is no functional involvement of the CNS; these patients have a macular halo that is considered diagnostic (Fig 13-9).

Fabry disease (angiokeratoma corporis diffusum) is an X-linked condition caused by mutations in the gene encoding α-galactosidase A. Ceramide trihexoside accumulates in the smooth muscle of blood vessels in the kidneys, skin, gastrointestinal tract, CNS, heart,

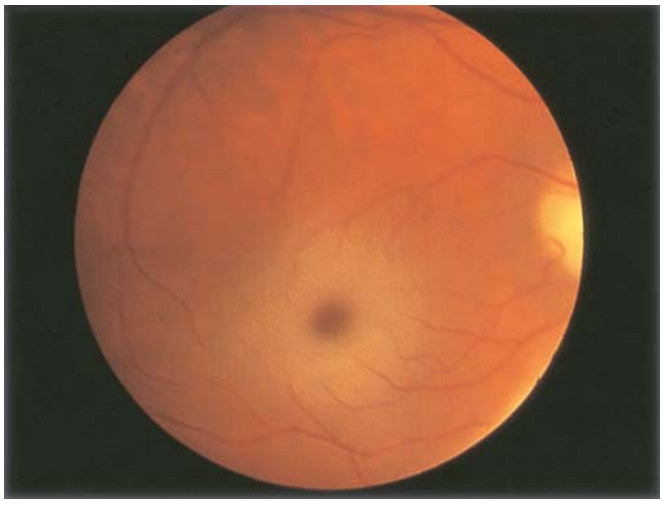

Figure 13-8 Tay-Sachs disease. Fundus photograph shows a cherry-red spot.

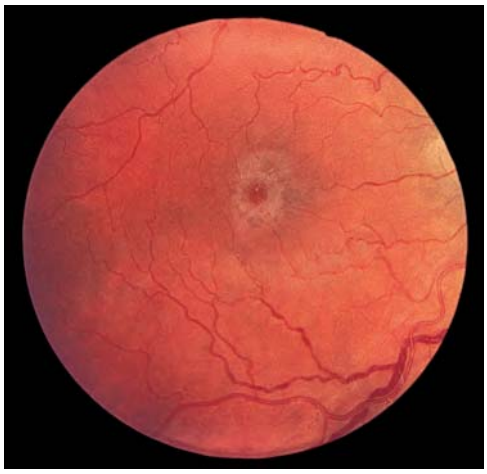

Figure 13-9 Chronic Niemann-Pick disease. Fundus photograph shows a macular halo. *(Courtesy of Mark W. Johnson, MD.)*

and reticuloendothelial system. Ocular signs include cornea verticillata (whorls), tortuous conjunctival vessels, tortuous and dilated retinal vessels, and lens changes. Tortuosity of conjunctival and retinal vessels is also characteristic of *fucosidosis,* a rare lysosomal storage disorder caused by buildup of complex sugars due to reduced or absent activity of the α-l-fucosidase enzyme. CNS abnormalities may include hemiparesis, vertigo, diplopia, dysarthria, nystagmus, and ataxia.

Gregory-Evans K, Pennesi ME, Weleber RG. Retinitis pigmentosa and allied disorders. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Ryan's Retina.* 6th ed. Elsevier/Saunders; 2018:861–935.

Amino Acid Disorders

In *cystinosis,* intralysosomal cystine accumulates because of a deficiency in the carrier protein cystinosin, which typically transports cystine out of lysosomes. Three types are recognized, all autosomal recessive: nephropathic, late-onset (or intermediate), and benign. Cystine crystals accumulate in the cornea and conjunctiva in all 3 types, but retinopathy develops only in patients with the nephropathic type; these patients present early (8 to 15 months of age) with progressive renal failure, growth delays, renal rickets, and hypothyroidism. The retinopathy is characterized by areas of patchy depigmentation of the RPE alternating with irregularly distributed pigment clumps and associated fine retinal crystals, but no significant visual disturbance. Treatment with cysteamine may be beneficial. *Bietti crystalline dystrophy* may also cause crystalline keratopathy and retinopathy associated with patchy loss of the choriocapillaris and RPE and with associated photoreceptor loss.

Oishi A, Oishi M, Miyata M, et al. Multimodal imaging for differential diagnosis of Bietti crystalline dystrophy. *Ophthalmol Retina*. 2018;2(10):1071–1077.

Mitochondrial Disorders

Chronic progressive external ophthalmoplegia (CPEO) belongs to a group of diseases collectively termed *mitochondrial myopathies* (Fig 13-10), in which mitochondria are abnormally shaped and increased in number. Muscle biopsy specimens may reveal ragged red fibers. In addition to CPEO, the syndrome is associated with atypical RP and various systemic abnormalities. When associated with cardiomyopathy and cardiac conduction defects (heart block), the disorder is known as *Kearns-Sayre syndrome;* onset is usually before the age of 10 years. The severity of the pigmentary retinopathy is highly variable. Many patients retain good visual function and a normal ERG signal. Other mitochondrial myopathies with pigmentary retinopathy include *MIDD* (*m*aternally *i*nherited *d*iabetes and *d*eafness; Fig 13-11), *MELAS* (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke), and *NARP* (*n*eurogenic muscle weakness, *a*taxia, and *r*etinitis *p*igmentosa) syndromes.

