Decreased Visual Acuity Associated With Cystoid Macular Edema in Neovascular Age-related Macular Degeneration

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Objective: To determine the prevalence and visual significance of cystoid macular edema (CME) in eyes with subfoveal neovascular age-related macular degeneration using optical coherence tomography (OCT).

Materials and Methods: The medical records of 61 consecutive patients initially seen with nondisciform subfoveal neovascular age-related macular degeneration were retrospectively reviewed. All patients underwent fluorescein angiography and OCT imaging. Eyes with intraretinal hyporeflective spaces in the macula in the OCT images were considered to have CME.

Results: Twenty-eight (46%) of 61 eyes demonstrated CME on the OCT images. The presence of CME and increased foveal thickness correlated with decreased visual acuity, but not with the duration of symptoms.

Twenty-six (93%) of 28 eyes with CME contained classic choroidal neovascularization, whereas 16 (48%) of 33 eyes without CME contained classic choroidal neovascularization.

Conclusions: Cystoid macular edema is a common finding in patients with choroidal neovascularization associated with age-related macular degeneration. The presence of CME and foveal thickening is associated with worse visual acuity in these patients. Cystoid macular edema is more common with choroidal neovascularization containing classic component. The OCT is a useful test to detect the presence of CME in these patients since CME may be difficult to identify on fluorescein angiogram.

Arch Ophthalmol. 2002;120:731-737

AGE-RELATED macular degeneration (AMD) is a major cause of legal blindness in people older than 65 years in the United States and Europe. The severe visual loss usually results from choroidal neovascularization (CNV). These new vessels are accompanied by fibrous tissue that can destroy central visual function over months to years.

The ophthalmoscopic signs of neovascular AMD include the presence of a green-gray lesion, subretinal blood, exudate, and often with what has been described as subretinal fluid. Another sign, cystoid macular edema (CME), has been infrequently reported in neovascular AMD since it may be difficult to detect angiographically in the presence of exudation from the CNV. While CME can be observed in some patients with neovascular AMD, the prevalence of CME and whether it may play a role in causing decreased visual acuity is not well characterized.

Macular structures can be studied in cross-section with optical coherence tomography (OCT), which allows imaging of a transverse scan of the retina with high resolution. Analogous to B-scan ultrasonography, OCT measures optical rather than acoustic reflection and provides noninvasive, noncontact cross-sectional imaging with a resolution of approximately 10 µm. Optical coherence tomography uses low-coherence interferometry to detect relative changes in reflectivity at optical interfaces. Optical coherence tomography has been used to study CME in various macular conditions such as uveitis, epiretinal membrane, vitreomacular traction, diabetic retinopathy, retinitis pigmentosa, and branch and central retinal vein occlusion. This study determined the prevalence of CME in eyes with neovascular AMD using OCT and evaluated whether CME may play a role in causing decreased visual acuity.

RESULTS

A total of 61 eyes of 61 patients met the inclusionary criteria for this study. The
PATIENTS AND METHODS

A retrospective review was performed on the medical records of 356 consecutive patients of one of us (C.A.T.). These patients underwent OCT imaging at Duke Eye Center, Durham, NC, for neovascular AMD as part of an institutional review board–approved study of OCT imaging of macular lesions from July 1, 1997, through December 31, 1999. The evaluation of patients with neovascular AMD included a comprehensive ophthalmic examination including a history of onset and duration of visual loss, slitlamp biomicroscopy, indirect ophthalmoscopy, stereoscopic fundus photography, and fluorescein angiography (FA). Best-corrected visual acuity was measured in a standard examination lane with an illuminated Snellen visual acuity chart.

Exclusionary criteria for the study eye were macular disease other than AMD, patient aged younger than 55 years, previous laser photocoagulation or surgical treatment for the CNV, disciform scar, and the absence of subfoveal CNV. Patients with inadequate FA or OCT imaging for analysis were excluded.

Fluorescein angiograms were reviewed (T.D.T., C.H.M., and C.A.T.) for inclusionary criteria and categorization. The FA reviewers were masked to visual acuity and OCT findings. Interpretation was based on the Macular Photocoagulation Study Group guidelines. Only eyes with subfoveal CNV as demonstrated on FA were included in the study. The total lesion size was determined from the FA. The size of any classic component present within the lesion was also determined from the FA and was represented as a percentage of the total lesion.

