

# Cystic macular oedema 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 oedema (CME) in patients with choroideremia (CHM) by using spectral-domain optical coherence tomography (SD-OCT).

**Methods** A total 16 patients affected with CHM 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  $44.0 \pm 16.0$  years (range, 13–63 years). Out of the 16 patients with CHM, 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 CHM patients by SD-OCT for the possible presence of CME and to identify those amenable to future treatment strategies for their macular oedema.

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**Keywords:** choroideremia; cystic macular oedema; SD-OCT

## Introduction

Choroideremia (CHM) is an X-linked progressive chorioretinal dystrophy.<sup>1</sup> 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.<sup>2–4</sup> Fully affected females have also been previously described.<sup>4,5</sup>

Choroideremia is caused by mutations in the *CHM* gene, encoding the *Rab escort protein-1*. The Rab escort protein-1 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 disc membranes by the RPE.<sup>6–8</sup>

A recent study by Affortit-Demoge *et al*,<sup>9</sup> by using time-domain OCT testing, showed a positive correlation between the retinal thickness and choriocapillaris preservation in CHM. Jacobson *et al*<sup>10</sup> 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 oedema (CME) is a common pathological 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.<sup>11</sup>

To our knowledge, there are no previous reports that demonstrate the presence of cystic macular lesions in patients with CHM, although

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it has been described in gyrate choroidal atrophy.<sup>12,13</sup> This paper aims to investigate the prevalence of CME in patients with CHM by using spectral-domain optical coherence tomography (SD-OCT).

## Materials and methods

A total of 30 eyes of 16 patients with a diagnosis of CHM 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 CHM 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 testing by either of two procedures previously described.<sup>14,15</sup>

Inclusion criteria were patients with a diagnosis of CHM without an ocular opacity that might hinder OCT scan acquisition. Exclusion criteria were patients with diabetic retinopathy, uveitis, retinal vascular occlusion, previous history of intraocular surgery, or poor OCT image quality. Twenty-eight patients previously seen by one of the authors (GAF) were contacted by telephone and asked to participate in the study based on their previous 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 chart (The Lighthouse, Long Island City, NY, USA), 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, USA), which is a combination OCT and confocal scanning ophthalmoscope 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 superluminescent diode 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  $\mu\text{m}$  axial resolution.

For the scan acquisition, both the three-dimensional 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 vitreoretinal, retinal, and chorioretinal structures. A red scanning line on the confocal scanning ophthalmoscope 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 confocal scanning ophthalmoscope images, which are captured and displayed as individual frames. The three-dimensional Retinal Topography mode covers an area of 8.5  $\times$  8.5 mm with a 2.0 mm depth.

The onboard software calculates average retinal thickness measured in each of nine early treatment diabetic retinopathy study-like zones.<sup>16</sup> Retinal thickness measurements were used to calculate the central 1-mm subfield. The mean  $\pm$  SD macular thickness from the central 1-mm subfield and from each of the four 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

**Table 1** Genetic mutation results of three patients in our cohort study

Patient no.	Age (years)/sex	Race	Genetic mutation	Visual acuity (logMAR)	
				OD	OS
1	31/F	Caucasian	<i>CHM</i> gene, C>T at position 907 exon 7 (R293X) creating a stop codon	0.14	0.04
2	55/M	Caucasian	<i>CHM</i> gene, IVS 3-2 A>G, hemizygous	2.00	0.44
3	44/M	Caucasian	<i>CHM</i> gene, C>T at position 787 exon 6	0.1	0.08

Abbreviations: F, female; M, male.

**Table 2** The mean  $\pm$  SD of the macular thickness in the study cohort compared with normative data

ETDRS-like zones	Mean $\pm$ SD thickness in $\mu\text{m}$ in our patients	Mean $\pm$ SD thickness in $\mu\text{m}$ from normative data	P-value <sup>a</sup>
Central foveal	249.0 $\pm$ 99.5	234.7 $\pm$ 23.7	0.1837
Inner superior	270.8 $\pm$ 89.5	304.7 $\pm$ 18.0	0.0003 <sup>a</sup>
Inner inferior	266.7 $\pm$ 109.0	302.4 $\pm$ -18.5	0.0012 <sup>a</sup>
Inner temporal	262.0 $\pm$ 96.8	290.7 $\pm$ 16.8	0.0034 <sup>a</sup>
Inner nasal	260.9 $\pm$ 94.5	304.0 $\pm$ 21.1	<0.0001 <sup>a</sup>

