INTRODUCTION

An epiretinal membrane (ERM) is a fibrocellular proliferation that develops on the surface of the internal limiting membrane, resulting in retinal wrinkling and distortion. Pars plana vitrectomy and membrane peeling is a standard surgical treatment for patients with symptomatic visual disturbances due to an ERM. Visual acuity improves in many patients after membrane peeling, whereas it has been reported that metamorphopsia can still be present, even if an ERM was successfully removed with an improvement in visual acuity. For evaluation of metamorphopsia, the preferential hyperacuity perimeter (PHP) in addition to the Amsler grid can be used as a reliable tool for diagnosing central visual field defects in patients with macular diseases. The aim of this study was to evaluate the spectral-domain optical coherence tomography (OCT) findings based on the PHP as markers for metamorphopsia after surgery for idiopathic ERM.

MATERIALS AND METHODS

This prospective study was designed to include consecutive patients who underwent vitrectomy with ERM removal for idiopathic ERM. All patients had disturbing metamorphopsia before surgery, which was reflected in distorted and non-uniform lines in the Amsler grid. The patients were classified into two groups based on the defect of hyperacuity by PHP: hyperacuity defect (n = 18 eyes) and hyperacuity intact (n = 22 eyes). There was no difference in age, gender, duration of symptoms, and visual acuity. The average macular thickness and inner nuclear layer thickness in the hyperacuity defect group was thicker than the hyperacuity intact group (P = 0.041 and P = 0.045, respectively). A disrupted photoreceptor layer was more common in the hyperacuity defect group compared with the hyperacuity intact group (P = 0.001).

Conclusion: With regard to metamorphopsia, a hyperacuity defect after epiretinal membrane surgery was associated with inner nuclear layer edema and photoreceptor disarrangement.

KEYWORDS: Epiretinal membrane; Metamorphopsia; Preferential hyperacuity perimeter; Spectral-domain optical coherence tomography; Surgery
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the Amsler grid. Patients with secondary epiretinal formation due to trauma, retinal vascular disorders, retinal detachment, or previous surgery, and patients with other ocular pathologies that could interfere with the functional results were excluded. We also excluded eyes for which accurate OCT images could not be obtained. Patients gave written consent to the described surgical procedure and the protocol was approved by the institutional review board of the hospital. All of the patients underwent a standard 23-gauge vitrectomy performed by the same retinal surgeon. After the core vitrectomy, a portion of the ERM, 2-3 disc diameters in size, was peeled with end-gripping forceps without the additional use of dyes. No gas or air tamponade was used. If the eyes were phakic, combined cataract surgery was performed for preventive purposes.

Three months after surgery, the best-corrected visual acuity, PHP, Amsler grid test, and OCT were assessed. All best-corrected visual acuity measurements were converted to the logarithm of the minimum angle of resolution (logMAR) equivalents before performing statistical analysis. A Cirrus SD high-definition OCT (Carl Zeiss Meditec AG, Jena, Germany) was obtained using macular cube (512 × 128) scans under monitoring the central fixation by a single experienced physician. The central 1-mm subfield thickness and the average macular thickness were automatically measured using Cirrus analysis software (version 3.0). To measure the thickness of the inner retinal layers, horizontal and vertical sections 1000 um from the fovea were used and the average was calculated. The retinal layer borders were determined based on the refractive differences between the inner retinal layers using the macular segmentation algorithm for OCT, as developed by Ishikawa et al. and Tan et al. The raw data from OCT were exported and analyzed with a computer program developed to measure automatically the segmentation of retinal layers. A Gaussian smoothing filter and a nonlinear smoothing filter were applied to image for further smoothing and edge enhancement. Then the inner nuclear layer (INL), outer nuclear layer (ONL), and outer plexiform layer (OPL) boundary were identified using the intensity profile of a single axial from the filtered image. The thickness of INL and ONL, defined as the width of the lowest black-scattering and lowest black-reflection layers, and the thickness of OPL, defined as the width of the highly reflective line between the INL and ONL, were measured. To improve the accuracy of segmentation, a progressive refinement procedure was applied to extract the boundaries between layers. The INL, OPL, and ONL thickness measurements were carefully obtained at points where there were obvious differences between the black reflective line and the highly reflective line.

The thickness measurements of the inner retinal layers were performed manually using the electronic calipers of the OCT. Figure 1 showed the original OCT image and an overlay of the detected boundaries on the OCT image. The status of the photoreceptor line was classified as intact or disrupted based on the integrity of the junction between the inner and outer segments of the photoreceptors. An intact photoreceptor line was defined as a continuous hyperreflective line corresponding to the photoreceptor inner segment/outer segment junction. A photoreceptor line disruption was defined as a hyporeflective disruption of the hyperreflective photoreceptor inner segment/outer segment junction.

