〈Regular Article〉

Evaluation of photoreceptors in amblyopic eyes using swept-source optical coherence tomography

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ABSTRACT　**Background**: While the foci responsible for amblyopia are thought to be in the cerebral cortex, it remains controversial whether the retina of amblyopic patients is completely normal. The present study measured foveal bulge (FB) using optical coherence tomography (OCT) and the longitudinal reflectivity profiles (LRP) method with ImageJ in patients with unilateral amblyopia in order to examine the effect of amblyopia on photoreceptor cell normality.

Methods: This study enrolled 48 patients (6.8 ± 2.3 years old) with unilateral amblyopia and 29 healthy control children (7.6 ± 3.0 years old) with no history of ocular disease. Macular 3D scan images were obtained using the DRI OCT-1 Atlantis (TOPCON). The FB vertex and foveal pit (FP) positions were then identified using analysis software to evaluate the positional relationship. In addition, FB height was quantified using the LRP method.

Results: The logarithm of the minimum angle of resolution (logMAR) was significantly higher in amblyopic eyes as compared to fellow or control eyes ($p < 0.001$). The FB position was deviated nasally relative to the FP in 14.6 % of the amblyopic eyes, in 0.4 % of the fellow eyes, and in 3.6 % of the control eyes, with others located on the FP. The mean deviation of the FB from the FP was 3.0 ± 7.1 μm in the amblyopic eyes, 2.2 ± 6.4 μm in the fellow eyes, and 0.8 μm in the control eyes. FB heights in the horizontal and vertical sections were 85.4 ± 7.9 μm and 87.5 ± 8.5 μm in the amblyopic eye, respectively, with these values not significantly different from those determined for the fellow or control eyes. Multiple regression analysis was used to evaluate the independent variables of age, logMAR, refractive error, axial length, and central retinal thickness with respect to the dependent variables of the FB height, which showed no significant association between the variables.

Conclusions: There was no significant difference between the amblyopic eyes and the

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fellow or control eyes for the FB position and height, which is considered to reflect the normality of photoreceptors. Our results suggest that amblyopia does not affect the normality of photoreceptors.
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Key words：Amblyopia, Foveal bulge, Optical coherence tomography, Photoreceptor, ImageJ

INTRODUCTION

The pathogenesis of amblyopia has been thought to be based on morphological and functional abnormalities in the visual cortex and lateral geniculate nucleus[1–4]. However, it has yet to be definitively determined whether dysfunction or structural abnormality of the retina is present in amblyopia[5]. In conjunction with the recent increased use of optical coherence tomography (OCT), there have been a number of studies reporting on the retinal microstructure of amblyopic eyes[6–8]. Our previous studies demonstrated that there were no characteristic findings for the retinal thickness and retinal vascular structure in amblyopic eyes, with these results appearing to support a previous theory that there is no structural abnormality of the retina in amblyopia[9–11].

When using OCT, the previous studies of the retinal structure in amblyopic eyes have primarily focused on the retinal thickness or vascular structure[9–11]. In contrast, only a few studies have examined the foveal bulge (FB) in amblyopic eyes[12, 13]. The FB is a bulge in the fovea of the ellipsoid zone, and is considered to be a high-density site of photoreceptor cells. In addition, the FB has been shown to be significantly associated with the visual acuity and is considered to be an indicator of photoreceptor normality[14, 15]. Furthermore, it has been recently reported that the use of longitudinal reflectivity profiles (LRP) utilizing ImageJ for OCT images is an objective method for the evaluation of the FB[16]. To the best of our knowledge, there have been no reports on the evaluation of the FB in amblyopic eyes when using the LRP method.

In this study, we evaluated the FB in amblyopic eyes using OCT and the LRP method with imageJ and then examined the effect of amblyopia on FB.

MATERIALS AND METHODS

This study evaluated 96 eyes of 48 patients with unilateral amblyopia (mean age 6.8 ± 2.3 years). Unilateral amblyopia was caused by strabismus, anisometropia, or both. The best-corrected decimal visual acuity of the amblyopic eye at the time of the OCT measurement was 0.9 or less, with a best-corrected decimal visual acuity of the fellow eye of 1.0 or more. The presence or absence of prior amblyopia treatment did not affect inclusion in the current study. The study also included 29 eyes of healthy control children, who were age-matched to the amblyopes with a mean age of 7.6 ± 3.0 years. The OCT measurements were performed in both eyes of the patients with amblyopia and in the right eye of the control children.

