13 Other Macular Dystrophies 1

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Abstract

Various rare macular dystrophies have been reported with various prognoses, some with known causative genes with mutation. Diagnosis can be made clinically with typical cases, but many require genetic testing for confirmative diagnosis.

Keywords

Occult macular dystrophy · Butterfly-shaped pigment dystrophy · Pattern dystrophy · Sorsby fundus dystrophy · Bietti's crystalline retinopathy · Autosomal dominant radial drusen · Doyne honeycomb retinal dystrophy · North Carolina macular dystrophy · Dominant cystoid macular dystrophy

13.1 Occult Macular Dystrophy

In 1989, Miyake et al first reported three patients from a family that a hereditary macular dystrophy with no visible fundus abnormality [1].

Occult macular dystrophy shows bilateral progressive decrease in vision of 20/25–20/200 [2], with severe color vision impairment in most cases [3]. Onset of symptom varies, but disease severity seems to be worse with earlier onset of symptoms [4].

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Typically, fundus appearance and fluorescein angiography show no abnormalities [5], but mild hyper-autofluorescence can be seen at the macula, which can aid in the diagnosis [6]. Cone function is decreased on electroretinography (ERG), and rod function is preserved especially in young age [7]. Macular waves are decreased or nearly absent on multifocal ERG [8]. Photoreceptor layer and outer nuclear layer defects can be found on optical coherence tomography [9–11]. Abnormal findings of multifocal ERG and optical coherence tomography were found to have significant correlation [12].

Most cases show autosomal dominant or sporadic inheritance patterns, and RP1L1 gene at 8p23 has been identified to be related with occult macular dystrophy [13]. Missense mutations in this gene are considered as the cause, but the exact pathophysiologic mechanism remains uncertain [14].

13.2 Butterfly-Shaped Pigment Dystrophy (Pattern Dystrophy)

Since its first reported in 1970 in a family of four siblings and their offspring with pigmentation in the macula in a butterfly-shaped pattern, many studies have been reported on butterfly-shaped pigment dystrophy, or pattern dystrophy [15].

Decreased visual function or metamorphopsia may be present, but many cases are identified on

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routine eye exams because vision is preserved and progression is slow in many cases [16]. Bilateral symmetric pigmentation can be observed showing various shapes. Most cases show butterfly-shaped pigmentation in deep layers of the central retina, thus pigmentation can be poorly visualized with red-free light. The fovea and foveal reflex are normal, and the superficial layers of the retina including retinal vessels and optic nerve and choroid are normal. The butterfly-shaped pigmentation shows blocked fluorescence on fluorescein angiography with sharp margins. The photoreceptor layer and inner retinal layers are normal, and visual acuity, visual field, color vision, dark adaptation, and ERG are normal. Diffuse dysfunction of the retinal pigment epithelium causes abnormal electrooculography. On autopsy, photoreceptors and retinal pigment epithelium are lost in the areas of pigmentation, while choriocapillaris are normal. Lipofuscin accumulation can be observed outside the involved area.

Most cases are autosomal dominant [17]. Peripherin/RDS gene mutations are identified in many cases, but other genes associated with other macular dystrophies have also been found to be associated [18], and mutation in the CTNNA1 gene has also been identified [19]. Some cases show incomplete penetrance as in vitelliform macular dystrophy, and carriers can be identified with electrooculography.

The typical pigmentation makes it readily discriminative from other inherited macular dystrophies, but macular dystrophy in Steinert–Curschmann myotonic dystrophy shows similar appearance requiring differential diagnosis.

13.3 Sorsby Fundus Dystrophy

In 1949, Sorsby et al reported change in the fundus resembling inflammation in the posterior pole [20]. Bilateral change in the fundus was observed with abrupt decrease of vision, with autosomal dominant inheritance pattern. This lesion was similar with autosomal dominant central areolar choroidal dystrophy, and difficult to differentiate from disciform macular degeneration or true inflammatory reactions.