<sup>a</sup>Statistically significant.

manufacturer and which were retrieved from 225 eyes of 119 normative control subjects (mean age of 47.8  $\pm$  16.3 years; Table 2). A paired Student's *t*-test was used to compare mean values between patients and control subjects to statistically analyse 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 >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 CHM with 2 eyes excluded because of 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  $\pm$  16.0 years (range, 13–63 years). All patients were males with the exception of one female patient, who was diagnosed with CHM based on characteristic clinical fundus appearance, electroretinogram changes, and a genetic molecular mutation. The study cohort was comprised of 15 Caucasian (93.8%) and 1 Hispanic (6.2%) patient. Full-field electroretinogram, 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 20–71% 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  $\pm$  0.72 logMAR (range, 0.08–2.80), which is equivalent to 20/20<sup>-2</sup>– light perception on a Snellen acuity chart.

Figure 1 shows the characteristic fundus changes among three different patients (age range from 13 to 63 years), at three different stages of disease severity, where there were either less severe choroidal and RPE

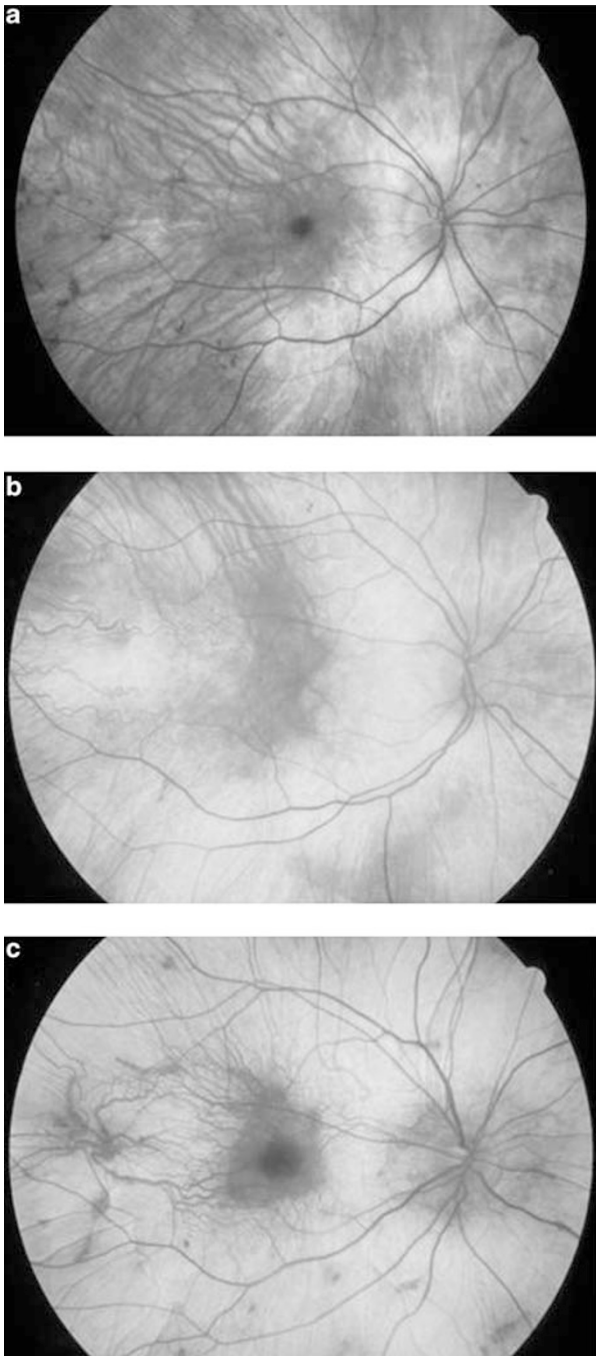
atrophic changes (panel a), or more severe fundus changes with diffuse atrophy of the choroid and RPE, and evidence of pigmentary changes in the posterior pole and mid-peripheral retina (panels b and c).

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 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  $\pm$  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  $\pm$  5.7 years.