The PHP (ForeseePHP 2.05; Notal Vision, Tel Aviv, Israel) was performed with the patient’s distance refraction adjusted to a near distance of 50 cm on a standard screen. The stimulus is a dot deviation signal flashed in a random order. By using artificial distortions of different magnitudes, the algorithm determines the depth of the visual field defect. The patient was asked to touch the touch-sensitive screen at the location of any such abnormalities. By these means, any existing visual field defects detected on the signal were recorded immediately when the stimulus was projected on a lesion. The participant’s responses were recorded and automatically analyzed by a predesigned algorithm. By repeating the stimulus projection, the reliability of the patients’ responses was determined by the PHP and the presence of the visual field defect, and

FIGURE 1 (A) Example of macular horizontal section by optical coherence tomography through a macular cube scan. Measurements of the inner retinal layer on the yellow vertical line (1000 um from the fovea) performed using electronic calipers. (B) Aligned image with boundary of retinal layers identified by the automated computer program in the same patient.
focal distortion similar to choroidal neovascularization-induced metamorphopsia were analyzed.

Comparison of data was performed using a Wilcoxon two-sample test, Chi-square test, or Mann-Whitney U test, with Bonferroni’s correction, as appropriate. Multivariate linear regression analyses were undertaken using OCT findings as dependent variables. Statistical analysis was performed using SPSS software (version 12.0 for Windows; SPSS Inc., Chicago, Illinois, USA). A P-value < 0.05 was considered significant.

RESULTS

Forty eyes of 40 patients were enrolled in the study. No intra-operative complications were encountered in this case series. The eyes were categorized into 2 groups according to the hyperacuity defects of the PHP, as follows: hyperacuity defect (18 patients, 18 eyes); and hyperacuity intact (22 patients, 22 eyes). The patients in the hyperacuity defect group exhibited metamorphopsia on the Amsler chart and patients in the hyperacuity intact group exhibited no metamorphopsia on the Amsler chart. One patient with a discrepancy on the PHP and Amsler grid test was excluded. The mean (± SD) age of the patients was 64.5 ± 6.8 years (range, 59–74 years), and the study group included 16 men and 24 women.

The demographic data (gender, age, and visual acuity) were not significantly different between the two groups (P > 0.05). Central subfield thickness, ONL thickness, and OPL thickness by OCT were not different between the two groups. The average macular thickness and INL thickness in the hyperacuity defect group were thicker than the hyperacuity intact group significantly (P = 0.041 and P = 0.045, respectively). The distribution of the status of the photoreceptor line was different between the two groups. In the hyperacuity defect group, all 18 eyes showed a disrupted and irregular photoreceptor line. In contrast, 16 of 22 eyes showed an intact photoreceptor line and the remaining 6 eyes showed a disrupted photoreceptor line in the hyperacuity intact group (P = 0.001). After correction for the status of the photoreceptor line, INL thickness was still different according to the hyperacuity defect (multivariate regression analysis, P = 0.040). The statistical significance on average macular thickness by hyperacuity defect was borderline (P = 0.055). The patient characteristics and OCT findings were shown in Table 1.

In addition, the Cirrus OCT provided two patterns of topographic maps (internal limiting membrane [ILM] and retinal pigment epithelium [RPE]), which showed the three-dimensional configuration of the surface. All of the patients in the two groups had a smooth surface of the RPE map. All 22 patients in the hyperacuity intact group had a smooth surface of the ILM map; however, 14 of 18 eyes in the hyperacuity defect group showed relative distortion of the ILM map. The representative cases were shown in Figures 2 and 3.

DISCUSSION

ERM surgery improved not only visual acuity, contrast sensitivity, and central macular thickness, but also metamorphopsia. The vision-related quality of life was significantly associated with the severity of metamorphopsia before and after surgery. Therefore, remaining metamorphopsia after surgery is thought to