Visual loss and nyctalopia in the third to fourth decades of life are typical, with prominent presentation in the 40s. Fastly progressing central scotoma with abrupt increase in size and depth causing visual loss within several months accompanied with decreased color vision is the usual presentation.

The first signs on fundoscopy include bilateral macular edema with hemorrhage and exudation, progressing to pigmentation and scar formation. Atrophy of the retinal pigment epithelium becomes prominent with time, and underlying choroidal vessels are visible. This process progresses to the periphery through 3–4 years, and abnormal pigmentation and retinal pigment epithelium extend to the far periphery, resembling diffuse choroidal atrophy. Fluorescein angiography findings vary according to the stage of the disease, with filling defect of the choriocapillaris in early stages, progressing to atrophy of the choriocapillaris and prominent larger choroidal vessels in late stages. Choroidal neovascularization or polypoidal choroidal vasculopathy has also been reported [21]. Dark adaptation is usually not affected, but sometimes delayed with progressed disease. ERG is normal, but b wave is decreased with decreased rod function with progression.

The typical pathologic finding of Sorsby fundus dystrophy is lipid and protein accumulation between the Bruch's membrane and retinal pigment epithelium, up to 30 μm in some cases [22]. Subretinal hemorrhage and exudation can be present in some cases. Autosomal dominant inheritance is associated with mutation in 22q13, and tissue inhibitor of metalloproteinase-3 (TIMP3) gene mutation is considered as the causative mutation.

Other retinal and choroidal dystrophies should be differentiated, including vitelliform macular dystrophy, which may have a similar appearance due to exudation. Diffuse choroiditis and disciform macular degeneration should also be differentiated. Diffuse atrophy in the progressed stages can mimic diffuse atrophy due to high myopia, gyrate atrophy of the choroid, and choroideremia. Also, autosomal dominant central areolar choroidal dystrophy should also be considered. Treatment includes anti-vascular endothelial

growth factor antibody injection for accompanied choroidal neovascularization or polypoidal choroidal vasculopathy [23–25].

13.4 Bietti's Crystalline Retinopathy

Crystalline retinopathy can be observed due to various causes, including toxic retinopathies, hereditary diseases, and chronic retinal detachment, but this rare form of crystalline retinopathy was first reported in 1937 by Bietti, described as yellow-white crystalline lipid deposits in the retina and sometimes cornea with tapetoretinal degeneration. The cause is unknown, but abnormality of the retinal pigment epithelium and disruption of the outer retinal blood barrier causing leak is the suspected pathophysiologic mechanism. Various degrees of retinal pigment epithelium and choriocapillaris loss are observed with crystalline deposits throughout all layers of the retina, also accompanied by superficial crystalline deposits in the corneal limbus [26, 27].

Typical crystalline deposits and choriocapillaris atrophy on fluorescein angiography usually lead to the diagnosis. Photoreceptor loss progresses with enlargement of this atrophy, and crystalline deposits disappear leaving choriocapillaris atrophy, which can be observed on optical coherence tomography [28, 29]. The size and location of the involved area determine the degree of involvement of visual acuity, dark adaptation, and ERG findings, with decrease of ERG and increased severity of nyctalopia with progression.

Differentiation with retinitis pigmentosa is needed, and up to 3–10% of cases of retinitis pigmentosa showing autosomal recessive pattern had been identified as crystalline retinopathy in a previous report. Less retinal vascular sclerosis is observed in crystalline retinopathy, and ERG is relatively preserved [27].

On biopsy of the cornea, complex lipid inclusions and cholesterol deposits were identified in fibroblasts and epithelial cells, also found in lymphocytes, leading to suspicion that abnormal systemic lipid metabolism is involved in the pathophysiology [30].

Autosomal recessive inheritance in suspected, but autosomal dominant cases has also been reported. Mutation in CYP4V2, one of the cytochrome p450 family, has been identified, which is involved in the metabolism of fatty acids. In a recent study on Korean and Japanese patients, over 50% of patients were found to have the c.802-8_810del17insGC mutation in both alleles, but was not associated with clinical severity [31].