Optical coherence tomographic imaging of the macula was obtained for all patients (Zeiss Humphrey Systems, Dublin, Calif). Optical coherence tomographic images are depicted in a false-color scheme. Red and white represent areas of high optical reflectivity, blue represents lower relative reflectivity, and black represents the absence of reflectivity. Areas of intraretinal or subretinal fluid have low reflectivity. Multiple scans of the macula in the vertical and horizontal axes were performed for each eye. At least one of the scans included fixation. In cases where fixation was equivocal, a scan through the foveal depression was used. Each tomogram has a scan depth of 1.5 mm that is represented by 300 pixels. Scan lengths varied from patient to patient and ranged from 2.50 to 6 mm. Analyses of foveal thickness, subretinal fluid, and cystoid spaces were performed on OCT images transferred to Adobe Photoshop (Adobe Systems Inc, San Jose, Calif).

Eyes demonstrating cystoid spaces in the macula on OCT were considered to have CME and are shown in Figure 1 and Figure 2. Cystoid space was defined in this study as an intraretinal area of low reflectivity encompassing a minimal block of 4 × 5-contiguous pixels (Figure 1B asterisks). Eyes that did not demonstrate cystoid spaces are shown in Figure 3. The foveal center was determined on OCT by the presence of the foveal depression. In eyes in which the foveal depression was not visible owing to retinal thickening or the presence of subretinal fluid, the OCT video image was used to determine the most appropriate scan through the fovea.

Retinal thickness was defined as the distance between the inner and outer neurosensory retinal surfaces (Figure 3B arrows). Therefore, subretinal hyporeflective zones representing subretinal fluid were not considered retinal components (Figure 3B asterisk). Retinal thickness measurements were obtained from the single best tomogram of the foveal center from each eye.

The prevalence of subretinal fluid in neovascular AMD was determined using OCT imaging. An eye that contained a hyporeflective zone between the outer retinal surface and the retinal pigment epithelium on any OCT image was considered to have subretinal fluid. The prevalence of subfoveal fluid was also determined on OCT imaging. Eyes that contain a subfoveal hyporeflective zone were considered to have subfoveal fluid.

Statistical analysis of the data was performed using either SAS 8.0 for Windows (SAS Institute Inc, Cary, NC) or StatXact 4 for Windows (CYTEL Software Corp, Cambridge, Mass). Statistical methods included the Fisher exact test, Wilcoxon rank sum test, and the mean score test. All statistical tests were 2-tailed.

mean age of the patients was 75.9 years (age range, 58-90 years). There were 29 men and 32 women enrolled in the study. Mean duration of symptoms was 83.2 days (range, 1 day to 1 year). Visual acuity measurements ranged from 20/30 to 8/200. On biomicroscopic examination, all eyes contained drusen as well as signs of neovascular AMD such as serous or hemorrhagic detachment of the retinal pigment epithelium, subretinal fluid, subretinal lipid, or intraretinal or subretinal hemorrhage.

OCT FINDINGS

Using the aforementioned criteria, CME was found on OCT imaging in 28 (46%) of 61 eyes. The average age of patients with and without CME was 75.2 and 76.5 years, respectively. The mean duration of symptoms was 88 days for eyes with CME and 69 days for eyes without CME. There was no statistically significant difference in the age of the patient or the duration of the symptoms between the 2 groups. Nine (32%) of 28 eyes with CME and 11 (33%) of 33 eyes without CME were pseudophakic. The average foveal thickness of the neovascular AMD study eyes was 185 μm compared with an average foveal thickness of 103 μm in eyes from 17 age-matched individuals without ocular disease. Average foveal thickness was significantly greater in eyes with CME (264 μm) compared with eyes without CME (118 μm) (P < .001). The results are summarized in the Table.

VISUAL ACUITY AND FOVEAL THICKNESS

The mean visual acuity for all 61 patients was 20/110. The mean visual acuity in eyes with CME was 20/150 and in eyes without CME was 20/85. This difference in visual acuity between the 2 groups (Figure 4) was statistically significant (P = .004). Only 3 (11%) of 28 eyes with CME had visual acuity better than or equal to
20/60, while 9 (27%) of 33 eyes without CME had visual acuity better than or equal to 20/60.

The correlation between foveal thickness and visual acuity for all 61 eyes is shown in Figure 5. Linear regression analysis demonstrated foveal thickness was a significant predictor ( \( P = .02 \)) for logMAR visual acuity.

