Pediatric genetic macular and choroidal diseases

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Abstract. Genetic diseases of the macula and choroid have various inheritance patterns and varying degrees of impact on vision. Herein, we review the literature including most recent advances in the understanding of the genetics of these diseases. Although many of these disorders have limited treatment options, knowledge of inheritance patterns can aid in early detection and with close monitoring can help the ophthalmologist preserve as much vision as possible (for example with early treatment of choroidal neovascularization).

Keywords: Genetic macular disorders, genetic choroidal disorders, macular dystrophy

1. Introduction

The macula is the area of the retina most critical for central visual acuity. It is contained between the optic disc and the emanating temporal vasculature, measures approximately 5.5 mm in diameter, and is defined histologically by the presence of two or more ganglion cell layers. Diseases of the macula are of critical importance given their impact on vision and thus quality of life. Several inherited diseases of the macula are well recognized. These diseases vary greatly in their prevalence, age of onset, symptoms, and severity, and in the degree to which prevention or treatment is available. In this review, we provide a summary of these features.

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2. Stargardt's disease

Stargardt's disease, first described in 1909 by Karl Stargardt, is the most common juvenile macular dystrophy, with an estimated prevalence of between one in 8–10,000 [1, 2]. It is a heterogeneous, autosomal recessive macular dystrophy caused, in the vast majority of cases, by various mutations in the *ABCA4* gene [3]. *ABCA4* encodes a photoreceptor-specific adenosine triphosphate (ATP)-binding cassette (ABC) transporter protein [4] that functions to transport N-retinylidene-phosphatidyle (NRPE), a byproduct of the photocoagulation cascade, out of photoreceptors. If not cleared, NRPE is converted to A2E, a bis-retinoid and lipofuscin fluorophore. A2E is toxic to the photoreceptors, and its accumulation results in photoreceptor degeneration and dysfunction [5], manifesting clinically as decreased vision. The heterogeneity of Stargardt's disease is thought to be a consequence of both the nature and severity of the particular *ABCA4* gene mutation in addition to as
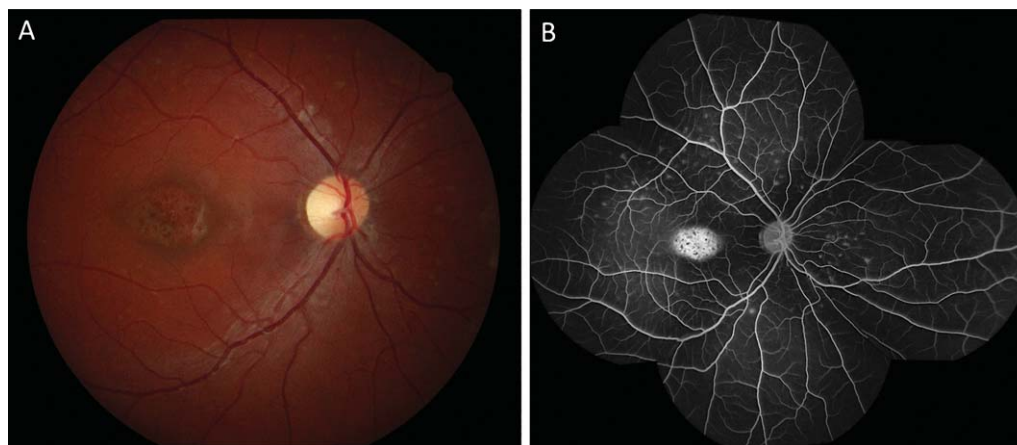
Fig. 1. (A) Fundus photograph of the right eye of an individual with Stargardt's disease. (B) Corresponding fluorescein angiogram. The fundus shows profound chorioretinal atrophy centrally, with pisciform flecks throughout the macula. A dark choroid is seen on the angiogram (Images courtesy of Dr. Thomas C. Lee, Children's Hospital Los Angeles).

yet uncharacterized features of the photoreceptors and retinal pigment epithelium (RPE) of the affected individual [6, 7]. Interestingly, mutations in the same gene also result in other disorders of the macula: cone dystrophy (discussed later in this review), cone-rod dystrophy, and retinitis pigmentosa (beyond the scope of this review) [8–11].