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

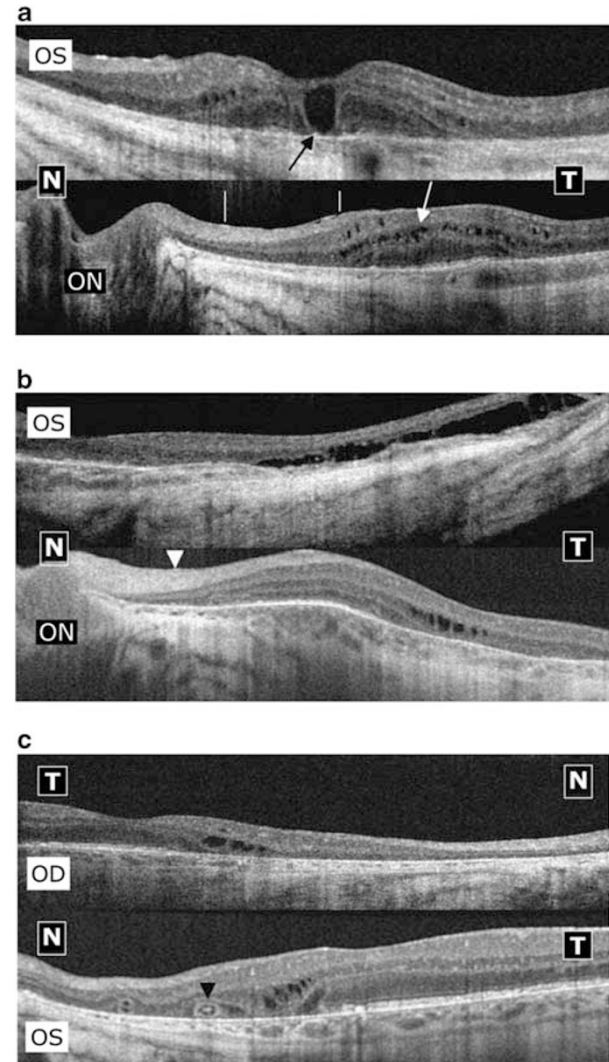
The sizes and shapes of the macular cysts were variable from localized microcystic (11 eyes) or macrocystic changes (4 eyes), to diffuse cysts (3 eyes). The locations of the macular cysts were mostly noted at the level of outer retinal layers in the outer plexiform and inner nuclear layers and extrafoveally at 10–15 degrees. However, central foveal cysts were occasionally observed as well (five eyes of three patients; Figures 2a 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 junction of the photoreceptors was either disrupted/disorganized or lost, even in the macula, from the degenerative process. Only three patients (younger group of patients, age range from 13 to 23 years) showed an intact inner segment/outer segment junction of the photoreceptors within the macula.



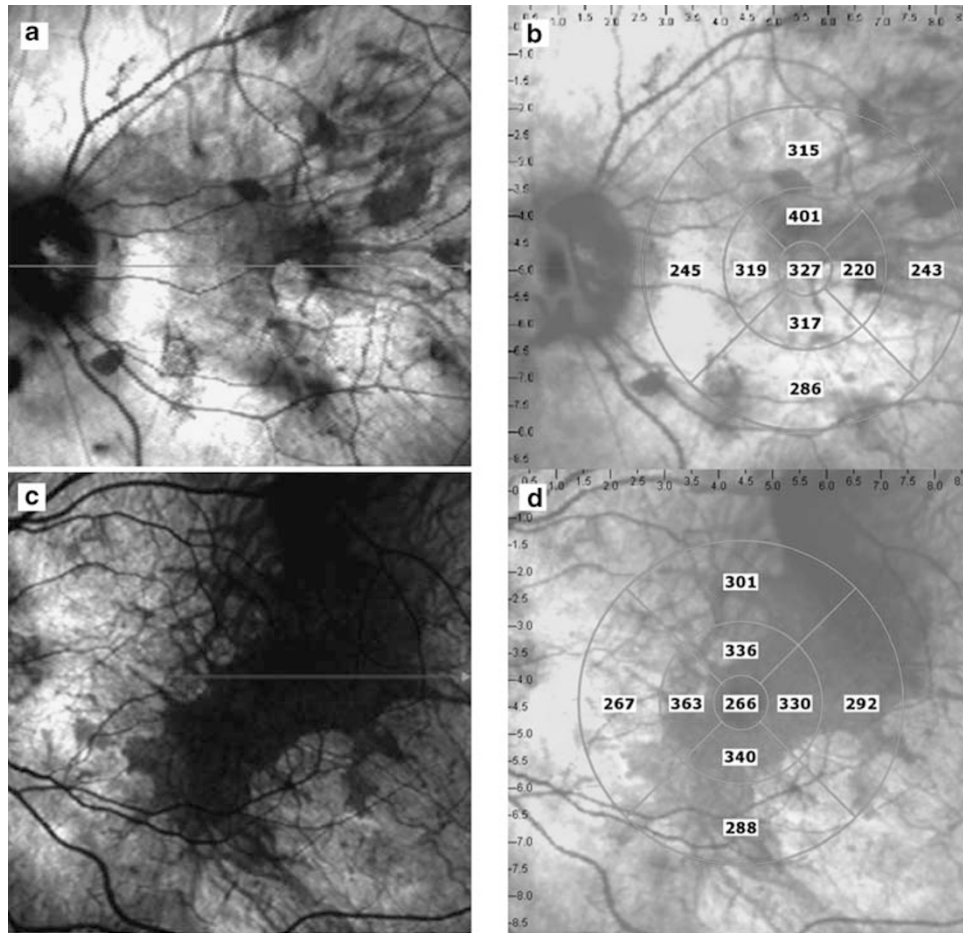
**Figure 1** Fundus photographs of right eyes in a 13-year-old (a), 44-year-old (b), and 63-year-old (c) choroideremia affected males that show areas of choroidal and RPE atrophy at an earlier stage (a), and more extensive atrophy of the choroid and RPE noted at later stages of the disease (b and c).

