Literature Review

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Choroideremia – A clinical insight and differential diagnosis

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Choroideremia is an X-linked recessive inherited, bilateral progressive chorioretinal dystrophy/degeneration leading to blindness by late adulthood. However, it can be confused occasionally with other conditions, especially retinitis pigmentosa due to their shared clinical manifestations. Since the management and patients' counseling differ between those conditions listed in the differential diagnosis, it is important for clinicians to come to the right diagnosis. This article is trying to make a differential diagnosis between choroideremia and other conditions based on the current knowledge of these disorders.

Introduction

The designated term "retinal dystrophy" is used to characterize a heterogeneous group of hereditary disorders in which the loss of photoreceptor function leads to progressive visual impairment [1]. The most common example is retinitis pigmentosa [1]. One of the most important disorders that may be confused with retinitis pigmentosa is choroideremia [1]. Retinitis pigmentosa has widely gathered the attention worldwide, but choroideremia is less heard [1].

Choroideremia, which is caused by mutations in the CHM gene which encodes Rab escort protein 1 (REP1), is an X-linked recessive (XLR) inherited, bilateral progressive chorioretinal dystrophy/degeneration leading to blindness by late adulthood [1-7]. It manifests as a progressive degenerative disorder of the photoreceptor layer, retinal pigment epithelium (RPE), and choroid [1, 6, 8]. Regions of RPE atrophy are observed early in the mid-periphery and then progressed centrally [1]. This is coupled with loss of photoreceptors and the choriocapillaris [1].

Prevalence

The prevalence of choroideremia is between 1 in 50,000-100,000 people predominantly seen in the Finish population [8-10].

X-linked recessive pattern

Due to the nature of XLR pattern in choroideremia, male patients predominantly show the representative aspects of early night blindness during the first decade of childhood that progress into severe peripheral vision loss followed by legal blindness in late adulthood around the fifth to sixth decades [6-8, 11, 12]. However, even if female carriers remain mostly asymptomatic, they can suffer from nyctalopia and show evidence of pigmentary changes and chorioretinal degeneration in the fundus with associated subnormal visual sensitivity [6-8, 12-15]. However, the chorioretinal degeneration found in female carriers is not noticeable until characteristically the 3rd-4th decade [14].

Clinical Symptoms and Signs

Preliminary symptoms of patients with choroideremia often consist of progressive reduction of central visual acuity, nyctalopia, and constriction of the peripheral visual field [1]. Nyctalopia is usually the first symptom often with onset during childhood [1].

A ring-like perimacular scotoma that progresses into the peripheral visual field throughout life with corresponding visual field loss (peripheral constriction) can be documented [1, 3, 7, 12]. This ring scotoma in general follows changes in the fundus appearance so that it matches areas of chorioretinal degeneration, eventually resulting in tunnel vision [1].

Fundus changes are highly variable [1]. In the early phase, the fundus exhibits peripheral pigmentary clumping at the level of the RPE that gradually progresses into obvious regions of chorioretinal atrophy with scleral exposure and visible choroidal vessels [6, 8]. These degenerative courses start at the equator and in the mid-peripheral fundus following a centripetal distribution approaching the anterior retina, posterior pole, and the ora serrata [2, 6, 11]. Comparable atrophic changes are also observed in the peripapillary area with some patients keeping a central region of reasonably preserved retinal tissue even in advanced phases [16]. Peripapillary atrophy of the RPE is

reported to happen at early stages and is progressive [16]. Moreover, even as the large choroidal and retinal vessels remain unaffected, there is a continuing reduction of choriocapillaris, eventually baring the sclera beneath [6, 16].

The typical blonde appearance of the fundus is a consequence of the atrophy of the RPE and choriocapillaris [1]. Nevertheless, the deep choroidal vasculature is frequently maintained and distinguished in funduscopy [17].

The central macular pigment, function, and anatomy of the central macula are characteristically maintained until very late in the course of the degeneration [2] and can be illustrated with fundus autoflourescence imaging [1]. At the early stage of the disease, reduced visual acuity is often demonstrated to be secondary to the development of cystoid macular edema, which can be observed on optical coherence tomography (OCT) examination [18]. Therefore, macular OCT is a useful method to detect the cause of reduced visual acuity in patients with choroideremia [1]. Change in vision from a slow to more rapid reduction was documented to be at the age of 39 years in a recent analysis of 1004 individual eyes from 23 studies [19]. Later in life approximately at age 50-70 years, central vision is noticeably affected [1].

Additional ophthalmological findings in choroideremia include posterior subcapsular cataracts, macular edema, cystoid macular edema, choroidal neovascularization (CNV), and myopia [1, 6, 18, 20].