Stargardt's disease is typically bilateral, and most commonly presents with decreased central vision, usually during childhood or adolescence. Visual field testing may show a central scotoma; peripheral vision typically remains intact. The fundi of affected invdividuals are notable for the presence of elongated, yellow-white lesions at the level of the RPE known as flecks, or pisciform flecks, on account of their fish-like appearance [12–15]. The disease classically progresses through four stages of fleck accumulation and then resorption resulting, ultimately, in chorioretinal atrophy, as described by Fishman [16] in 1976 (Fig. 1A). A significant number of individuals; however, do not show progression from their initial presentation [17]. A fairly specific clinical finding in Stargardt's disease is a "dark choroid" on fluorescein angiography (FA), or the absence of dye filling the choroidal circulation (normally the choroid shows a generalized faint hyperfluorescence, or "blush") (Fig. 1B). This is thought to be due to the presence of A2E, a lipofuscin fluorophore, in the RPE, which absorbs short-wavelength visible light and thus prevents transmission of choroidal illumination [17–19]. A recent study shows that as many as 94% of patients with *ABCA4*-associated Stargardt's disease have this dark choroid on FA [20].

It is important to note that Stargardt-like dominant macular dystrophy (SLDMD), so-named because of its clinical similarity to Stargardt's disease, is a different entity. As the name suggests, SLDMD is inherited with an autosomal dominant pattern. In the majority of cases, SLDMD can be attributed to mutations in the *ELOVL4* gene, which encodes an endoplasmic reticulum enzyme involved in long chain fatty acid synthesis [21–24]. When mutated, mistrafficking of this enzyme can result in increased lipofuscin formation and photoreceptor cell death [25, 26]. Clinically, these patients possess a phenotype similar to those with Stargardt's disease; they display progressive central vision loss, and their fundi are characterized by pisciform flecks, macular atrophy, and peripapillary sparing. Unlike those with Stargardt's disease, patients with SLDMD do not show a dark choroid pattern on FA [21].

At this time, there is no treatment or prevention for Stargardt's disease. Attempts at gene therapy are ongoing, and may prove promising in the future [27–29]. Affected individuals, therefore, should be provided with support and genetic counseling, and with instruction in behavior modifications that may be undertaken to maximize visual potential. Patients with Stargardt's disease should be counseled to wear dark glasses when exposed to bright light, as the deleterious accumulation of A2E is dependent on the light-mediated activation of the photocoagulation cascade. Further, they should avoid high-dose vitamin A, which, as a primary component of A2E, can contribute to its accumulation in the RPE. Finally, they should be counseled against smoking, which
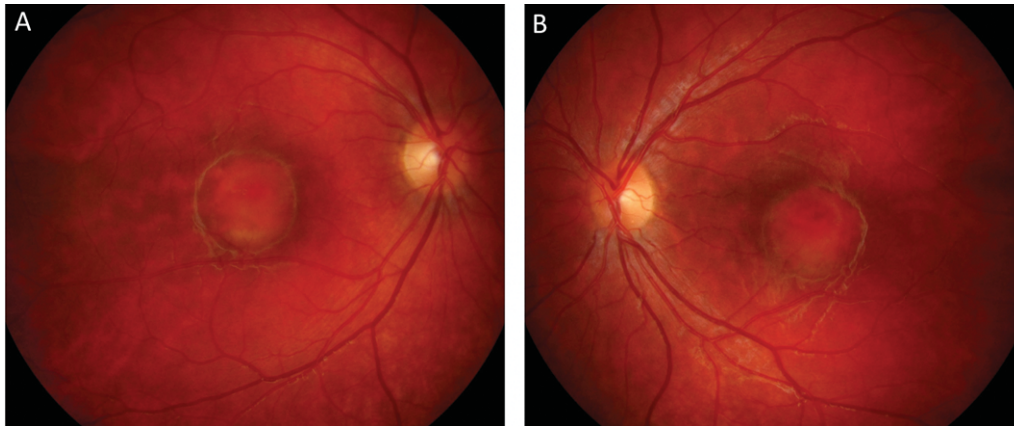
Fig. 2. Fundus photographs of the right (A) and left (B) eyes of an individual with Best disease. Both fundi show the classic "vitelliform" or "egg yolk" lesion characteristic of stage 2 disease. Note the symmetric appearance of the two eyes, which is a common, though not universal finding (Images courtesy of Dr. Thomas C. Lee, Children's Hospital Los Angeles).

anecdotally, has been reported to result in decreased vision [15].

3. Best disease

Best disease, or vitelliform macular dystrophy, is an autosomal dominant condition with an incidence of approximately one in 10,000 that results from mutation of the *BEST1/VMD2* gene, which encodes bestrophin-1, a retinal pigment endothelium (RPE) protein [30–32]. Best disease classically presents bilaterally in childhood or adolescence, with initial preservation of normal vision. The disease then progresses, with gradual loss of central vision and metamorphopsia (a visual distortion wherein straight lines appear wavy). At age 40, the majority of patients (76%) with Best disease maintain visual acuity of 20/40 or better in one eye, but by age 50, this number decreases to 20%. Visual acuity in the weaker eye diminishes to 20/100 or worse by age 30 in 74% of patients [33]. Approximately 2–9% of patients will experience choroidal neovascular membrane (CNVM) formation in one eye, which is typically accompanied by dramatic vision loss (e.g. 20/200) [34–38].

