Cystic Macular Edema on Spectral-Domain Optical Coherence Tomography in Choroideremia Patients without Cystic Changes on Fundus Examination

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Abstract

Purpose

To determine the prevalence of cystic macular edema (CME) in patients with choroideremia by using spectral-domain optical coherence tomography (SD-OCT).

Methods

Sixteen patients affected with choroideremia were enrolled in the study. All patients underwent a complete eye examination. SD-OCT was performed using an OPKO spectral-domain OCT/SLO instrument.

Results

The average age of the study patients was 44.0 ± 16.0 years (range, 13-63 years). Out of the 16 patients with choroideremia, 10 patients (62.5%) showed a degree of CME on SD-OCT testing in at least one eye, and 8 patients (50%) showed CME in both eyes.

Conclusions

Because of its notable prevalence, it would seem prudent to screen choroideremia patients by SD-OCT for the possible presence of CME and to identify those amenable to future treatment strategies for their macular edema.

Keywords:

Choroideremia; Cystic macular edema; SD-OCT

Introduction

Choroideremia (CHM) is an X-linked progressive chorioretinal dystrophy.[1] Affected males develop early onset night blindness, restriction of the peripheral visual field, and a decrease in central visual acuity, often leading to legal blindness in the advanced stages of the disease. Fundus examination shows a slowly progressive atrophy of the choroid and retinal pigment epithelium (RPE). Heterozygous female carriers are usually asymptomatic; however some can show patchy areas of chorioretinal degeneration and an abnormal electroretinogram.[2,3,4] Fully affected females have also been previously described.[4,5]

CHM is caused by mutations in the *CHM* gene, encoding the *Rab escort protein-1* (*REP1*). The REP1 protein facilitates posttranslational modification of Rab proteins, which regulate intracellular trafficking in the RPE and photoreceptors and are likely involved in the removal of outer segment disk membranes by the RPE.[6-8]

A recent study by Affortit-Demoge and associates,[9] by using time-domain OCT (TD-OCT) testing, showed a positive correlation between the retinal thickness and choriocapillaris preservation in CHM. Jacobson and co-workers[10] showed the presence of retinal thickening and normal retinal laminar structures in early stages of the disease with subsequent retinal thinning and disorganization with disease progression.

Cystic macular edema (CME) is a common pathologic finding of the macula that is the result of cystic accumulation of extracellular intraretinal fluid **predominately** in the outer plexiform and inner nuclear layers of the retina as a result of breakdown in the blood-retinal barrier.[11]

To our knowledge, there are no prior reports that demonstrate the presence of cystic macular lesions in patients with choroideremia, although it has been described in gyrate choroidal atrophy.[12,13] This paper aims to investigate the prevalence of cystic macular edema in patients with choroideremia by using spectral-domain optical coherence tomography (SD-OCT).

Materials and Methods

Thirty eyes of 16 patients with a diagnosis of choroideremia were included in this prospective investigational study including 3 patients with identified *CHM* gene mutations (Table 1). The study was conducted in the Department of Ophthalmology at the University of Illinois at Chicago; approval was obtained from an institutional review board at the University of Illinois and the investigation was conducted in accordance with tenets of the Declaration of Helsinki. An informed consent was obtained from all subjects after the study protocol and procedures were explained to each participant.

The diagnosis of choroideremia was based on the patients' history of nyctalopia, variable degrees of peripheral field restriction, and the characteristic fundus findings (including choroidal and RPE degenerative changes throughout the posterior pole and mid-peripheral retina). Most patients (N=13) underwent full-field electroretinogram (ERG) testing by either of 2 procedures previously described.[14,15]

Inclusion criteria were patients with a diagnosis of choroideremia without an ocular opacity that might hinder OCT scan acquisition. Exclusion criteria were patients with diabetic retinopathy, uveitis, retinal vascular occlusion, prior history of intraocular surgery, or poor OCT image quality. Twenty eight patients previously seen by one of the authors (G.A.F.) were contacted by telephone and asked to participate in the study based

on their prior diagnosis of CHM. A total of 16 patients agreed to participate in the present study.

All patients had a complete eye examination that included best-corrected visual acuity using an early treatment diabetic retinopathy study (ETDRS) chart (The Lighthouse, Long Island City, NY), slit-lamp biomicroscopy and intraocular pressure testing using a Goldmann applanation tonometer. Both pupils were dilated with 1% tropicamide and 2.5% phenylephrine. Detailed fundus examinations were performed with a +78 diopter lens by stereobiomicroscopy, and by both direct and indirect ophthalmoscopy.

