Ocular Risk Factors for Choroidal Neovascularization in Pathologic Myopia

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PURPOSE. To identify the risk factors for development of myopic choroidal neovascularization (mCNV), a major cause of visual impairment.

METHODS. Enrolled in the study were 23 consecutive patients with bilateral high myopia (axial length, ≥26.5 mm or refractive error, ≤8 D) and unilateral newly developed mCNV who presented to the Myopia Clinic, Osaka University Hospital. Spectral-domain optical coherence tomography (SD-OCT) showed that the fellow eyes had a normal macula. The parameters in the affected and fellow eyes were compared between the individual patients, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), refractive error, axial length, choroidal thickness (CT) (subfoveal, 1.5 mm superiorly and inferiorly), posterior staphyloma height 3 mm from the fovea, length of retinal pigment epithelium (RPE) curvature, and choroidal degeneration and lacquer crack formation, graded according to a published method.

RESULTS. The IOP, axial length, refractive error, and chorioretinal degeneration did not differ significantly. Affected eyes had a significantly higher lacquer crack grade (P < 0.05). The superior CT was not significantly different; the subfoveal and inferior CTs were significantly lower in the affected eyes (P < 0.05) and P < 0.001, respectively). The absolute value of the nasal posterior staphyloma height from the fovea was significantly greater in the affected eyes (P < 0.05), and the affected eyes had a significantly (P < 0.05) longer RPE curvature.

CONCLUSIONS. Choroidal thinning resulting from increased RPE/choroid curvature is a risk factor for unilateral mCNV. (Invest Ophthalmol Vis Sci. 2010;51:3721–3725) DOI:10.1167/iovs.09-3493

The incidence of high myopia varies by ethnic group and country; however, high myopia is very common in Japan¹ and China² and is moderately common in Latin³ or Caucasian⁴ Americans; altogether, the incidence ranges from 2% to 5.5% in subjects older than 40 years. Myopia is also a major cause of visual impairment in many countries.⁵–⁷ The development of myopic choroidal neovascularization (mCNV) characterized by serous retinal detachments and subretinal hemorrhage with fibrotic membrane formation is one of the major causes of visual loss. Intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA) is generally injected to treat mCNV; however, only 40% to 70% of patients achieve substantial visual improvement in the short term.⁹–¹¹ mCNV also causes progressive chorioretinal atrophy, and more than half of patients ultimately have visual acuity lower than 20/200 after several years.¹²¹³

The mechanism of mCNV is still controversial. Lacquer cracks are often present, and an association has been documented in angiographic studies.¹⁴¹⁵ However, the details of the association are not clearly understood. Curtin and Karlin¹⁶ reported the incidence of various myopia-related diseases based on axial length and reported that the incidence of temporal crescents, posterior staphyloma, and chorioretinal atrophy increased along with axial length elongation, but not the lacquer cracks or Fuchs’ spot (mCNV). They investigated the incidence of mCNV every 1 mm of axial length between 28.5 and 35.4 mm and reported that it ranged from 4.4% to 9.6% and did not show any consistent association with axial length. Based on this finding, we hypothesized that axial length elongation alone does not cause mCNV and that there may be other latent factors.

Investigating the risk factors for mCNV is important for understanding the pathogenesis and developing treatment options; however, myopic eyes have a variety of pathologic features that affect the posterior segment. For instance, the shape of the posterior staphyloma can vary greatly and there are 10 morphologic patterns.¹⁷ The degree of chorioretinal atrophy and lacquer crack also varies among patients. In addition, posterior staphyloma formation normally progresses with age. Thus, an interindividual comparison is difficult.

Spectral-domain optical coherence tomography (SD-OCT) obtains optimized images from the vitreous to the deep choroid. Because of the rapid scanning speed, SD-OCT can minimize the effect of ocular movement, allowing a more precise view of the retinal/choroidal curvature.¹⁸ In addition, SD-OCT has a high signal-to-noise ratio and can more easily scan the outer choroid, especially in patients with thinning. In the present study, SD-OCT was used to determine the morphologic risk factors for mCNV.

METHODS

Patients

The study included 23 consecutive patients who presented to the Myopia Clinic of Osaka University Hospital with bilaterally high myopia (axial length, ≥26.5 mm, or refractive error, ≤8 D) and unilateral newly developed mCNV diagnosed with fluorescein angiogram. The fellow eyes were confirmed to have no diseases such as foveoschisis, a macular hole, epiretinal membrane, CNV, or whitish round/oval atrophy on fundus examination and SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA). mCNV was defined as CNV associated with myopic changes. Eyes with CNV associated with punctuate inner choroidopathy or tilted disc syndrome were also excluded. The Institutional Review Board (IRB) of the Osaka University Hospital did not...
require that the protocol be approved. The study complied with the Declaration of Helsinki.