Histopathologically, patients with Best disease show increased RPE lipofuscin, accumulation of fluid and/or debris in the subretinal space, and resultant photoreceptor degeneration [1, 39, 40]. These changes stem from disrupted function of bestrophin, which normally functions as chloride channel in the RPE. Bestrophin-1 is expressed in the RPE throughout the retina, but the lesions of Best disease typically localize to the macula (though they can be found elsewhere in some cases). This spatial selectivity may be due to quantitative differences in bestrophin-1 expression throughout the retina or to the expression patterns of other RPE or photoreceptor proteins, which interact with bestrophin-1, or which influence photoreceptor stability [15, 41, 42].

Clinically, Best disease is often described in five stages, though it is important to note that progression does not always occur in a stereotypical fashion across all individuals. In stage 0, the fundus is completely normal in appearance, and in stage 1, only minor RPE changes are seen. The classic early lesion in Best disease is the "vitelliform" or "egg-yolk" lesion, which is a round or ovoid, yellow-orange, slightly-raised lesion centered on the fovea (Fig. 2) [36, 43]. This characterizes Stage 2 disease, and despite its dramatic appearance, central vision at this stage is typically quite good (20/20–20/60) [33]. Stage 2a occurs as lipofuscin begins to resorb, and the lesion assumes a heterogeneous "scrambled-egg" appearance. The yellow material comprising the vitelliform lesion may settle inferiorly, resulting in a yellow-colored fluid level within the macula, the "pseudohypopyon" of stage 3 disease. Finally, stage 4 disease is characterized by RPE atrophy (4a), subretinal fibrosis (4b), and CNVM formation (4c) [36, 43].

Historically, one very specific marker for Best disease has been a loss of light response on electrooculography (EOG). The EOG measures the

Fig. 3. Fundus photographs demonstrating lesions of various grades in North Carolina macular dystrophy. In grade I disease (A), the macula shows fine, confluent drusen. In grade II (B), a subretinal scar is present, indicating a cite of previous choroidal neovascularization. In grade III (C), a macular caldera (a well-circumscribed excavation) is seen [194].

electric potential difference between the skin and the eye elicited when moving the eyes in the dark and when moving the eyes in the light. In normal individuals, the ratio of the light potential to the dark potential (the Arden ratio) is greater than 1.85 [44]. In individuals with Best disease, it is less than 1.45, and may be as low as 1.0. This is true whether or not macular lesions are present [45]. Of note, carriers of the disease will have abnormal EOG [45], but if they maintain normal or minimally abnormal appearance of the fundus in early adult life, they will normally also maintain good vision [46]. More recently, however, a number of studies have identified families with Best disease (demonstrated by fundus appearance and *Best1* mutation) in which patients and/or carriers maintain normal EOG [47–53].

While there is no prophylaxis or treatment, per se, for Best disease, these patients should be monitored by an ophthalmologist. Yearly examinations are critical for helping to prevent the development of amblyopia, for identifying and treating commonly co-occurring conditions such as hyperopia and angle closure glaucoma, and for identifying CNVM formation and treating it, most commonly with intravitreal anti-VEGF (vascular endothelial growth factor) injections [54–60]. Furthermore, patients should be educated on the warning signs of CNVM, decreased vision or increased metamorphopsia, which should provoke a more urgent examination.

As with all individuals with one poorly seeing eye and one well-functioning eye, protective polycarbonate spectacles (with or without a prescription) are recommended at all times. Additionally, because of increased propensity for subretinal hemorrhage with relatively minor trauma, it is recommended that these

individuals do not engage in sports involving frequent blows to the head. Finally, these patients should be counseled against smoking to reduce the risk of retinal neovascularization [61].

To date, there are no known systemic associations with Best disease.

4. North Carolina macular dystrophy (NCMD)

NCMD is a completely penetrant, variably expressed, autosomal dominant macular dystrophy first described in 1971 based on a large family in North Carolina [62]. Since that time, many additional families with the condition have been identified internationally [63–67], though the disorder is still rare enough that the true prevalence is unknown. Genetic linkage analyses have localized the causative genetic locus, *MCDR1* (macular dystrophy retinal 1) to chromosome 6q16, but the causative gene has not been identified [68–70].