Diagnosis

Funduscopy, fundus autofluorescence (FAF), OCT, optical coherence tomography angiography (OCTA), confocal adaptive optics scanning light ophthalmoscopy (AOSLO), visual fields/microperimetry, electroretinography, and colour vision testing have been applied for the assistance in the diagnosis of ocular manifestations of choroideremia [1]. Fundus fluorescein angiography (FFA) has also been used if CNV is suspected when leakage is the main diagnostic feature [1].

Differential diagnosis of choroideremia

Despite the distinguishing genetic and clinical phenotype, choroideremia shares comparable features with other conditions that need further exploration [1, 6]. Differential diagnoses of choroideremia include 1. Retinitis pigmentosa (advanced), 2. Generalized choroidal dystrophy, 3. Gyrate atrophy, 4. Rubella, 5. Syphilis, 6. Thioridazine retinopathy, 7. Ocular Albinism, 8. Kearns–Sayre syndrome (KSS), 9. Bietti's crystalline dystrophy, and 10. Myopic retinal degeneration [1, 6].

Retinitis pigmentosa

Leading differential diagnosis is retinitis pigmentosa [1]. X-linked inheritable retinal diseases demonstrate a characteristic family pedigree so that the course of the disease is different between males and females [1, 21]. Choroideremia and X-linked retinitis pigmentosa are two of the most common X-linked inheritable retinal diseases [21]. Initially, an X-linked family history of visual field loss generally raises the suspicion of one of these two disorders [22]. They share a number of common clinical aspects, including the same family pedigree, nyctalopia, constriction of the visual field (tunnel vision), gradually reduced visual acuity, and retinal degeneration [1, 21]. These make difficulties in their differential diagnosis and result in diagnostic confusion, especially in the absence of a typical fundus appearance [1, 21, 23]. In this regard, it is noted that approximately 6% of patients initially diagnosed with retinitis pigmentosa truly have choroideremia [10].

Retinitis pigmentosa shares nyctalopia, visual field restriction, and in some patients choroidal engagement with choroideremia [1]. However, other clinical results can help in differential diagnosis [1]. These include a bone spicule pigment migration pattern in the peripheral retina, optic disc pallor, retinal vessel narrowing, and probable epiretinal membrane formation in retinitis pigmentosa [1, 6, 10, 24-26]. The degree of pigment migration into the retina that represents retinitis pigmentosa is not observed in patients with choroideremia [1]. In this regard, bilateral mid-peripheral intraretinal perivascular 'bone spicule' pigmentary alterations and RPE atrophy related to arteriolar narrowing are observed in retinitis pigmentosa [1]. In addition, a gradual rise in density of the pigment with anterior and posterior spread and a tessellated fundus appearance evolves in patients with retinitis pigmentosa due to uncovering of large choroidal vessels [1]. Peripheral pigmentation in retinitis pigmentosa may become severe, with noticeable arteriolar narrowing and disc pallor [1]. Therefore, the key classic triad of results in retinitis pigmentosa includes 'bone spicule' retinal pigmentation, arteriolar attenuation, and 'waxy' disc pallor [1].

Furthermore, retinitis pigmentosa may occur as a sporadic (simplex) disorder, or be inherited in an autosomal dominant (AD), autosomal recessive (AR) or XLR mode [1]. However, the mode of inheritance is only XLR in patients with choroideremia [1].

The CHM gene is the only gene isolated in patients with choroideremia [1,27]. Genetic analysis can be performed, which demonstrates a deletion on the CHM gene in line with the diagnosis of choroideremia [1]. In this regard, genetic testing shows hemizygous deletion of exons 9-11 on the CHM gene in patients with choroideremia [1]. Mutation specific carrier analysis should also be advised for all first degree female relatives [1].

Generalized choroidal atrophy

Generalized choroidal atrophy, which may manifest phenotypic similarities to an intermediate phase of choroideremia, is inherited in an AD or infrequently AR manner [1]. The diverse regional types of choroidal atrophies frequently produce a milder visual dysfunction [1].

Gyrate atrophy

Gyrate atrophy of the choroid and retina is identified by a circular degeneration in the choroid and retina of the eye with atrophic chorioretinal areas on funduscopy and distinctive (well-demarcated) scalloped borders of centripetal retinal degeneration so that the patients with gyrate atrophy manifest nyctalopia, peripheral visual field defects, early

cataract, and myopia [1, 6, 28, 29]. However, this condition is inherited as an AR trait, and is associated with increased plasma ornithine levels (hyperornithinemia) due to ornithine-delta-aminotransferase (OAT) deficiency [1, 6, 28, 29]. So, the genetic test and blood test can be used to help in differential diagnosis of this condition from choroideremia. In general, patients with gyrate atrophy have other medical issues, such as muscle weakness [1, 6, 28, 29].