Swept-source OCT (DRI OCT-1 Atlantis, Topcon Corporation, Tokyo, Japan) was used for the measurement. A 3D scan was employed for imaging that covers a 12 × 9 mm area with a resolution of 512 × 256 A-scans. The FB's position relative to the foveal pit (FP) from both the horizontal and vertical tomographic images and the height of the FB were assessed.

For the analysis, after taking the 3D scan images, the deepest position of the FP was identified from the B scan images using EnView (Topcon Corporation, Tokyo, Japan), which is the analysis software installed in the DRI OCT-1 Atlantis. We then evaluated the position of the FB relative to the FP. In addition, after correction for the magnification by the axial length, the distance from the FP to the vertex of the FB was measured using the number of A scan images and then converted to microns. The distance between the vertex of the FB and the Bruch's membrane was quantified as the height of the FB, and then analyzed by LRP using ImageJ[16] (Fig. 1).

Statistical analysis was performed by comparing the heights of the FB between the groups. The comparisons included the amblyopic eye vs. the fellow eye, and the amblyopic eye vs. the control eye (amblyopic eye vs. fellow eye: paired-samples t-test, amblyopic eye vs. control eye: two-sample t-test). Subsequently, a multiple regression analysis was used to evaluate the independent variables of age, logarithm of the minimum angle of resolution

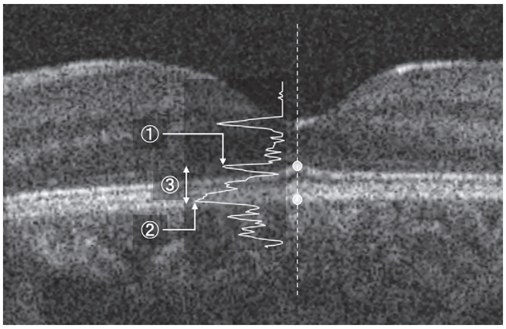

Fig. 1. Evaluation of the foveal bulge (FB) height using the longitudinal reflectivity profiles (LRP) method
The height of the FB was evaluated by the LRP method using imageJ. First, a perpendicular line (dashed line) is drawn between the peak of the FB reflectivity profile for the ellipsoid zone and Bruch's membrane. Subsequently, the OCT image on the perpendicular line is analyzed by the LRP method using imageJ. As a result of the waveform analysis, the peak of the reflectivity profile for FB (①) and the peak of the reflectivity profile for Bruch's membrane (②) are extracted, with the distance between ① and ② then quantitatively evaluated as the height of the FB (③).

(logMAR), refractive error, axial length, and central retinal thickness with respect to the dependent variables of the height of the FB. All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), with a p-value < 0.05 considered statistically significant.

All of the procedures conformed to the tenets of the Declaration of Helsinki. This study was approved by the Ethics Committee of Kawasaki Medical School (registration number: 3473-01).

RESULTS

Table 1 presents the subjects' demographic data. The logMAR was significantly higher in the amblyopic eyes as compared to the fellow or control eyes (p < 0.001). The spherical equivalent was significantly higher in the amblyopic eyes versus those of the fellow or control eyes (p < 0.001). Also, the axial length was shorter in the amblyopic eyes as compared to the fellow or control eyes. Lastly, although the central retinal thickness in the amblyopic eyes was not significantly different from that observed in the fellow eyes (p = 0.718), the amblyopic eyes were thinner than the control eyes (p < 0.001).

We were able to detect the FB in all 77 eyes examined. The position of the FB relative to the FP was deviated in 13 of 77 eyes of all of the subjects (16.9 %). In addition, the direction of the FB deviation was nasally in all cases. The percentage of the nasal deviation was 14.6 % (7 eyes) in the amblyopic eye, 10.4 % (5 eyes) in the fellow eye, and 3.6 % (1 eye) in the control eye (Fig. 2). There

Table 1. Demographic data of subjects included in the study

	amblyopic eye	fellow eye	healthy eye	*P* Value amblyopic vs. fellow eye	*P* Value amblyopic vs. healthy eye
logMAR	0.36 ± 0.23	- 0.13 ± 0.01	- 0.12 ± 0.07	< 0.001	< 0.001
spherical refractive error (D)	5.32 ± 1.81	1.80 ± 1.51	0.44 ± 1.44	< 0.001	< 0.001
axial length (mm)	21.11 ± 0.96	22.29 ± 1.04	22.77 ± 1.11	< 0.001	< 0.001
central retinal thickness (μm)	207.7 ± 25.9	208.1 ± 24.5	229.4 ± 27.3	0.718	0.001

logMAR, spherical refractive error, axial length, and central retinal thickness are shown as the mean and standard deviation.
logMAR: logarithm of the minimum angle of resolution