NCMD presents during infancy and, despite early reports to the contrary, does not appear to be progressive [71]. The dystrophy is typically bilateral and symmetric, and it is classified into grades based on the appearance of the macula (Fig. 3). Grade 1 is characterized by scattered drusen-like yellow or white lesions at the level of the RPE, grade 2 is characterized by confluent drusen at the level of the RPE, which may be accompanied by RPE atrophy, pigmentary changes, or a disciform scar, and grade 3 consists of a large (1-2 disc diameter), well-circumscribed area of macular excavation, termed a caldera, which is classically bordered by a thick, white rim of scar tissue. Visual acuity varies with the grade of dis-

Fig. 4. Fundus photographs of the right (A) and left (B) eyes of an individual with Sorsby fundus dystrophy. In the left eye, which had normal vision, yellow drusen can be seen in the posterior pole. The right eye shows hemorrhagic choroidal neovascularization, further complicated by a retinal detachment [99].

ease; grade 1 is typically associated with acuity of 20/20–20/30, grade 2 with acuity of 20/25–20/60, and grade 3 with acuity of 20/40–20/200. Just as the grade of the lesions tends to be stable, so too does visual acuity [71–74]. The preservation of relatively good visual acuity in the face of large macular lesions is thought to be due to the plasticity of the visual system at the young age at which they emerge; patients learn to fixate on the uncompromised retina at the edge of the lesions, and the visual pathways mature accordingly [15].

A notable exception to the stability of visual acuity in NCMD is in eyes in which a CNVM develops. CNVMs form when abnormal choroidal vessels grow into the outer retina, resulting in mechanical disruption of these retinal layers, and further damage via fibrosis or hemorrhage. This devastating phenomenon has been described in grade 2 and 3 lesions in several studies, and in a patient as young as 3 yr of age [65, 70, 73, 75–77]. Thus, patients and their parents should be counseled to seek care immediately in the case of sudden vision loss or new onset of metamorphopsia (straight lines appearing wavy). Treatment for subfoveal CNVMs has not been well studied in these patients; intravitreal anti-VEGF injections or photodynamic therapy may be considered.

Although the original report of NCMD described an associated aminoaciduria [62], this has not been found to be a consistent finding and no additional systemic features have been reported to be associated with the disease.

5. Sorsby fundus dystrophy (SFD)

SFD is an autosomal dominant macular condition that results commonly in severe, bilateral vision loss during middle age as a consequence of choroidal neovascularization (CNV), RPE atrophy (Fig. 4A), or both [78–80]. As a result, vision loss is often sudden and profound. Younger individuals with SFD are typically asymptomatic and may escape medical attention unless they have a known family history. Nyctalopia, or poor night vision, is commonly the first symptom, but often does not manifest until middle age [78, 79, 81].

On examination, SFD is characterized by macular deposition of drusen-like material (Fig. 4B), usually in the third decade of life [79, 82] often extending further into the periphery, to the equator [79, 81], a feature that distinguishes it from the clinically related age-related macular degeneration [15]. Histopathologically, SFD is characterized by marked thickening of Bruch's membrane [83, 84], which may be clinically evident as a sheet-like yellow-gray deposition on ophthalmoscopy (Fig. 4A) [15]. Despite the presence of drusen, visual acuity typically remains fairly good initially [79]. Drastic deterioration in visual acuity (to 20/200 or worse) results from CNV or central macula RPE atrophy. In a study of forty-two individuals with SFD, Sivaprasad et al. [79] found that 62% of patients developed CNV (81% bilateral) and 19% of patients developed central macular atrophy (100% bilateral), typically in the 5th or 6th decade of life.

SFD is caused by mutations in the gene encoding tissue inhibitor of metalloproteinase-3 (TIMP3) [85], a protein that has roles in maintaining extracellular membrane homeostasis [86–88] and in inhibiting angiogenesis [89, 90]. In the eye, TIMP3 is expressed in Bruch's membrane, the tissue that separates the retina from the underlying choroid [85, 89, 91–93] and in SFD, these expression levels are found to be elevated [83, 84]. Additionally, TIMP3 is expressed in drusen in SFD and other related diseases [93–95]. At least 12 causative mutations have been described, most of which involve alterations in cysteine residues, resulting in altered disulfide bonding and disrupted tertiary structure [79, 80, 85, 91, 96–103]. It is thought that the accumulation of mutant TIMP3 in Bruch's membrane results in altered turnover and thickening of the matrix, causing deranged flow of growth factors and nutrients [15, 80, 97]. The exact mechanism by which this process produces the clinical features of SFD is still being elucidated. Additionally, it is logical to hypothesize that the neovascularization in SFD may result, at least in part, from defective inhibition of angiogenesis by TIMP3, but again, the pathophysiology is still being investigated.

