Cone Dystrophy/Cone-Rod Dystrophy

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Abstract

Cone dystrophy is a rare genetic retinal disorder characterized by primary cone degeneration and secondary rod involvement, with a variable fundus appearance. The loss of cones leads to predominant symptoms such as decreased visual acuity, color vision defects and day blindness. Cone dystrophies are genetically heterogeneous and can be inherited by autosomal recessive, autosomal dominant or X-linked recessive patterns.

Keywords

Cone dystrophy · Cone-rod dystrophy · ERG · Genetic counseling · Day blindness · Color vision defects

10.1 Introduction

Cone dystrophy or cone-rod dystrophy is a rare genetic retinal disorder characterized by primary cone degeneration and secondary rod involvement or concomitant loss of both cones and rods (cone-rod dystrophy), with a variable fundus appearance. The prevalence of cone/cone-rod dystrophy is estimated at 1/40,000 [1].

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Cone dystrophies usually present in childhood or early adult life, with many patients developing rod photoreceptor involvement in later life, thereby leading to considerable overlap between cone and cone-rod dystrophies.

10.2 Clinical Feature and Diagnosis

Cone dystrophies are characterized by retinal pigment deposits visible on fundus examination, predominantly localized to the macular region. In contrast to typical retinitis pigmentosa (RP), also called the rod-cone dystrophy which is caused by primary loss in rod photoreceptors and later followed by the secondary loss in cone photoreceptors, cone dystrophy reflects the opposite sequence of the events.

The predominant symptoms are decreased visual acuity, central scotoma, color vision defects, hemeralopia (day blindness), photoaversion (avoidance of light due to decreased visual acuity) and decreased sensitivity in the central visual field, later followed by progressive loss in peripheral vision and night blindness. The age of onset of vision loss may be from the late teens to the sixties.

The clinical course of cone dystrophy is generally more severe and rapid than RPs, leading to earlier central vision loss. At the end stage, however, cone dystrophies do not differ from RPs.

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Early color vision abnormality appears even when visual acuity is still not significantly affected in patients with cone dystrophy. This distinguishes cone dystrophy from Stargardt disease and other macular dystrophies. At birth, no symptoms of cone dysfunction are present, unlike the disorders of cone or rod monochromatism.

The fundus appearance is variable. In the early stage, the fundus appears normal, or fine macular lesions and optic disc pallor may be the only signs. Pigmentary deposits resembling bony spicules can be found frequently in the macular area. Macular atrophy or a bull's-eye maculopathy, peripheral retinal pigment epithelium atrophy, intra-retinal pigmentation migration and arteriolar attenuation are shown as the disease progresses. It may be difficult to establish the correct diagnosis in the early stage of the disease because of the lack of observable retinal changes.

Electrophysiologic test confirms a marked generalized abnormality of cone function with comparatively little change in rod function in the early stage. The ERG shows a substantial loss of single-flash and 30-Hz flicker response, whereas rod and mixed responses are relatively spared. Older patients may show some loss of rod sensitivity also [2]. A subset of patients has been described in whom the full-field ERG appears normal, and involvement of only the foveal or central cones has been documented [3]. Macular focal cone ERG is useful to detect cone dystrophy as most of the patients show smaller responses than normal individuals and also to anticipate the progression of cone-rod dystrophy [4].

Peripheral visual fields remain normal, whereas the central visual field and visual acuity are decreased in young patients. Patchy losses of peripheral vision follow in the later phase of the disease.

10.3 Genetics of Cone/Cone-Rod Dystrophy

Cone dystrophies are most frequently nonsyndromic, however, they may also be part of several syndromes, such as Alström syndrome, Bardet-Biedl syndrome and Spinocerebellar Ataxia Type 7.

Nonsyndromic cone dystrophies are genetically heterogeneous (28 genes have been identified). The four most commonly mutated genes are ABCA4 (1p22.1), responsible for 30–60% of autosomal recessive CRDs, CRX (19q13.33) and GUCY2D (17p13.1), responsible for many reported cases of autosomal dominant CRDs, and RPGR (Xp11.4), responsible for X-linked CRDs [5–8].

Most of the sporadic cases of cone dystrophies are considered to be autosomal recessive genetic abnormality. The AR genes causing cone dystrophy include ABCA4, ADAM9, CACNA2D4, CDHR1, CNGB3, KCNV2, PDE6C, RAX2, RDH5, RPGRIP1. Biallelic variants of POC1B were recently reported to cause autosomal recessive nonsyndromic cone dystrophy [9]; POC1 B has been shown to play important roles in centriole assembly and/or stability and ciliogenesis [10].

Clinical features and progression patterns vary, even in the same family members with autosomal dominant cone dystrophy [11]. The genes inherited AD are PRPH2, AIPL1, HRG4, RIMS1, PITPNM3, PROM1, CRX, GUCA1A and GUCY2D. The GUCA1A and GUCY2D are associated with the cGMP pathway. CRX is a transcription factor of photoreceptor homeobox.