**VISUAL ACUITY AND SUBRETINAL FLUID**

The presence of submacular fluid had no significant influence on visual acuity. Submacular fluid was found in 33 (54%) of 61 total eyes, and subfoveal fluid was found in 14 (23%) of 61 total eyes. There was no statistical difference in the mean logMAR visual acuity in eyes with and without submacular or subfoveal fluid (20/110 in all groups).

**FA FINDINGS**

The FA characteristic of representative eyes with and without CME is shown in Figures 1C, 2C, and 3C. The average CNV size in all eyes was 5.4 Macular Photocoagulation Study (MPS) disc areas. The average CNV size in eyes with CME was 5.3 MPS disc areas and without CME was 5.6 MPS disc areas. There was no statistical significance between lesion size and visual acuity.

Eyes with CME had a proportionally greater area of classic CNV than eyes without CME (Figure 6). Classic CNV composed an average of 54% of the lesion in eyes with CME and 20% of the lesion in eyes without CME. Eyes with CME were also more likely to contain 100% classic CNV than eyes without CME. Eyes without CME were more likely to have 100% occult CNV (Table 1). There is a strong association between CME and classic CNV ( \( P < .001 \)). The association between visual acuity (logMAR) and CME remains significant ( \( P = .008 \)) when classic CNV is controlled for in a linear model.

**COMMENT**

Visual acuity in eyes with neovascular subfoveal CNV can vary widely, even among groups with similar angiographic components and duration of disease.\(^3,20\) Many factors have been associated with the loss of vision from
AMD. Although this study was retrospective and was limited to a few patients from a tertiary referral center, the number of patients was sufficient to demonstrate a correlation between both the presence of CME and retinal thickness with vision loss associated neovascular AMD.

The presence of CME in neovascular AMD may be difficult to identify angiographically in the setting of leakage from the CNV. Bressler et al have noted the presence of a "well-demarcated area of hyperfluorescence which represented pooling of fluorescein in a compartmentalized (loculated) space anterior to the choroidal neovascular leakage"7 in one third of the eyes with well-defined subfoveal CNV associated with AMD. The authors stated that the observed "loculated fluid" may conform to a pattern of typical CME, but may also pool within an area deep to the sensory retina in a shape that does not resemble CME.

In a retrospective review of 100 eyes with CNV secondary to AMD and concurrent CME, Soubrane et al8 detected CME in all forms of neovascular AMD, including classic CNV, occult CNV, pigment epithelial detachments, and disciform scars. The authors obtained photographs with blue monochromatic light and stereoangiographic FAs to detect the presence of CME. The authors stressed the importance of distinguishing fluorescein leakage due to CME from leakage due to CNV on FA. This study demonstrated that the presence of CME was not related to the duration of symptoms, nor to the location, extent, or type of CNV. The study also noted that the presence of CME was compatible with preservation of useful vision, especially in patients with occult CNV.

Similar to Soubrane et al,8 this study found no association between the duration of symptoms and presence of CME. However, unlike Soubrane et al, this study found a correlation between CME and decreased visual acuity. Using OCT techniques, this study demonstrated that CME was found in 46% of patients with nondisciform subfoveal CNV secondary to AMD. Both increased retinal thickness and the presence of CME were correlated with decreased visual acuity. A direct correlation between foveal thickness measured by OCT and visual acuity has also been reported in diabetic retinopathy11 and in epiretinal membrane.18 While retinal thickening is certainly not the only factor that leads to decreased visual acuity in patients with neovascular AMD, it may be a contributing factor. However, retinal thickening may

Figure 2. Example of an eye with age-related macular degeneration, subfoveal classic choroidal neovascularization (CNV), and cystoid macular edema. A, Color fundus photograph demonstrates the presence of a green-gray subretinal lesion with minimal hemorrhage. The arrow indicates the location and direction of the optical coherence tomographic (OCT) scan. B, The OCT image demonstrates loss of the foveal depression with cystoid spaces. C and D, Fluorescein angiography demonstrates a classic CNV with early hyperfluorescence, well-demarcated boundaries, and late leakage.
simply be a marker associated with retinal damage sufficient to decrease visual acuity.