Examination
A masked technician performed all examinations including measurement of best corrected visual acuity (BCVA), intraocular pressure (IOP), refractive error, and axial length using partial optical coherence interferometry (IOLMaster; Carl Zeiss Meditec). IOP was measured by noncontact tonometry (Topcon, Tokyo, Japan). The SD-OCT scan patterns included the macular cube 512 × 128 combination protocol that generates a data cube in a 6-mm² grid by acquiring a series of 128 horizontal scan lines composed of 512 A-scans. A dome-shaped (convex) macula has been reported among eyes with pathologic myopia19; however, no such eyes were observed in this group of patients.

Fundus Changes and Grading
Color fundus photographs were taken and used to observe myopic degeneration or lacquer crack grading. Myopic degeneration was quantitated according to the method of Avila et al.,12 on a grading scale of M0 to M5, with grade M0 indicating a normal-appearing posterior pole; grade M1, choroidal pallor and tessellation; grade M2, choroidal pallor and tessellation with posterior pole staphyloma; grade M3, choroidal pallor and tessellation with posterior staphyloma and lacquer cracks; grade M4, choroidal pallor and tessellation with posterior pole staphyloma, lacquer cracks, and focal areas of deep choroidal atrophy; and grade M5, large geographic areas of deep choroidal atrophy at the posterior pole. Lacquer cracks were evaluated with color fundus photographs and FA. The morphology of the lacquer cracks was classified as two types: linear or crisscrossing, according to our previous retographs and FA. The morphology of the lacquer cracks was classified as two types: linear or crisscrossing, according to our previous report.13 Grading was defined as 0, indicating no lacquer cracks; 1, only linear horizontal or vertical lacquer cracks; and 2, crisscrossing lacquer cracks with or without linear cracks.

Measurement of Retinal/Choroidal Morphologic Parameters
Two independent clinicians masked to the presence or absence of mCNV used SD-OCT to measure the choroidal architectural parameters. Each examiner performed one measurement, and the average of the two measurements was recorded and analyzed. The printout values of the horizontal length, which is affected by the axial length, in the long eyes were lower than the true values. In another words, the actual scan length was longer than 6 mm in the axes of these long eyes. This difference was adjusted by a formula previously reported20 with a slight modification based on the recommendation from Carl Zeiss Meditec. The formula used was:

\[
\text{Actual size} = 3.5 \times 0.013062 \times (\text{AL} - 1.82) \times (\text{size in OCT})
\]

where AL represents the axial length.

The choroidal thickness was measured by applying the software scale at the fovea, 1.5 mm superiorly and 1.5 mm inferiorly (Fig. 1). The retinal and choroidal thicknesses were measured according to a published method.21 Briefly, retinal thickness was defined as the vertical distance from the retinal pigment epithelial (RPE) cells (the outermost hyperreflective line at the retina–choroid interface) to the retinal surface. The choroidal thickness was defined as the distance from the RPE line to the hyperreflective line posterior to the large vessel layers of the choroid. All eyes showed this clear choroidal–scleral interface because of choroidal thinning. If the retina/choroid was tilted, the distance was always measured to the right of the RPE line.

The angle of the posterior staphyloma in relation to the horizontal plane was also evaluated in the OCT image. The vertical distance from the subfoveal RPE line to 3 mm nasal, temporal, superior, and inferior—namely, the posterior staphyloma height—was measured from the B-scan including the fovea (Fig. 1). The relative height of the posterior staphyloma was expressed as a positive number in cases in which the edge was located anteriorly. This value is advantageous because it represents the vertical distance from the fovea and the posterior or anterior location in relation to the fovea. The absolute height of this posterior staphyloma also was used in some specific analyses (Fig. 2).

Because Cirrus HD-OCT does not provide the software to measure the length of the curve in the image, we obtained an approximate value by (1) connecting the points along the RPE line, the curvature of which was divided into quarters (C1–C4, Fig. 1), (2) adding the length of the four lines, and (3) adjusting by multiplying with the ratio: the true B-scan length obtained with the previously described formula ($\mu$m)/6000 ($\mu$m).

Statistical Analysis
We used the paired t-test and signed rank test to determine statistical significance (JMP ver. 7.0 software; SAS system Inc., Cary, NC). The generalized estimating equation (GEE) based on a binary logistic regression were also used (SAS ver. 9.1 for Windows; SAS Institute Inc.). In any case, $P < 0.05$ was considered significant.