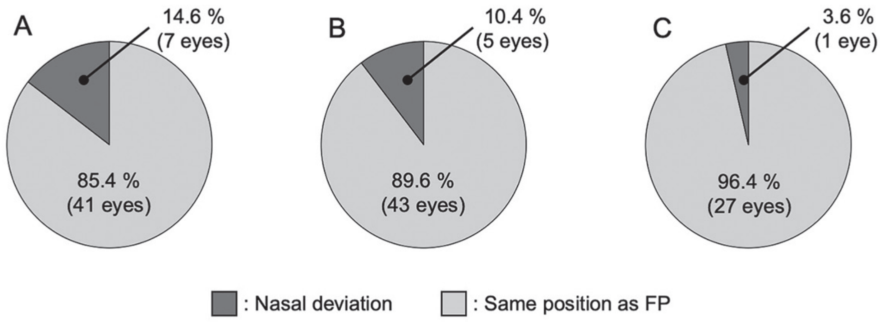

Fig. 2. The position of the foveal bulge (FB) relative to the foveal pit (FP)
The percentage of the position of the FB relative to the FP that showed nasal deviation was 14.6 % (7 eyes) in the amblyopic eye (A), 10.4 % (5 eyes) in the fellow eye (B), and 3.6 % (1 eye) in the control eye (C). There was no deviation observed in the other subjects. There was also no significant difference observed in the percentage of the nasal deviation among the groups.

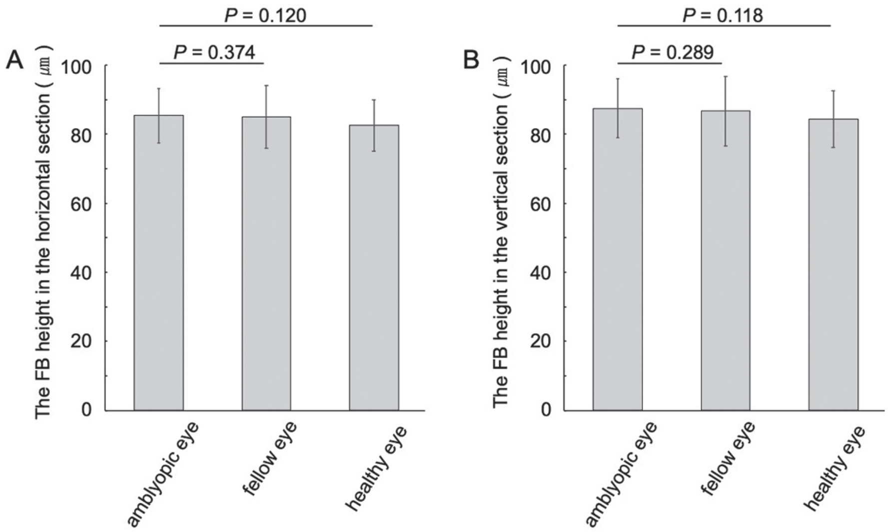

Fig. 3. The height of the foveal bulge (FB)
A indicates the FB height in the horizontal section, while B indicates the FB height in the vertical section. The FB height in the horizontal and vertical sections in the amblyopic eye was not significantly different from that observed for the fellow or control eyes. In addition, there was no significant difference in the FB height between the horizontal and vertical sections in any group.

was no significant difference in the percentage comparing the two proportions of the nasal deviation between the amblyopic and fellow eyes, or between the amblyopic and control eyes (amblyopic eye vs. fellow eye: p = 0.537, amblyopic eye vs. the control eye: p = 0.131). The mean deviation of the FB relative to the FP was 3.0 ± 7.1 μm in the amblyopic eyes, 2.2 ± 6.4 μm in the fellow eyes, and 0.8 μm in the control eye (with only one subject found to have a deviated FB among the control eyes).