Treatment of SFD is aimed at control of CNV, and is challenging due to its aggressive and recalcitrant nature. Many therapies used to treat CNV with other etiologies have been attempted, but at this time, there is no definitive treatment. In two small studies, argon laser photocoagulation proved to be ineffective [79, 104]. There have been case reports of successful treatment with photodynamic therapy [105, 106], though in a small case series, no clinical improvement was seen [79]. Two recent reports have shown that intravitreal injection of anti-VEGF may yield improvement in visual acuity and regression of CNV [107, 108]. From a symptom standpoint, a small study investigating the effect of vitamin A on nyctalopia in SFD found that high dose supplementation increased rod sensitivity and resulted in decreased subjective night blindness, suggesting that this genetic condition may have environmental modulating effects, and providing an important marker for treating physicians to be aware of [101].

6. Central areolar choroidal dystrophy (CACD)

CACD is a rare, progressive, hereditary, bilateral disease of the macula that typically presents with a central scotoma in middle age, and progresses to severe visual impairment (e.g. counting fingers acuity) by the seventh decade. It is characterized by the presence of a well-circumscribed area of RPE and choroidal atrophy in the macula, which eventually becomes so pronounced that the sclera is visible. Histopathological findings are striking, with absence or near absence of the photoreceptors, RPE, and choriocapillaris in the area of the lesion [109]. CACD was first described by Nettleship in 1884 in the United Kingdom under the name, "central senile areolar choridal dystrophy," and since that time, has been described throughout the globe, and has been demonstrated to be inherited primarily in an autosomal dominant fashion, though in some cases autosomal recessive inheritance has been seen [110–119].

CACD progresses through four stages, best demonstrated by FA (Fig. 5) [120]. In stage I disease, visual acuity is normal. FA demonstrates subtle parafoveal pigmentary abnormalities, which may or may not be evident by ophthalmoscopy as small hypofluorescent areas. In stage II, visual acuity is normal or slightly reduced (better than 20/40). Hypofluorescence can be seen by ophthalmoscopy, and FA demonstrates areas of hyperfluorescence, often encircling the fovea. Stage III is characterized by at least one area of choriocapillaris and RPE atrophy on FA, which is outside of the fovea. Visual acuity is typically, though not always, diminished (range 20/20–20/200). By stage IV, visual acuity is poor; at best, 20/80 is seen, but counting fingers is more typical. Foveal atrophy of the choriocapillaris and RPE is evident on both FA and fundoscopy. Although visual disturbances typically begin between ages 25 and 55, patients as young as 11 yr of age have reported symptoms [118, 120]. Many patients also show some degree of impairment in color vision and multifocal electroretinogram responses [120, 121].