RESULTS
The patient demographic data are shown in Table 1. There were no significant differences in axial length, refractive error, and IOP. The myopic degeneration grade was divided into two groups (0–2 and 3–5), as was the lacquer grade (0 or 1, and 2), and the signed rank test was performed. The myopic degeneration grade was nonsignificant ($P = 0.22$); however, the rate of highest lacquer crack grading (grade 2) was significantly higher in the affected eyes ($P < 0.01$). The mean logMAR value in the affected eyes was 0.52 and in the fellow eyes, 0.16.

When the choroidal thickness was compared bilaterally (Table 2), the choroid was found to be thinner at the fovea and inferiorly ($P < 0.05$ and $P < 0.001$, respectively). The superior choroidal thicknesses were similar ($P = 0.23$). The average choroidal thickness of all three points was less in the involved eye ($P < 0.01$).
We attempted to identify an association between the position of the posterior staphyloma and the development of mCNV (Table 2). There was no association between the relative height of the edge of the posterior staphyloma nasal, temporal, superior, and inferior to the fovea and the development of mCNV. When we used an absolute number, the nasal height ($P < 0.05$) and the average of all four posterior staphyloma heights ($P < 0.01$) were significantly greater in eyes with mCNV. The length of the nasal–posterior RPE curvature was significantly ($P < 0.05$) greater in mCNV; however, the superior–inferior RPE curvature was not.

We analyzed all eyes and performed logistic regression analysis to detect the factors that had the most influence on the development of mCNV. The generalized estimating equation (GEE) showed that the inferior choroidal thickness had the greatest correlation with the development of mCNV, followed by the nasal posterior staphyloma height and nasal–temporal RPE curvature length. The logistic regression model suggested that inferior choroidal thickness was the most important factor with the greatest odds ratio for the development of mCNV (Table 3).

DISCUSSION

The development of mCNV has been generally believed to involve axial length elongation, simply because axial length is elongated in highly myopic eyes. However, it is questionable whether elongated axial length is the sole contributing factor, because the incidence of mCNV was similar in eyes with axial lengths ranging from 27 to 32 mm. In that study, mCNV did not develop in eyes with an axial length exceeding 33 mm. Therefore, factors other than axial length must contribute to mCNV. In the present study, the axial length and refractive error did not differ between the affected eyes and the fellow eyes, indicating that these factors were not the major risk factors in this setting.

An increased risk of mCNV in the unaffected fellow eyes was reported in patients with newly developed mCNV. In a retrospective study of 218 patients (325 eyes) with pathologic myopia, the incidence of CNV was 34.8% in the fellow eyes of patients with preexisting CNV in the other eye compared with 6.1% in patients with no previous CNV. Bilaterally, healthy eyes can be an ideal control group; however, there are many factors that may affect the development of mCNV (i.e., age, degree of myopia, refractive error, axial length, degree and shape of posterior staphyloma, and others). It is challenging to equalize the baseline characteristics and adjust for accurate analysis.