Subretinal fluid identified on OCT was not included as a component of retinal thickening in this study. This delineation of components of retinal elevation over a CNV using OCT is different from the 1988 blue light photographic examination of the retina in attempts to discern retinal edema. The difference in macular examination techniques may have resulted in our differentiating subretinal fluid from CME in eyes with nondisciform CNV. Subretinal fluid, in contrast to retinal edema, was not associated with worse visual acuity in our group of patients. These results based on OCT imaging suggest that macular edema rather than subretinal fluid plays a greater role in causing decreased visual acuity in eyes with neovascular AMD.

In addition, unlike the biomicroscopic examination-based study, this study found a correlation between CME and the presence of FA classic CNV. Classic CNV composed a greater percentage of the total lesion in eyes with CME than eyes without CME. Lesions containing mainly classic CNV were more common in eyes with CME than eyes without CME. Conversely, lesions containing mainly occult CNV were more common in eyes without CME than eyes with CME. Thus, CME, a retinal structural finding, may be “hidden” in FAs by the hyperfluorescence of classic CNV, but is frequently found in classic CNV when nonangiographic structural imaging is used. Previous reports have demonstrated that visual acuity is worse in eyes with AMD that have

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 61)</th>
<th>Patients With CME (n = 28)</th>
<th>Patients Without CME (n = 33)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>75.9 (7.1)</td>
<td>75.2 (7.2)</td>
<td>76.5 (7.1)</td>
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<tr>
<td>Visual acuity</td>
<td>20/110</td>
<td>20/150</td>
<td>20/85</td>
</tr>
<tr>
<td>Percentage of classic component in entire lesion</td>
<td>36 (37)</td>
<td>54 (37)</td>
<td>20 (30)</td>
</tr>
<tr>
<td>Foveal thickness, m</td>
<td>185 (94)</td>
<td>264 (82)</td>
<td>118 (31)</td>
</tr>
<tr>
<td>100% Classic CNV (%)</td>
<td>10 (16)</td>
<td>8 (29)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>100% Occult CNV (%)</td>
<td>19 (31)</td>
<td>2 (7.1)</td>
<td>17 (52)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise noted. CNV indicates choroidal neovascularization.
predominantly classic subfoveal CNV than in eyes with occult CNV. This study found that an association between decreased visual acuity and the presence of CME exists even when classic CNV is controlled for in a statistical model. This raises the possibility that macular edema may play a role in contributing to the worse visual acuity found in eyes containing predominantly classic subfoveal CNV compared with eyes containing occult CNV. Additional studies will need to be conducted to test this hypothesis.

The cause of CME in patients with neovascular AMD is not well elucidated. Gass hypothesized that the extension of a CNV into the capillary-free zone in the macula may disrupt the photoreceptor-external limiting membrane complex and lead to CME. The capillary-free zone may be particularly at risk due to structural weakness of the external limiting membrane where Müller cell processes are reduced in number and due to the scarcity of retinal vessels to provide a pathway of return of the extracellular fluid to the intravascular compartment.

Disruption of retinal pigment epithelial metabolism has been implicated to alter the structure and permeability of the retinal capillary circulation. If this implication is true, the formation of CNV may disrupt retinal pigment epithelial metabolism and cause CME by altering the permeability of retinal capillaries. Alternatively, CME formation in neovascular AMD may be mediated by an inflammatory pathway as electron microscopic studies have identified inflammatory cells such as macrophages, fibroblasts, lymphocytes, and mast cells in CNV associated with AMD.

In some treatments of AMD, vision improvement may be associated with a decrease in retinal thickening. Monitoring retinal thickness may also be useful in evaluating efficacy of treatment. The OCT is a useful tool for detecting and monitoring the presence of CME. Further studies will be needed to determine the cause of CME in patients with neovascular AMD. Further studies will also be needed to determine if treatments such as surgical removal of CNV, restoring interaction with normal retinal pigment epithelium through macular translocation, photodynamic therapy, transpupillary thermotherapy, or injection of periocular steroid may improve vision by decreasing macular edema.

Submitted for publication July 24, 2001; final revision received February 12, 2002; accepted February 28, 2002.

This research was supported in part by the grant 5 R24 EY-13015-02, from the National Institutes of Health, Bethesda, Md; the Heed-Knapp Foundation Fellowship Award, Cleveland, Ohio (Dr Ting); the Adler Foundation, Rye, NY (Dr Meyer); and the McLaughlin Foundation, Toronto, Ontario (Dr Oh).

We thank Melissa Keller for excellent technical assistance and Katrina Winter for preparation of the manuscript and figures.

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