Mutations in multiple genes have been associated with CACD, but the most common is peripherin/*PRPH2/RDS*, which encodes a photoreceptor surface glycoprotein [122, 123]. At least six different mutations of peripherin/*PRPH2/RDS* have been demonstrated to be associated with CACD [117, 124–131]. Interestingly, peripherin/*PRPH2/RDS* mutations underlie a host of macular dystrophies including pattern dystrophies, adult vitelliform macular dystrophy, cone and cone-rod dystrophies, and some forms of retinitis pigmentosa (reviewed in [131]), speaking to the prominent role of this glycoprotein in photoreceptor structure and function. Recently, a novel mutation in *GUCY2D*, which encodes a retina-specific
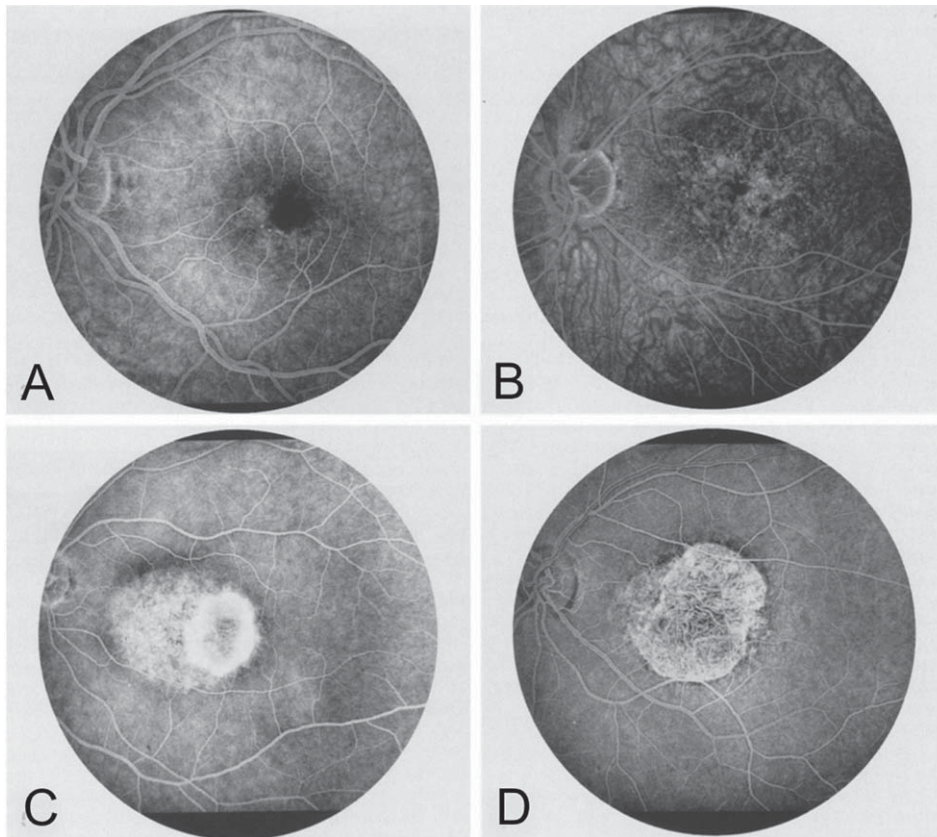
Fig. 5. Fluorescein angiograms demonstrating the stages of central areolar choroidal dystrophy. In stage I (A), small hypofluorescent and hyperfluorescent spots are observed. In stage II (B), hyperfluorescent areas encircle the fovea. In stage III (C), there is retinal pigment epithelium and choriocapillaris atrophy, both outside of the fovea. In stage IV (D), the atrophy seen in stage III extends to the fovea [120].

guanylate cyclase, was found to be associated with CACD [132]. Still other, as yet unidentified genes are thought to contribute to the genetic heterogeneity underlying this disorder, as a study of a large Chinese family with autosomal dominant CACD failed to show linkage of any of the known candidate genes to the disease [118].

Systemic associations with CACD remain limited to case reports. Mansour reported the presence of CACD in three brothers with pseudoachondroplastic spondyloepiphyseal dysplasia, another autosomal dominant condition, and suggested a genetic association [133]. Hoyng et al. [134] described two unrelated individuals with CACD and sensiorneural hearing loss, whose ocular and auditory symptoms had similar timing of onset and posited that the etiology of the symptoms may be related.

Currently, no treatment exists for CACD. Although presentation in childhood is rare, families with a family history should be counseled, as awareness of the likelihood of vision loss may affect career and lifestyle choices.

7. Choroideremia

Choroideremia is a rare, progressive X-linked recessive disorder of the retina, retinal RPE, and choroid, first described in 1872 and with a prevalence of about one in 50,000 [135]. It is characterized by nyctalopia and progressive visual field loss beginning in the first or second decade of life, but with relatively well-preserved central visual acuity until late in the disease course [136, 137].

Choroideremia is caused by mutation or deletion of the *CHM* gene on chromosome Xq21.2, which encodes Rab escort protein-1 (REP1). REP1 is a part of a complex that is important for prenylation (lipid modification) of Rab GTPases, which serve
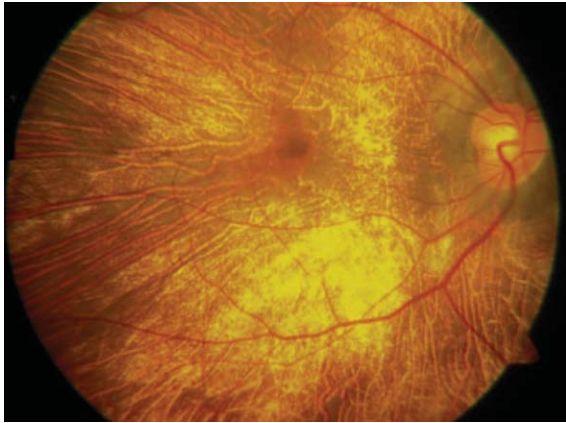
Fig. 6. Fundus photograph of the right eye of a patient with choroideremia reveals diffuse atrophy of the retinal pigment epithelium and choroid, but with sparing of the central macula [195].

as regulators of intracellular vesicular transport [138–140]. Failure of Rab prenylation results in damage to and degeneration of both photoreceptors and RPE cells, and interestingly, damage to the RPE cells alone results in accelerated photoreceptor degeneration, thus accentuating the effect of the mutation [141–143].