Lacquer crack was confirmed as a risk factor for mCNV. They are mechanical cracks at the RPE/Bruch’s membrane, indicating the presence of mechanical stress at the RPE/Bruch’s membrane level. Not only axial length elongation but...
TABLE 2. Intraindividual Comparison of Choroidal Morphologic Parameters between Eyes with mCNV and the Fellow Eyes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Involved Eye (A) (Range)</th>
<th>Fellow Eye (B) (Range)</th>
<th>A – B (95% CI)</th>
<th>P (Two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroidal thickness, μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subfoveal</td>
<td>52 (27.5–119.5)</td>
<td>67 (31.5–111.0)</td>
<td>−16 (−29– −2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Superior</td>
<td>67 (36.5–107.5)</td>
<td>74 (29.5–110.5)</td>
<td>−7 (−19–5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Inferior</td>
<td>52 (12.5–81.5)</td>
<td>69 (46.5–116.5)</td>
<td>−18 (−27–−9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average of three choroidal thickness</td>
<td>57 (37.9–95.9)</td>
<td>70 (36.7–112.0)</td>
<td>−14 (−22–−4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relative posterior staphyloma height, μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>594 (136–1181)</td>
<td>495 (−4–1041)</td>
<td>99 (−22–220)</td>
<td>0.11</td>
</tr>
<tr>
<td>Nasal</td>
<td>325 (135–1186)</td>
<td>325 (−317–1281)</td>
<td>1 (−168–167)</td>
<td>0.99</td>
</tr>
<tr>
<td>Superior</td>
<td>748 (−261–1407)</td>
<td>664 (−20–1473)</td>
<td>84 (−57–225)</td>
<td>0.23</td>
</tr>
<tr>
<td>Inferior</td>
<td>181 (−588–885)</td>
<td>247 (−269–1049)</td>
<td>−66 (−216–84)</td>
<td>0.58</td>
</tr>
<tr>
<td>Average of four heights</td>
<td>462 (−107–883)</td>
<td>432 (113–821)</td>
<td>30 (50–110)</td>
<td>0.45</td>
</tr>
<tr>
<td>Absolute posterior staphyloma height, μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>594 (136–1181)</td>
<td>496 (24–1041)</td>
<td>98 (−23–220)</td>
<td>0.11</td>
</tr>
<tr>
<td>Nasal</td>
<td>508 (150–1186)</td>
<td>380 (56–1281)</td>
<td>128 (1–257)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Superior</td>
<td>771 (196–1407)</td>
<td>666 (20–1472)</td>
<td>105 (−34–244)</td>
<td>0.13</td>
</tr>
<tr>
<td>Inferior</td>
<td>296 (55–885)</td>
<td>293 (25–1049)</td>
<td>4 (−83–90)</td>
<td>0.93</td>
</tr>
<tr>
<td>Average of four parameters</td>
<td>542 (328–883)</td>
<td>458 (113–821)</td>
<td>84 (−28–139)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RPE curvature length, μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior-inferior</td>
<td>6111 (5859–6634)</td>
<td>6096 (5954–6238)</td>
<td>15 (−25–55)</td>
<td>0.44</td>
</tr>
<tr>
<td>Nasal-temporal</td>
<td>6175 (6024–6385)</td>
<td>6078 (5733–6426)</td>
<td>97 (28–166)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

also posterior staphyloma expansion are major causes of mechanical stress. However, posterior staphyloma has large interindividual morphologic variations, and it has been difficult to quantify the shape by using conventional methods. Others have proposed posterior staphyloma grading using ultrasonography, well correlated with macular disease.23 However, ultrasonography is inadequate for presenting detailed morphologic variations.

In eyes with mCNV, the subfoveal and inferior choroid was significantly thinner than in the fellow eyes. OCT and partial coherence interferometry have shown that the normal choroidal thickness in nonmyopic eyes is an average of ~300 μm.24–26 Choroidal thinning is a hallmark of high myopia27–29; however, the present study showed that choroidal thinning is more prominent in eyes with mCNV. It is unknown how choroidal thinning is associated with mCNV development. One mechanism is that the choroidal vessels supply retinal oxygen to the outer retina. The outer retina is believed to be a major source of vascular endothelial growth factor (VEGF), and the choroidal thinning at the fovea may lead to outer retinal hypoxic changes via factors such as hypoxia-inducible factor (HIF),30 resulting in VEGF secretion at the fovea. VEGF strongly induces CNV,31 which is also confirmed by the clinical finding that bevacizumab, an anti-VEGF monoclonal antibody, shrinks CNV and improves vision.9–11 VEGF secretion is stimulated at the RPE level by mechanical stretching in vitro.32 Also the stretch-induced HIF-1 and consequent VEGF upregulation through the phosphatidyl 3-kinase (PI3K) pathway has been shown in heart tissue.33 Thus, we hypothesized that choroidal thinning probably results from enhanced mechanical stretching, a major cause of mCNV.

We also found that the absolute value of the height of the nasal posterior staphyloma and the average height of the posterior staphyloma in four directions were significantly greater. The data suggest that the RPE curve is steeper in relation to the horizontal plane, resulting in a longer distance. This feature agrees with another finding that the length of the horizontal RPE curvature was significantly greater in the eyes with mCNV. This evidence indicates that the posterior staphyloma is steeper and perhaps more protruding in eyes with mCNV. We believe this is the main cause of choroidal thinning in affected eyes and is caused by more mechanical stress related to stretching at the macula. This conclusion agrees with the finding of more prominent lacquer cracks in the eyes with mCNV.

In summary, we found that inferior choroidal thinning is a primary contributor to the development of mCNV. Choroidal thinning, the extent of the RPE curve, and posterior staphyloma protrusion seem to be closely related. However, stepwise regression analysis indicated that these parameters are not totally related. Other factors also may affect these. This study has several limitations requiring careful interpretation. First, the reproducibility of choroidal thickness measurements has not been well established. Second, this was a retrospective study and did not provide an accurate number of the prediction. In the future, this study will be extended to determine how these pathologic changes are actually related to mCNV development.

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**References**


