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Phenotyping choroideremia and its carrier state with multimodal imaging techniques

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Abstract

Purpose—To describe findings in a patient with choroideremia (CHM) and his mother, an obligate CHM carrier.

Methods—Case report.

Results—A 25-year-old man with nyctalopia and poor peripheral vision since childhood, as well as a family history consistent with an X-linked retinal disorder was diagnosed with CHM. His asymptomatic 50-year-old mother, an obligate carrier, was also examined. Fundus exam of the affected man showed significant atrophy of the choroid and RPE while the carrier female showed patchy pigmentary mottling. Imaging of the affected male showed diffuse RPE atrophy on OCT and extensive areas of decreased choriocapillaris flow on OCT angiography. In contrast, the carrier female showed subtle RPE changes on OCT and mild flow alterations on OCT angiography.

Conclusion—This case demonstrates the findings seen in CHM and while CHM carrier females are often asymptomatic, they may exhibit a mosaic pattern of pigmentary change on fundus examination. OCT angiography may show mild choroidal flow abnormalities. This finding serves to further characterize the extent of dysfunction in CHM and its carrier state.

Summary statement

We present a case report of a 25-year-old man with choroideremia and his 50-year-old mother who is an obligate choroideremia carrier. The phenotypic findings using multimodal imaging techniques are described.

Keywords

choroideremia carrier; OCT angiography; pigmentary retinopathy

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Introduction

Choroideremia (CHM) is an X-linked retinal dystrophy caused by loss-of-function mutations in Rab escort protein-1 (REP1), a gene product that facilitates vesicular trafficking. This rare disorder typically only affects males, who experience nyctalopia, loss of peripheral vision, and eventual blindness.¹ Characteristic of this disease are pigmentary changes and a progressive degeneration of photoreceptors, choriocapillaris, and retinal pigment epithelium (RPE), which can lead to visibly bare sclera.¹ Female carriers of CHM are typically asymptomatic, although retinal findings may include patchy fundus pigmentation thought to be secondary to random X-chromosome inactivation.¹ We present a case of a patient with CHM and his mother who is an obligate carrier using multimodal imaging techniques, including optical coherence tomography (OCT) angiography.

Case Report

A 25 year-old African-American man with night blindness and poor peripheral vision since childhood was referred to our clinic. His family history was notable for poor night vision in his maternal grandfather and maternal cousin. He experienced acute loss of vision in his left eye 15 years ago from a subretinal hemorrhage secondary to choroidal neovascularization, and on exam visual acuity was 20/25 in the right eye and hand motion in the left eye. Amsler grid showed peripheral metamorphopsia in the right eye. Fundus exam and fundus autofluorescence (FAF) revealed significant atrophy of the choroid with the exception of a crescent-shaped region of preservation in the macula (Figure 1A and 1C). Additionally, white subretinal fibrosis was present centrally in the left eye (Figure 1B). OCT demonstrated diffuse RPE atrophy as well as loss of overlying photoreceptor and outer nuclear layer (Figures 2A and 2B). Foveal thickening, outer retinal tubulations, and cystoid macular edema were present on the right (Figure 2A), while central subretinal fibrosis was present on the left (Figure 2B). En-face OCT angiography (Zeiss Meditec Cirrus 5000, Dublin, CA) showed prominent choroidal vasculature secondary to the relative absence of choriocapillaris and RPE on the 3x3 mm slabs (Figures 2E and 2H). In contrast to the relatively preserved deep retinal vasculature on en-face OCT angiography (Figures 2C and 2F), there was dramatically decreased flow in the choriocapillaris (Figures 2D and 2G), which appeared to correspond to areas of RPE atrophy visible on FAF. Genetic analysis confirmed a diagnosis of CHM, and the patient was subsequently enrolled in the phase II clinical trial using adeno-associated viral vector encoding REP1.

Given the patient's diagnosis of CHM, his 50-year old mother was examined to determine the severity of her carrier state. She had no visual complaints and visual acuity was 20/20 in both eyes. Slit-lamp exam was unremarkable, but fundus exam revealed patchy peripheral pigmentary mottling with areas of hypopigmentation and pigment clumping in both eyes (Figure 3A and 3B). FAF imaging showed corresponding hyperfluorescence in areas with pigmentary change (Figure 3C and 3D). Horizontal OCT scan through the macula demonstrated subtle abnormalities in the RPE and ellipsoid zone in both eyes (Figure 4A and 4B). En-face OCT angiography of the deep retinal vasculature revealed no obvious abnormalities (Figure 4C and 4F), while slabs through the choriocapillaris and choroid

showed flow voids more prominent in the right than the left eye. (Figures 4D-E, G-H, yellow arrows). Overall, the choriocapillaris was significantly more preserved in the mother than in her son; thus the larger choroidal vessels were not as well visualized on OCT angiography.