As the name suggests, choroideremia is characterized by atrophy of the RPE and choroid, initially in the periphery, and then progressively moving centrally with time and involving the macula (Fig. 6). The atrophy is so profound that the bare sclera may be seen on fundoscopic examination. Prior to the onset of atrophy, RPE changes may be noted in the periphery. As mentioned above, patients with choroideremia classically experience nyctalopia and early visual field loss in the first or second decade of life, but with relatively maintained central visual acuity over a long period. Two large cross-sectional analyses examining patients ages 3 mo - 69 yr found visual acuity in the better seeing eye to be better than 20/50 in 79–90% of the examined population, with many patients demonstrating 20/20 vision or better. Only 6–7% of patients had vision 20/200 or worse, and of these, the majority were in the seventh decade of life [137, 144]. Female carriers of the disease are typically, but not always, asymptomatic, but usually possess characteristic fundus findings, albeit to a lesser degree [145, 146]. That said, in one study of 18 choroidemia patients and eight carrier females, the individual with the most severely compromised vision was a female carrier whose retinal findings were similarly profound [147].

While there is currently no treatment or cure for choroideremia, initial gene therapy studies are underway with promising results. One group used adeno-assoicated virus vectors to deliver CHM cDNA to cell lines from patients with choroideremia, and demonstrated that this treatment resulted in restoration of REP1 activity and normal downstream protein trafficking [148]. Furthermore, another group injected a similar construct subfoveally in six patients with choroideremia and found improvements in both visual acuity and light sensitivity [149]. It was recently reported that a large percentage of patients with choroideremia exhibit cystic macular edema, [150] and as such studies are ongoing to determine treatment options for this complication. In a small study, topical dorzolamide was found to be effective [151].

Although REP1 is expressed ubiquitously, other tissues are not affected by CHM mutation or deletion. This is thought to be due to the functional redundancy of REP2, a related protein that is also expressed ubiquitously and that can compensate for lack of REP1 in other tissues, but not in the eye, where REP1 shows particularly high levels of expression [152, 153]. As a result, there are no known systemic associations with choroideremia.

8. Gyrate atrophy

Gyrate atrophy is a rare, progressive, autosomal recessive disease of the choroid and retina, so-named because of the characteristic sharply demarcated, round areas of chorioretinal atrophy that begin in the peripheral retina, and spread centrally (posteriorly) with time (Fig. 7) [154, 155]. It has a prevalence of about one in 50,000 [155], and is caused by mutations in the gene encoding ornithine-delta-aminotransferase (OAT), an enzyme which catalyzes the conversion of L-ornithine, a byproduct of dietary arginine) to proline and glutamic acid, using vitamin B6 as a cofactor. Gene mutation results in accumulation of ornithine (hyperornithemia) and consequent damage to the retina and choroid by unknown mechanism [156–160]

Clinically, gyrate atrophy typically presents with progressive myopia or nyctalopia in the first three decades of life [154, 155, 161, 162]. Overall, visual acuity declines with age, though in cross sectional analyses, there is great variability in acuity across ages [155, 161]. Peltola et al. [161] found average visual acuity in 33 patients to be 20/50, with an average of
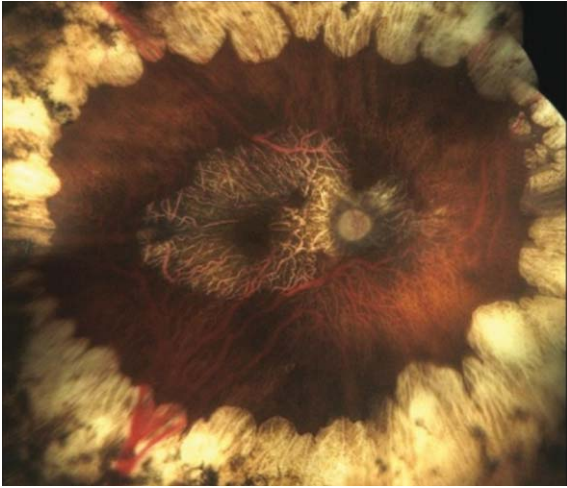
Fig. 7. Fundus photograph of the right eye of a patient with gyrate atrophy showing the characteristic scalloped pattern of chorioretinal atrophy peripherally in addition to a central area of atrophy [196].

about 20/45 for those less than 30 yr of age and about 20/70 for those greater than 30 yr of age. Ten percent of eyes had acuity of worse than 20/400 (count fingers, hand motions, or light perception). Early cataract formation is a near-universal feature of gyrate atrophy, usually of the posterior subcapsular variety, and extraction is commonly indicated [155, 161, 163]. Visual field defects and deficiency in dark adaptation mirror each other and worsen with age, though interestingly the degree of impairment often exceeds that predicted by the extent of retinal damage [155, 161]. Multiple case reports have noted macular edema in this disease, and one small study found it to be a uniform finding in seven patients [162, 164–166]. Peltola et al. [161] reported optic disc atrophy in 70% of patients.