Rubella

Congenital rubella, caused by transplacental transmission of virus to the fetus from an infected mother, can result in congenital abnormalities of numerous organ systems [1]. Ocular manifestations of congenital rubella include conjunctivitis (Rubella virus produces a nondescript, catarrhal follicular conjunctivitis associated with the systemic disease), rubella keratitis, cataract (Pearly nuclear or more diffuse unilateral or bilateral cataract), lenticular malformation, iritis, anterior uveitis, 'salt and pepper' pigmentary retinopathy (Postinfectious pigmentary retinopathy) or retinitis (Retinitis can be associated with exudative detachments of the retina and retinal pigment epithelium), glaucoma, and microphthalmos [1].

Salt and pepper appearance of congenital rubella retinopathy can be easily differentiated from choroideremia [1].

Syphilis

Ocular manifestations, while uncommon, are characteristically related to neurosyphilis [1]. Salt and pepper pigmentary retinopathy (Postinfectious Pigmentary retinopathy) in syphilis can also be simply differentiated from choroideremia [1].

Early systemic manifestations consist of failure to thrive, a macula-papular rash, mucosal ulcers, characteristic fissures around the lips (rhagades), and a range of organ involvement [1]. Late systemic signs contain sensorineural deafness, saddle-shaped nasal deformity, sabre tibiae, bulldog jaw (mandibular prominence due to maxillary underdevelopment), Hutchinson teeth (notched, small, widely spaced teeth), and Clutton joints (painless effusions in large joints, especially the knees) [1].

If clinical findings suggest a diagnosis of syphilis, the case should be referred to a physician specializing in infectious or sexually transmitted diseases [1]. Serology is the foundation of the diagnosis [1]. Treponemal and cardiolipin antibody tests should be performed to confirm the diagnosis of syphilis [1].

Thioridazine hydrochloride retinal toxicity

Thioridazine hydrochloride retinal toxicity is associated with decreased visual acuity, nyctalopia, pigmentary changes, and chorioretinal degeneration [1, 6, 28]. However, a history of psychiatric disease and medication intake in high doses can help the clinician to come to the right differential diagnosis [1, 6, 28].

Ocular albinism

Ocular albinism is commonly XLR but sometimes AR [1]. Female carriers are asymptomatic, but they may demonstrate mild iris and characteristic fundus changes [1]. Affected males have hypopigmented irides and fundi [1]. Patients with ocular albinism may demonstrate some degree of phenotypic similarity to those patients with choroideremia; however, absence of nyctalopia, presence of nystagmus, iris transillumination defects, photophobia, strabismus, foveal hypoplasia, and misrouting of fibres in the optic chiasm (Increased proportion of decussating axons in optic chiasm can be detected by electrodiagnostic testing) assist to make the differential diagnosis between these two conditions [1].

In addition, genetic counselling with an experienced clinician through drawing a family tree and examination of family members can be very helpful to come to the right diagnosis of ocular albinism [1].

Kearns – Sayre syndrome

KSS is due to mitochondrial DNA deletions and advanced imaging of the fundus may reveal diffuse chorioretinal atrophy resembling advanced choroideremia phases [1, 6, 28, 30]. Supplementary clues that help differential diagnosis consist of progressive external ophthalmoplegia, cerebellar ataxia, cardiac conduction irregularities, increased protein in the cerebrospinal fluid, and microscopic mitochondrial malformations in the muscle biopsy [1, 6, 28, 30].

Bietti's crystalline dystrophy

Bietti's crystalline dystrophy is a rare AR degenerative chorioretinal disorder [1]. Patients with Bietti's crystalline dystrophy may show symptoms similar to choroideremia between the second and fourth decades of life [1]. However, the distinguishing presence of cholesterol crystals in the posterior pole of the retina and corneal stroma assists in precise differential diagnosis [1, 6, 28, 31].

Myopic retinal degeneration

Myopic retinal degeneration occasionally may mimic the presentation of choroideremia [1]. However, the myopic degeneration usually is not as diffuse as the lesions of choroideremia, and patients with myopic degeneration do not typically complain of nyctalopia [1].

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Abbreviation: *REP1 – Rab escort protein 1; XLR – X-linked recessive; RPE – retinal pigment epithelium; OCT – optical coherence tomography; CNV – choroidal neovascularization; FAF – fundus autoflorescence; OCTA – optical coherence tomography angiography; AOSLO – confocal adaptive optics scanning light ophthalmoscopy; FFA – Fundus florescein angiography; AD – Autosomal dominant; AR – autosomal recessive; OAT – ornithine-delta-aminotransferase.*