SD-OCT Examinations

All subjects included in the study underwent SD-OCT measurements by using an OPKO spectral-domain OCT/SLO instrument (OPKO Instrumentations, Miami, FL), which is a combination OCT and confocal scanning ophthalmoscope (CSO) designed to image the retinal layers as well as provide a confocal fundus image. Both the confocal fundus image and the OCT image are produced simultaneously from the same super-luminescent diode (SLD) light source through the same optics and therefore provide pixel to pixel correspondence. The system provides up to 27,000 A-scans per second with a 5 µm axial resolution.

For the scan acquisition, both the 3D Retinal Topography and Line Scan (B-scan) exam protocols were used, which can suitably detect cystic macular lesions. The Line Scan mode allows the capture of cross sectional B-scan OCT images of the vitreo-retinal, retinal, and chorio-retinal structures. A red scanning line on the CSO image represents the exact location of the cross-sectional OCT image. We used the “Max Frame Count” of

64 frames that is defined as the maximum sequentially captured frames of OCT and CSO images, which are captured and displayed as individual frames. The 3D Retinal Topography mode covers an area of 8.5 x 8.5 mm with a 2.0 mm depth.

The onboard software calculates average retinal thickness measured in each of 9 ETDRS-like zones.[16] Retinal thickness measurements were used to calculate the central 1-mm subfield. The mean ± SD macular thickness from the central 1-mm subfield and from each of the 4 sectors of the inner circle (between 1 and 3-mm in diameter) was calculated. The macular thickness values were compared with normative data provided by the manufacturer and which were retrieved from 225 eyes of 119 normative control subjects (mean age of 47.8 ± 16.3 years) (Table 2). A paired Student *t*-test was used to compare mean values between patients and control subjects to statistically analyze mean retinal thickness differences. A P value <0.05 was considered to be significant. The number of macular cysts based on SD-OCT examinations were classified as (mild) if the number of cysts were from 4-9 and microcystic in appearance, (moderate) if the number of microcysts were from 10-15 or one or more macrocystic lesions were observed, and (severe) if the number of microcysts were more than 15 or if there were diffuse and confluent cysts in any single scan image.

Results

Our study cohort included 30 eyes of 16 patients with choroideremia with 2 eyes excluded due to the presence of an old traumatic retinal detachment in **one** patient and poor fixation that made the acquisition of a reliable scan difficult in a second patient. The average age of the patients was 44.0 ± 16.0 years (range, 13-63 years). All patients were males with the exception of 1 female patient, who was diagnosed with choroideremia based on characteristic clinical fundus appearance, ERG changes, and a genetic molecular mutation. The study cohort was comprised of 15 Caucasian (93.8%) and 1 Hispanic (6.2%) patient. Full-field ERG, which was performed on 13 patients, showed a non-detectable rod function for the isolated dark-adapted response, in 5 patients a non-detectable cone function, and in 8 patients' cone function that was reduced 20% to 71% below the lower limits of normal for the single flash light-adapted response.

The average best-corrected visual acuity for all patients was 0.54 ± 0.72 logMAR (range, 0.08-2.80), which is equivalent to $20/20^{-2}$- light perception on a Snellen acuity chart.

Fig. 1 shows the characteristic fundus changes among 3 different patients (age range from 13 to 63 years), at 3 different stages of disease severity, where there were either less severe choroidal and RPE atrophic changes (A), or more severe fundus changes with diffuse atrophy of the choroid and RPE and evidence of pigmentary changes in the posterior pole and mid-peripheral retina (B and C).

Of the 16 patients (30 eyes) without cystic-appearing macular lesions on fundus examination, 18 eyes (60%) of 10 patients (62.5%) showed a degree of cystic macular edema (CME) on SD-OCT testing in at least one eye, and 8 patients (50%) showed CME

in both eyes. The average age in the group of patients with CME on SD-OCT testing was 39.0 ± 18.4 years. Six patients (37.5%) did not show CME on SD-OCT testing in either eye with an average age of 52.3 ± 5.7 years.

Among the group of patients with CME (N=10), 10 eyes (55.6%) of 7 patients (70%) showed mild CME, 4 eyes (22.2%) of 4 patients (40%) showed moderate CME, and 4 eyes (22.2%) of 2 patients (20%) showed severe CME in at least one eye.

The sizes and shapes of the macular cysts were variable from localized microcystic (11 eyes) or macrocystic changes (4 eyes), to diffuse cysts (3 eyes). The locations of the macular cysts were mostly noted at the level of outer retinal layers in the outer plexiform and **inner** nuclear layers and extrafoveally at 10-15 degrees. However, central foveal cysts were occasionally observed as well (5 eyes of 3 patients) (Figs 2 A and B).