Several studies have investigated the effects of dietary interventions in gyrate atrophy, attempting to decrease plasma ornithine levels, either by restricting dietary arginine or by supplementing vitamin B6. Successful reduction of plasma ornithine levels was typically seen with restriction of dietary arginine, while vitamin B6 supplementation seems to be effective in only a subset of patients. Using fundoscopic findings as well as visual metrics as outcome measures, restoration of normal or near-normal levels of plasma ornithine has yielded encouraging results in some studies [167–170], but has proven ineffective in others [171, 172]. Excitingly, a recent study found that amino acid profiling; specifically assessment of the plasma proline/citrulline ratio, in neonatal dried blood spots

(used for routine newborn screening) may be effective in identifying OAT deficiency and thus diagnosing gyrate atrophy long before the onset of symptoms, thus augmenting our ability to manage these patients from an earlier age [173].

9. Cone dystrophy

The photoreceptor layer of the retina, which is responsible for converting light into electrical signals, consists of two types of neurons, rods and cones. The more numerous rods play a more prominent role in peripheral vision and vision in dim conditions, while the cones, which are concentrated in the fovea, play a more prominent role in central vision and vision in bright conditions, and also in color vision. There are multiple dystrophies that affect rod and cone function, named to reflect the cell type(s) affected: rod, rod-cone, cone-rod, and cone. In this chapter, we will focus on the cone dystrophies. It is important to note that here, dystrophy refers to a progressive condition; there exist additionally congenital cone disorders, which manifest in infancy. These are beyond the scope of this chapter.

Cone dystrophies are rare, with an estimated prevalence of 1:30,000–1:40,000 [174]. Inheritance can be autosomal dominant, autosomal recessive, or X-linked, with autosomal recessive being the most common [175, 176]. Mutations in at least ten different genes have been implicated in the disorder [177–186]. Most patients with cone dystrophy present in the first or second decade of life, most commonly with decreased visual acuity [187]. Photophobia and hemeralopia (reduced vision in bright light) are common [187–189], and at presentation, reduced color vision and a central scotoma (either relative or absolute) are near-universal findings [175, 187, 188]. On ophthalmoscopy, fundus appearance shows great variability. Pigmentary changes or a bulls-eye maculopathy are often observed, but a significant number of patients also show a normal fundus. Interestingly, the percentage of patients with each of these fundus characterizations may not change from the time of diagnosis to 10 yr subsequent [175].

Diagnostically, electroretinogram testing shows diminished cone responses, but normal rod responses [188]. Many patients with isolated cone dystrophy ultimately develop rod dysfunction as well [187], suggesting that cone dystrophy and cone-rod dystrophy may represent a spectrum of disease. Recent studies suggest that optical coherence tomography and

wide-field fundus autofluorescence may be useful adjuncts in diagnosing and characterizing cone dystrophy. Specifically, optical coherence tomography shows thinning and structural changes that correlate with visual acuity in patients with cone dystrophy [190], and abnormalities in fundus autofluorescence reflect the extent of macular dysfunction as evidenced by scotoma size in this population [191].

At this time, there is no cure for cone dystrophy, but gene therapy approaches are being pursued for related disorders such as achromatopsia and cone-rod dystrophy, and may ultimately be transferrable (reviewed elsewhere [192]). Patients should be managed symptomatically with spectacle or contact lens correction, and provided with low vision aids. Gene testing may be helpful in determining prognosis and providing genetic counseling [193]. Photophobia, if severe, may be treated with miotics or red contact lenses, which may also provide improvement in visual acuity [194].

10. Summary

Inherited diseases of the macula are rare, but of critical importance given their profound impact on vision. These diseases vary greatly in their prevalence, age of onset, signs and symptoms, and severity. Our understanding of the genetic bases for these diseases is, in many cases, well established, and in other cases growing rapidly. Gene therapy is an active area of investigation for many of these diseases. Currently, there are relatively few therapies available to treat or prevent these diseases. Management is aimed, instead, at symptom management and at the recognition and treatment of associated sequelae (e.g. choroidal neovascularization, cataract).

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