X-linked recessive cone dystrophies are associated with the genes such as RPGR, CACNA1F, or COD2 [12]. The female carrier may show subtle symptoms with various clinical presentations.

Taken together, it seems that most genes responsible for cone dystrophies or cone-rod dystrophies are involved in other types of retinal dystrophies, including RPs and other macular dystrophies. Any gene causing retinal dystrophy may potentially be involved in the pathogenesis of cone dystrophies, and the challenge is to understand the underlying mechanisms. Likewise, the question of why some mutations in a gene lead to CRD whereas others cause RP remains unresolved for several genes.

10.4 Differential Diagnosis

Differential diagnosis of cone dystrophy includes other hereditary cone disorders (including achromatopsia and allied cone dysfunction syndromes, cone dystrophy and Stargardt disease) and the rod-cone dystrophy, also known as retinitis pigmentosa, which is distinguished by the sequence of photoreceptor involvement (rod photoreceptors followed by cone photoreceptors).

Patients with retinitis pigmentosa typically present with night blindness in the early stage of the disease. In the fundus, pigment deposits are located in the periphery. In some cases, retinitis pigmentosa has a typical slow progression, but macular involvement occurs quite early, with some loss of central visual acuity. A disease history characterized by predominant night blindness and prominent rod involvement on ERG supports the diagnosis of retinitis pigmentosa. In the late-stage RP or cone dystrophy, the differential diagnosis may be difficult. At that time, the typical changes in ERG are undetectable.

Leber congenital amaurosis (LCA) is associated with a high degree of visual impairment, which is already present at birth, and appears either as a rod- or cone-predominant disease, or both. Nystagmus, poor light fixation and reactivity, visual acuity lower than 20/400 and flat ERG are cardinal signs of the disease. Differential diagnosis with early-onset CRD may be difficult because both diseases share the same clinical signs. The presence of a lapse time of several years before dramatic worsening of the visual disability will allow to classify the disease as CRD rather than LCA.

Stargardt disease is a maculopathy in which the peripheral retina usually remains free of lesions. The disease is easy to recognize with the presence of yellow flecks that may cover the entire fundus (fundus flavimaculatus), hyperfluorescent macular lesions (bull's eye) and dark choroid on the fluorescein angiography. However, there are extended lesions in some late-stage Stargardt cases, and in addition, a number of CRD are caused by the "Stargardt gene," ABCA4. In these cases, the early stage of the CRD may be similar to Stargardt disease, but in a decade, signs of peripheral involvement occur.

Achromatopsia is stationary cone dystrophy that appears at an earlier age and is inherited as an autosomal recessive trait. To date, three genes associated with achromatopsia have been characterized: CNGA3 and CNGB3, located at 2q11 and 8q21, which encode the α- and β-subunits of the cGMP-gated cation channel in cone cells, respectively, and GNAT2, located at 1p13, which encodes the cone α-transducin subunit [13–17]. Achromatopsia can be differentiated with progressive cone dystrophy based on the lack of disease evolution and the normal fundus.

10.5 Treatment

Currently, there is no therapy that stops the evolution of the disease or restores the vision, and the visual prognosis is variable, with early central vision loss and progressive visual dysfunction leading to legal blindness before 40 years of age in most cases.

Management aims at slowing down the degenerative process, treating the complications and visual rehabilitation.

Dark sunglasses or miotics may be helpful in reducing photophobia in some patients with cone dystrophies. Many patients also benefit from low vision aids such as magnifiers, closed-circuit television devices, and software for computer screen text enlargement.

Genetic counseling may be of benefit for patients and their families. A precise phenotypic diagnosis is always mandatory and is particularly useful in the absence of familial history or in sporadic cases (Fig. 10.1).