Discussion

Choroideremia is an X-linked retinal dystrophy characterized by progressive degeneration of the choroid and RPE in affected males, with milder phenotypes in carrier females. While most women carriers exhibit no visual impairment, the severity of findings can vary greatly, with occasional cases of severe retinal abnormalities likely due to unbalanced X-chromosome inactivation.²⁻⁴ The mosaic pattern seen on retinal exam and multifocal ERG testing, even in asymptomatic carriers, is also attributed to random X-chromosome inactivation early in development, where variable expression of the mutated REP1 protein leads to patches of normal and mutated cells.^{5, 6}

A clinical diagnosis of CHM can often be made on fundus exam, where yellowish-white sclera can be visible due to extensive RPE loss. As in our case, foveal thickening on OCT in young individuals with CHM is not uncommon.⁷ Furthermore, it has previously been reported that OCT angiography can reveal more extensive damage to choriocapillaris blood flow in CHM compared to deep retinal flow, consistent with our results.⁸

Findings in our CHM carrier were also consistent with cases previously reported. Renner et al. similarly described a case with peripheral pigmentary stippling with regions of hypopigmentation on fundus exam, corresponding hyperfluorescent specks on FAF, and subtle RPE irregularities on horizontal OCT scans through the macula.² In particular, it is important for the clinician to distinguish these characteristic fundus findings in CHM carriers from other disease states that demonstrate salt-and-pepper retinopathy. While X-linked choroideremia carriers have subretinal flecks in a reticular pattern, ocular albinism carriers tend to have pigment mottling in a radial pattern, X-linked carriers of retinitis pigmentosa demonstrate a characteristic tapetal reflex, and congenital rubella show pigment mottling in the macula.

CHM carriers can progress slowly over time. A report of two female CHM carriers that were followed for 11 and 17 years demonstrated a slow progression of retinal and/or RPE abnormalities and the eventual development of subnormal 30-Hz flicker responses on full-field ERG.² As the female carrier in this case displayed subtle areas of flow loss in the choriocapillaris and choroid on OCT angiography, we suspect over long-term follow-up that further decrease in the choriocapillaris circulation may result. Thus, OCT angiography may be another means by which to further characterize and quantify the extent of dysfunction in the carrier state with the likelihood of other carriers demonstrating a spectrum of abnormalities on OCT angiography given the condition's variable presentation.

Considering the advancement of retinal imaging, modalities such as OCT angiography are being more frequently used to study retinal disease. Its use in choroideremia and its carrier state aids in the characterization of disease progression.

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Figure 1. CHM proband fundi: **A-B**, Color fundus photograph demonstrating atrophy of the choroid and RPE, with subretinal fibrosis present centrally in the left eye (**B**). **C-D**, Fundus autofluorescence showing an island of preserved RPE in the macula in the right eye (**C**) and corresponding fibrosis in the left eye (**D**).

Figure 2.

CHM proband OCT: **A-B**, Horizontal OCT scan through macula revealing RPE atrophy and loss of overlying photoreceptor and outer nuclear layer. Foveal thickening and cystoid macular edema is present in the right eye (**A**). Central subretinal fibrosis is seen in the left eye (**B**). **C-H**, En-face OCT angiography- 3x3 mm en-face images at the level of the deep retinal vasculature, showing preserved flow (**C&F**); choriocapillaris, showing loss of flow in the choriocapillaris with prominence of choroidal vessels (**D&G**); choroid, showing prominence of medium and large size vessels secondary to loss of choriocapillaris and RPE cells (**E&H**).

Figure 3. Obligate CHM carrier fundi: **A-B**, Fundus photographs showing patchy peripheral pigmentary mottling with areas of hypopigmentation and pigment clumping. **C-D**, Fundus autofluorescence revealing corresponding hyperfluorescence in hypopigmented areas.

Figure 4.

Obligate CHM carrier OCT: **A-B**, Horizontal OCT scans through macula revealing subtle RPE and ellipsoid zone changes. **C-H**, En-face OCT angiography- 3x3 mm en-face images at the level of the deep retinal vasculature with preserved flow (**C&F**); choriocapillaris (**D&G**) and choroid (**E&H**) slabs with subtle areas of flow void (yellow arrows).