13.5 Autosomal Dominant Radial Drusen (Doyne Honeycomb Retinal Dystrophy)

Autosomal dominant radial drusen are found inner to the Bruch's membrane and are thought to be secreted from the retinal pigment epithelial cells. Initially patients are asymptomatic and identified through routine funduscopic examinations, but eventually vision decreases accompanied by metamorphopsia. Usually patients present in their 20s and 30s [32], with a few round yellowish brown lesions in their posterior poles that turn white later. In their middle-ages, multiple white discrete dots cover the posterior pole, in a mosaic or honeycomb pattern. Usually bilateral and symmetric, the drusen are larger near the fovea, and are round and white and discrete compared to fundus flavimaculatus. As the disease progresses, the drusen near the center conglomerate, and retinal pigment epithelial atrophy appears in the retina. Pigmentation may increase and atrophy of the choriocapillaris and larger choroidal vessels occurs. Often drusen disappear leaving atrophic areas. Usually autosomal dominant radial drusen progress in radial fashion from the macula and optic disk area, leaving the optic disk and vessels and far periphery intact. On fluorescein angiography, multiple round hyperfluorescent dots are visible in the arterial phase, which partially correspond with the lesions visible on fundoscopy. Areas of retinal pigment epithelial atrophy not definitely visible on fundoscopy can be visualized with fluorescein angiography. Large drusen do not show hyperfluorescence due to blockage of choroidal fluorescence, while smaller ones allow visualization

of the underlying background hyperfluorescence of the choroid. The lesions show no leakage, sparing the optic nerve, retinal vessels, and peripheral retina. Choroidal neovascularization may occur, which can be observed on optical coherence tomography [33, 34]. Vision remains normal in the early stages, progressively declining in further stages. As deposits are accumulated under the retinal pigment epithelium toward the choroid, photoreceptors remain intact longer than in fundus flavimaculatus, but after 10–20 years, photoreceptor damage may occur. Vision loss is rare before 40, but may progresses to central scotoma. Color vision remains normal while visual function is spared as in other macular diseases. Dark adaptation is normal, but may be slightly decreased in advanced cases. ERG is normal, but increased b wave latency may be observed in advanced cases. Electrooculography is normal, but becomes subnormal with increased area of involvement. Symptoms and findings are usually less severe than fundus flavimaculatus.

Round accumulation of hyaline bodies in retinal pigment epithelium is observed histologically. When compared to drusen in age-related macular degeneration, collagen type IV was found only in autosomal dominant radial drusen, but other components were similar [35].

Autosomal dominant inheritance with mutation of the fibulin gene (EFEMP1) on chromosome 2 is reported as the genetic cause [36, 37].

Differentiation with degenerative drusen of age-related macular degeneration is required. Degenerative drusen can also be observed in other diseases such as hyalinosis cutis et mucosae (Urbach–Wiethe syndrome). Fundus flavimaculatus, fundus albipunctatus, and fleck retina of Kandori should also be differentiated.

13.6 Others

13.6.1 North Carolina Macular Dystrophy

North Carolina macular dystrophy was first reported in 1971 by Lefler et al in an Iris family in North Carolina with retinopathy and aminoaciduria [38]. Symmetric bilateral large lesions are seen on the macula at birth, with no progression during lifetime. Mutation in the MCDR1 gene on 6q [39] involved in regulation of retinal transcription factor PRDM13 has been reported [40, 41].

13.6.2 Dominant Cystoid Macular Dystrophy

Initially cystoid macular edema occurs with progression to macular atrophy and surrounding pigmentation. Mild decrease in vision occurs in young patients, but progresses with age. The retinal vessels and optic nerve head are spared late into the disease. On fluorescein angiography, typical capillary leak around the macula can be found, which progresses to window defects in atrophic areas. ERG is usually normal, but electrooculography is subnormal, also progressing with age. Yellow-blue and red-green color vision are all decreased. Initially the retinal pigment epithelium is involved, but inner and outer blood retinal barrier seems to be broken down secondarily. Mutation at 7p15.3 is thought to be associated, but the exact gene has not been identified yet [42].

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