Besides the presence of CME in 62.5% of our study patients by a qualitative method of assessment, the SD-OCT testing showed the presence of normal central macular structure and thickness (N=2 patients, ages 16 and 42 years), a central macular thickening (N=7 patients, mean age of 44.4 years, range from 23 to 55 years), and a central macular thinning was also noted (N=7 patients, mean age of 52.4 years, range from 42 to 63 years). In most of our study patients (N=13), the inner segment/outer segment (IS/OS) junction of the photoreceptors was either disrupted/disorganized or lost, even in the macula, from the degenerative process. Only 3 patients (younger group of patients, age range from 13 to 23 years) showed an intact IS/OS junction of the photoreceptors within the macula.

Of interest, 6 patients (37.5%) showed the presence of rosette-like retinal structures at the level of RPE, mostly extrafoveally, with disorganization and loss of the RPE (Fig 2 C).

In the entire study cohort, the mean ± SD of the macular thickness in the central foveal subfield combined with all sectors of the inner circle are displayed in (Table 2), which are compared to the normative data provided by the manufacturer. No statistically significant differences in the central foveal subfield thickness were detected (p=0.18), while the mean retinal thickness in all of the 4 sectors of the inner circle (between 1 and 3- mm in diameter) was selectively thinner than normal, which was highly statistically significant (Table 2). The central foveal subfield thickness in patients who had CME in at least one eye was 327±62 µm, which was significantly thicker statistically when compared to normative data (p< 0.0001) (Fig 3).

Discussion

OCT is a sensitive tool for detecting the presence of cystic macular edema in various retinal diseases, which may be observed independent of leakage on fluorescein angiography.[17,18] Improvements in OCT technology have recently been introduced, including 3-dimensional (3D), high-resolution, and high-speed OCT that uses spectral-domain (SD) detection to provide increased resolution.

In our current study on patients with choroideremia, we report the presence of cystic macular changes of variable degrees on SD-OCT with an overall prevalence of 62.5% in at least one eye (10 patients) and 50% in both eyes (8 patients). CME has been previously reported in different hereditary retinal diseases such retinitis pigmentosa and Usher syndrome.[19-21] CME has also been described in patients with gyrate atrophy,

another hereditary choroidal dystrophy.[12,13,22] Feldman and associates[22] reported a patient with an epiretinal membrane and cystic macular edema associated with gyrate atrophy of the choroid and retina. Vannas-Sulonen,[23] from a series of 21 patients with gyrate atrophy, observed that 9 (43%) had macular involvement, 1 (5%) with bilateral cystoid macular edema confirmed by fundus fluorescein angiography.

The presence of macular edema in a high percentage of our choroideremia patients is consistent with malfunction of the blood-retinal barrier, with diffusion of fluids to within the retina.

Previous studies[10,24] that used TD-OCT testing on choroideremia patient (N=1) and carriers (N=21) did not show any evidence of CME. However, they noted the presence of retinal thickening, which was similar in our study cohort. We similarly observed that the central foveal thickness in the group of CME patients was thicker (327±62 µm) when compared to normative data (235±24 µm). This finding could relate to the macular edema itself or may be related to retinal gliosis as has been previously described by MacDonald and associates.[25]

One of the interesting findings we observed in our patients (N=6) was the presence of rosette-like retinal structures at the level of outer retinal layers observed on SD-OCT testing. This finding was similar to a prior report by Rodrigues et al,[26] who described that these rosette-like structures in choroideremia may be due to a defect in outer segment phagocytosis. A more recent report by MacDonald et al,[25] described these rosette-like structures as formed by abnormal photoreceptors.

Our study showed that choroideremia patients can have CME on SD-OCT exam. This finding has potential significance for future treatment trials in such patients where

patient selection might be influenced by the degree of macular edema. The use of high-speed, high-resolution tools such as SD-OCT may be useful to measure macular thickness during patient selection and for monitoring patients with choroideremia in future therapeutic trials.

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Titles and legends to figures

Figure 1: Fundus photographs of right eyes in a 13-year old (A), 44-year-old (B), and 63-year-old (C) choroideremia affected males that show areas of choroidal and RPE atrophy at an earlier stage (A), and more extensive atrophy of the choroid and RPE noted at later stages of the disease (B and C).

Figure 2: Horizontal SD-OCT scans of the left eyes (A and B) and both eyes (C) of 3 affected males with choroideremia (ages, 62, 44, and 63-year-old, respectively), which show evidence of cystic macular edema in the fovea and parafoveal regions (arrows). Black arrow head (C) shows a rosette-like retinal structure, while the white arrow head (B) shows retinal nerve fiber layer thickening temporal to optic nerve (ON). Patient (A) shows evidence of an epiretinal retinal membrane (between the 2 white lines).

Figure 3: Confocal scanning ophthalmoscopic images (A and C) and retinal thickness measured in ETDRS-like zones (B and D) of the left eyes in 2 affected males with choroideremia (ages, 62 and 63-year-old, respectively), which show characteristic fundus changes and the presence of central foveal and parafoveal retinal thickening.