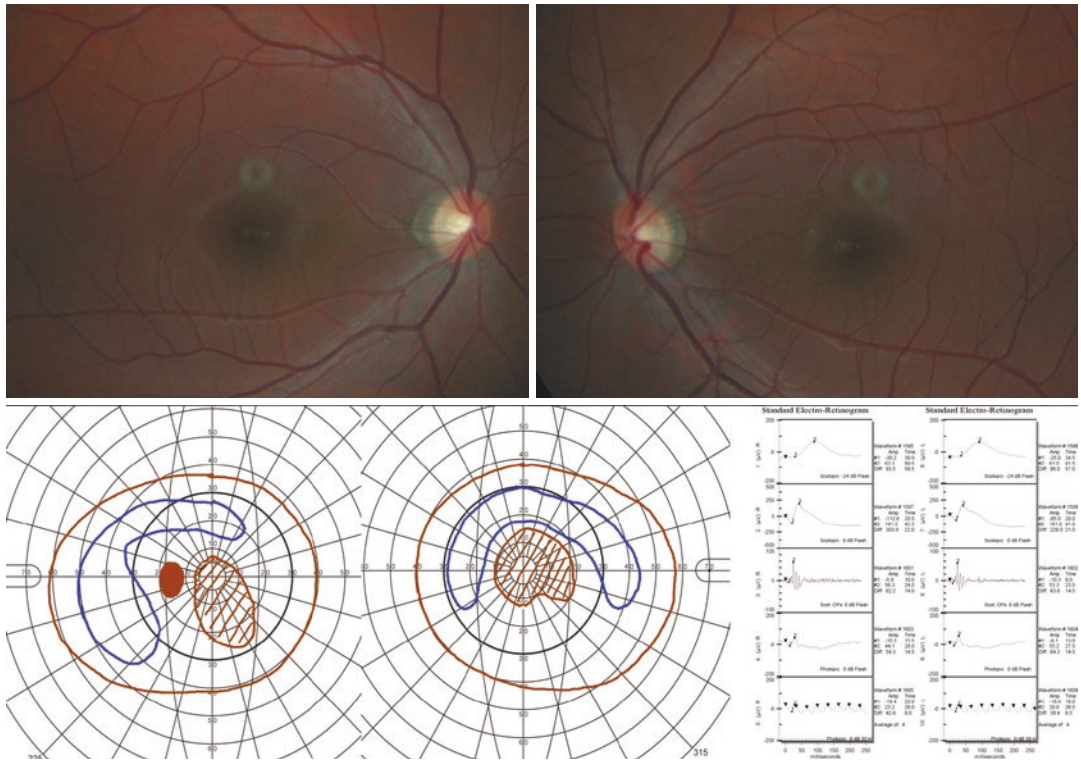

Fig. 10.1 A 19-year-old man has experienced a gradual decline of visual acuity for several years. The best-corrected visual acuities were 20/100 in OD and 20/200 in OS. Goldmann's visual field examination shows relative central scotoma. The fundus appears grossly normal; however, the electroretinography shows the decreased amplitude of cone responses (30 Hz flicker) which findings are compatible with cone dystrophy

References

1. Hamel CP, et al. Molecular genetics of pigmentary retinopathies: identification of mutations in CHM, RDS, RHO, RPE65, USH2A and XLRS1 genes. J Fr Ophtalmol. 2000;23(10):985–95.
2. Vincent A, et al. Phenotypic characteristics including in vivo cone photoreceptor mosaic in KCNV2-related "cone dystrophy with supernormal rod electroretinogram". Invest Ophthalmol Vis Sci. 2013;54(1):898–908.
3. Gundogan FC, Tas A, Sobaci G. Electroretinogram in hereditary retinal disorders. Electroretinograms. 2011;95–132.
4. Galli-Resta L, et al. Early detection of central visual function decline in cone-rod dystrophy by the use of macular focal cone electroretinogram. Invest Ophthalmol Vis Sci. 2013;54(10):6560–9.
5. Xiao X, et al. A recurrent mutation in GUCY2D associated with autosomal dominant cone dystrophy in a Chinese family. Mol Vis. 2011;17:3271–8.
6. Thiadens AA, et al. Homozygosity mapping reveals PDE6C mutations in patients with early-onset cone photoreceptor disorders. Am J Hum Genet. 2009;85(2):240–7.
7. Chowers I, et al. Cone and rod dysfunction in the NARP syndrome. Br J Ophthalmol. 1999;83(2):190–3.
8. Kelsell RE, et al. Mutations in the retinal guanylate cyclase (RETGC-1) gene in dominant cone-rod dystrophy. Hum Mol Genet. 1998;7(7):1179–84.
9. Kominami A, et al. Case of cone dystrophy with normal fundus appearance associated with biallelic POC1B variants. Ophthalmic Genet. 2018;39(2):255–62.
10. Keller LC, et al. Molecular architecture of the centriole proteome: the conserved WD40 domain protein POC1 is required for centriole duplication and length control. Mol Biol Cell. 2009;20(4):1150–66.
11. Krill AE, Deutman AF. Dominant macular degenerations. The cone dystrophies. Am J Ophthalmol. 1972;73(3):352–69.
12. Jalkanen R, et al. X linked cone-rod dystrophy, CORDX3, is caused by a mutation in the CACNA1F gene. J Med Genet. 2006;43(8):699–704.
13. Wissinger B, et al. Human rod monochromacy: linkage analysis and mapping of a cone photoreceptor expressed candidate gene on chromosome 2q11. Genomics. 1998;51(3):325–31.

14. Kohl S, et al. Total colourblindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. Nat Genet. 1998;19(3):257–9.
15. Kohl S, et al. Mutations in the CNGB3 gene encoding the beta-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. Hum Mol Genet. 2000;9(14):2107–16.
16. Aligianis IA, et al. Mapping of a novel locus for achromatopsia (ACHM4) to 1p and identification of a germline mutation in the alpha subunit of cone transducin (GNAT2). J Med Genet. 2002;39(9):656–60.
17. Kohl S, et al. Mutations in the cone photoreceptor G-protein alpha-subunit gene GNAT2 in patients with achromatopsia. Am J Hum Genet. 2002;71(2):422–5.