Of interest, six 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 (Figure 2c).



**Figure 2** Horizontal SD-OCT scans of the left eyes (a and b) and both eyes (c) of three affected males with choroideremia (ages, 62-, 44-, and 63-year-old, respectively), which show evidence of cystic macular oedema in the fovea and parafoveal regions (arrows). Black arrow head (c) shows a rosette-like retinal structure, whereas the white arrow head (b) shows retinal nerve fibre layer thickening temporal to optic nerve (ON). Patient (a) shows evidence of an epiretinal retinal membrane (between the two white lines).

In the entire study cohort, the mean  $\pm$  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 with the normative data provided by the manufacturer. No statistically significant differences in the central foveal subfield thickness were detected ( $P = 0.18$ ), whereas the mean retinal thickness in all of the four sectors of the inner circle (between 1- and 3-mm in diameter) was selectively thinner than normal, which was highly statistically significant (Table 2).



**Figure 3** Confocal scanning ophthalmoscopic images (a and c) and retinal thickness measured in early treatment diabetic retinopathy study-like zones (b and d) of the left eyes in two 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.

The central foveal subfield thickness in patients who had CME in at least one eye was  $327 \pm 62 \mu\text{m}$ , which was significantly thicker statistically when compared with normative data ( $P < 0.0001$ ; Figure 3).

### Discussion

OCT is a sensitive tool for detecting the presence of CME in various retinal diseases, which may be observed independent of leakage on fluorescein angiography.<sup>17,18</sup> Improvements in OCT technology have recently been introduced, including three-dimensional, high-resolution, and high-speed OCT that uses spectral-domain detection to provide increased resolution.

In our current study on patients with CHM, 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 as retinitis pigmentosa and Usher syndrome.<sup>19–21</sup> CME has also been described in patients with gyrate atrophy, another hereditary choroidal dystrophy.<sup>12,13,22</sup> Feldman *et al*<sup>22</sup> reported a patient with an epiretinal membrane and CME associated with gyrate atrophy of the choroid and retina. Vannas-Sulonen,<sup>23</sup> from a series of 21 patients with gyrate atrophy, observed that 9 (43%) had macular involvement, 1 (5%) with bilateral cystoid macular oedema confirmed by fundus fluorescein angiography.

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

Previous studies<sup>10,24</sup> that used time-domain OCT testing on CHM 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 ( $327 \pm 62 \mu\text{m}$ ) when compared with normative data ( $235 \pm 24 \mu\text{m}$ ). This finding could relate to the macular oedema itself or may be related to retinal gliosis as has been previously described by MacDonald *et al.*<sup>25</sup>

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 previous report by Rodrigues *et al.*,<sup>26</sup> who described that these rosette-like structures in CHM may be due to a defect in outer segment phagocytosis. A more recent report by MacDonald *et al.*,<sup>25</sup> described these rosette-like structures as formed by abnormal photoreceptors.

Our study showed that CHM 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 oedema. 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 CHM in future therapeutic trials.

## Summary

### What was known before

- To the best of our knowledge, no previous reports described the presence of cystic macular lesions in choroideremia patients.

### What this study adds

- Because of its notable prevalence (62.5%) in our 16 choroideremia patients, it would seem prudent to screen choroideremia patients by spectral-domain optical coherence tomography for the possible presence of cystic macular oedema and to identify those amenable to future treatment strategies for their macular oedema.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgements

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