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperacuity defect group (n = 18)</th>
<th>Hyperacuity intact group (n = 22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.3 ± 4.7</td>
<td>61.8 ± 7.9</td>
<td>0.528a</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>8:10</td>
<td>8:14</td>
<td>0.677b</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>19.1 ± 9.2</td>
<td>15.3 ± 5.2</td>
<td>0.156c</td>
</tr>
<tr>
<td>Pre-operative visual acuity (logMAR)</td>
<td>0.45 ± 0.09 (0.3–0.6)</td>
<td>0.36 ± 0.33 (0.3–0.6)</td>
<td>0.731a</td>
</tr>
<tr>
<td>Post-operative visual acuity (logMAR)</td>
<td>0.36 ± 0.24 (0.1–0.5)</td>
<td>0.20 ± 0.15 (0–0.4)</td>
<td>0.189c</td>
</tr>
<tr>
<td>Central subfield thickness (μm)</td>
<td>334.5 ± 96.7 (348–521)</td>
<td>410.5 ± 64.0 (235–489)</td>
<td>0.383d</td>
</tr>
<tr>
<td>Average macular thickness (μm)</td>
<td>348.5 ± 26.0 (321–422)</td>
<td>321.6 ± 8.5 (318–380)</td>
<td>0.041d</td>
</tr>
<tr>
<td>INL thickness (μm)</td>
<td>65.5 ± 10.4 (47–98)</td>
<td>43.5 ± 14.8 (30–50)</td>
<td>0.045e</td>
</tr>
<tr>
<td>OPL thickness (μm)</td>
<td>27.1 ± 4.0 (25–34)</td>
<td>26.0 ± 3.2 (22–28)</td>
<td>0.350f</td>
</tr>
<tr>
<td>ONL thickness (μm)</td>
<td>147.4 ± 76.8 (95–259)</td>
<td>135.8 ± 56.9 (80–210)</td>
<td>0.455f</td>
</tr>
<tr>
<td>Photoreceptor layer integrity (intact: defect)</td>
<td>0:18</td>
<td>16:6</td>
<td>0.00g</td>
</tr>
</tbody>
</table>

logMAR, logarithm of the minimum angle of resolution; INL, inner nuclear layer; ONL, outer nuclear layer; OPL, outer plexiform layer,

*aMann-Whitney U test, bChi-square test, cWilcoxon two-sample test.
be the main cause leading to subjective visual impairment despite visual acuity improvement.

The PHP, based on the visual phenomenon of hyperacuity, was specifically designed for a reproducible and quantitative assessment of metamorphopsia to replace the Amsler grid test in patients with age-related macular degeneration. It has also been reported that PHP is sensitive to detecting metamorphopsia in patients with ERM. Hyperacuity is defined as the ability to perceive a minute difference in the relative spatial localization of two or more visual stimuli. When a geometric shift in photoreceptor location occurs, such as retinal pigmentary epithelium elevation in macular disease, a hyperacuity defect may be perceived at a different distorted location from the true location in space and is recorded by the PHP.

In the present study, INL thickness at parafovea and average macular thickness differed significantly between the hyperacuity defect group and the hyperacuity intact group. Even correcting the status of the photoreceptor, the statistical significance was maintained in INL thickness. The foveola contains only a photoreceptor cell body, and the parafovea surrounding a 1-mm foveolar center contains a multi-layered retina. The central subfield thickness and the average macular thickness were less significant by the defect of hyperacuity. Thus, it was indicated that remaining macular edema, especially INL layer edema at parafovea was associated with a hyperacuity defect after surgery. We suggest that hyperacuity defects are associated with the remaining macular edema, resulting in insufficient synaptic junctions and photoreceptor disarrangement, and interfere with the one-to-one correspondence between the retinal image and the central nervous system, leading to metamorphopsia. Watanabe et al. also reported that metamorphopsia induced by ERM before surgery may be related to the edematous areas of the INL detected with OCT. Our findings suggested that edema of the INL is associated with metamorphopsia before and after ERM surgery. The simplest retinal circuit is a three-neuron chain, as follows: photoreceptor to bipolar cell to ganglion cell. The INL contains the cell bodies

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**FIGURE 2** (A,B) The results of preferential hyperacuity perimeter, and (C,D) macular horizontal section by optical coherence tomography. (A,C) There is no hyperacuity defect on preferential hyperacuity perimeter. Optical coherence tomography showed an intact photoreceptor line and the thickness of the inner nuclear layer was 29 μm. (B,D) Preferential hyperacuity perimeter showed multiple hyperacuity defects. Optical coherence tomography showed a disrupted photoreceptor line and the thickness of the inner nuclear layer was 40 μm.
of horizontal, bipolar, amacrine, and Muller cell bodies. Cells take a signal from photoreceptor from the outer retina to the inner retina and the major synaptic layer was the IPL. The exact cause of a relationship between cellular changes in the INL and metamorphopsia has not been elucidated.

The ILM map findings were another noteworthy finding in the current study. Although quantification of distortion by an ILM map is difficult, an ILM map in the hyperacuity defect group tended to show an uneven irregular surface. This finding was in line with the previous reports. Theoretically, a hyperacuity defect is related to the outer retinal layers, including the RPE. However, smoothness of the inner retinal surface is also important in hyperacuity defects and metamorphopsia.

The limitations of the present study included a relatively small sample size, measurements based only on vertical and horizontal cross sections, inclusion of erroneous values based on measurements of layers with indistinct signals, and manual measurement using electronic calipers. We evaluated the patients 3 months post-operatively and didn’t consider pre-operative findings. Also, further recovery of visual or anatomical impairment may be expected after a longer follow-up period. Future studies with a large sample size and longer follow-up period are needed.

In summary, a hyperacuity defect, reflecting metamorphopsia, may be associated with INL layer edema and photoreceptor disarrangement detected with OCT.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES