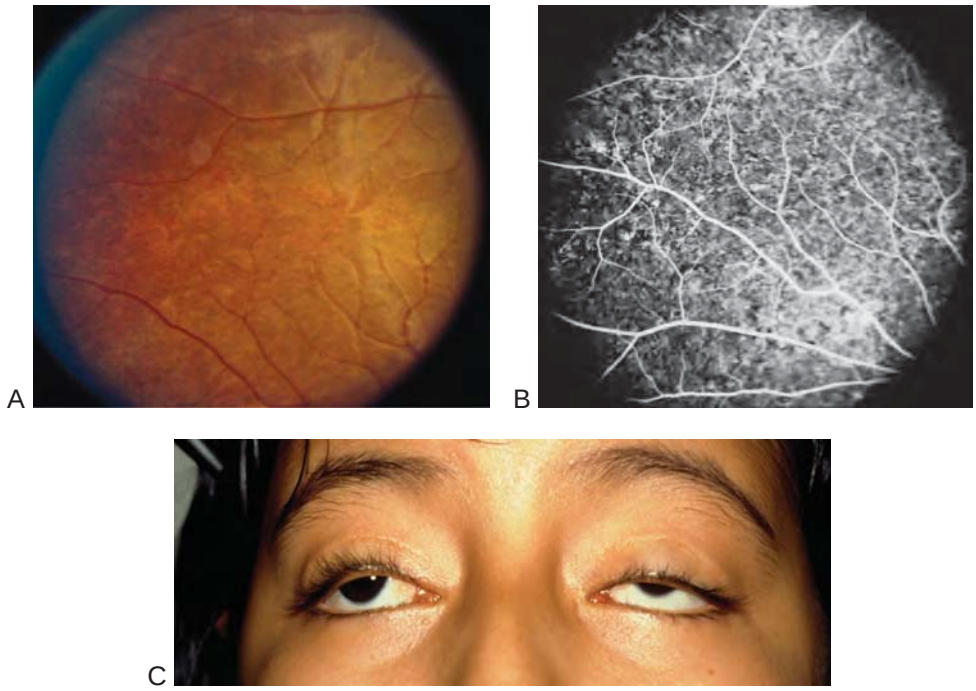

Figure 13-10 Chronic progressive external ophthalmoplegia (CPEO) and retinopathy associated with mitochondrial myopathy. **A,** Fundus photograph shows diffuse RPE mottling. **B,** Corresponding mottled hyper- and hypofluorescence in the arteriovenous phase of fluorescein angiography. **C,** Photograph shows bilateral ptotic eyelids and eyes in a misaligned exotropic position from poor extraocular muscle function, features consistent with CPEO caused by a mitochondrial mutation. *(Courtesy of David Sarraf, MD.)*

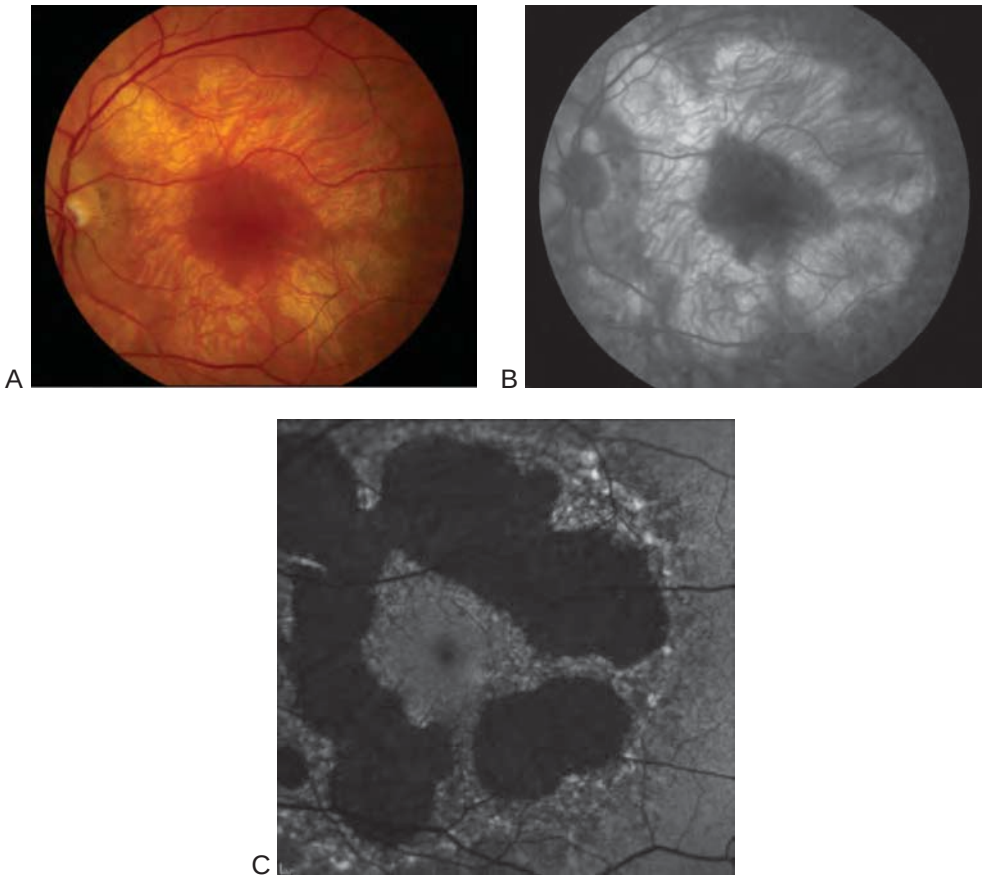

Figure 13-11 Maternally inherited diabetes and deafness (MIDD) caused by a mitochondrial mutation. Color fundus photograph **(A),** late fluorescein angiography frame **(B),** and fundus autofluorescence image **(C)** show RPE atrophy in a perifoveal distribution. These findings were all symmetrically present in the fellow eye. *(Courtesy of Herb Cantrill, MD.)*