The FB height in the horizontal section was 85.4 ± 7.9 μm in the amblyopic eye, 85.0 ± 9.0 μm in the fellow eye, and 82.5 ± 7.4 μm in the control eye (Fig. 3). The horizontal FB height in the amblyopic eye was not significantly different from the fellow or the control eyes (amblyopic eye vs. fellow eye: p = 0.374, amblyopic eye vs. control eye: p = 0.120). The FB height in the vertical section was 87.5 ± 8.5 μm in the amblyopic eye, 86.7 ± 10.1 μm in the fellow eye, and 84.3 ± 8.2 μm in the control eye (Fig. 3). Similar to the horizontal FB height, the vertical FB height in the amblyopic eye was not significantly different from the fellow and control eyes (amblyopic vs. fellow eye: p = 0.289, amblyopic vs. control eye: p = 0.118). There was no significant difference in the FB height between horizontal and vertical sections in any group (amblyopic eye: p = 0.105, fellow eye: p = 0.132, control eye: p = 0.170).

Finally, multiple regression analysis of the factors affecting the FB height demonstrated that there was no significant association for any factor (age: p = 0.706, logMAR: p = 0.221, refractive error: p = 0.909, axial length: p = 0.330, central retinal thickness: p = 0.278).

DISCUSSION

This study initially compared the FB of amblyopic and healthy control eyes, with the effect of amblyopia on the photoreceptor normality then examined. In addition, we also examined the factors influencing the height of the FB.

Current results showed that the FB could be found in all amblyopic patients and control subjects, with 14.6 % of the amblyopic eyes exhibiting a nasal deviation of the FB. However, the percentage of cases with deviated FB was not significantly different among the amblyopic, fellow, and control eyes. Therefore, the deviation was not specifically associated with the amblyopic eyes. In a previous report, Parthasarathy *et al*. reported that the FB deviated nasally from the FP in 75 out of 146 eyes (51 %) of healthy subjects (mean age: 43.9 ± 14.4 years)[17]. Similarly, Matsui *et al*. additionally studied 147 healthy eyes (mean age: 24.9 ± 4.5 years) and reported that the FB was deviated nasally from the center of the FP in 97 eyes (66 %)[16]. Our current results showed the same trend as that reported in the previous reports in which the FB was shown to deviate nasally with respect to the FP. It has been hypothesized that the normal development of FP is the reason for the nasal deviation of the FB[12]. During development, the FP expands more temporally than nasally, and thus, the FP is considered to be deviated to the temporal side. As a result, the FB will be positioned nasal to the temporally deviated FP. In our present study, the proportion of the FB nasal deviations tended to be smaller as compared to that reported in previous studies. A possible reason for this is the influence of the subjects' age. The outer structure of the retina develops rapidly from 4 to 6 years of age, reaching adult levels by 13 years of age[18]. The mean age of the subjects in our current study was 6.8 ± 2.3 years, which suggests that this may have been during a period of fluctuation with regard to the positional relationship between the FP and FB. Furthermore, it should be noted that we did not examine whether the position of the FBs in amblyopic eyes as compared to the control eyes showed any specific changes during the follow-up period. Thus, future studies that follow the same eyes will need to be undertaken.

Cakir *et al.*[13] and Nishi *et al.*[12] have both reported on the outer segment length (OS length), which corresponds to the FB height, in amblyopic eyes. Cakir *et al.*[13] evaluated the OS length in 34 strabismic amblyopic eyes without anisometropia (mean age 10.3 ± 4.9 years) and reported that there was no significant difference between the amblyopic and healthy eyes. Nishi *et al.*[12] evaluated the OS length in 21 eyes (mean age 6.0 ± 2.3 years) with anisometropic amblyopia before and after amblyopia treatment. Although Nishi *et al*. also reported that the OS length of the amblyopic eyes was significantly shorter than that of the fellow eyes before treatment, after undergoing treatment, it was significantly increased and subsequently became no different from that observed in the fellow eyes, with the OS length significantly correlated with the visual acuity[12]. In contrast, the FB height in the amblyopic eye was not significantly different between the fellow and control eyes in our present study. There was no factor, including for the logMAR that affected the FB height when analyzed by multiple regression analysis. One possible reason for the difference between the report of Nishi *et al.* and our current study may be due to the difference in the methods for evaluating the FB height. Nishi *et al.* evaluated the scanning mode of a single scan when using the Spectralis OCT (Heidelberg Engineering, Germany), which is a spectral domain OCT. In contrast, our current study used swept-source OCT, which permits higher speed scanning than the spectral domain OCT. In addition, we also used a 3D scan mode that was able to capture multiple images, including the fovea. Therefore, it is conceivable that the detection of the FB could have been more accurate in our present study. Furthermore, Cakir *et al.* and Nishi *et al.* both measured the FB height manually using built-in calipers. In contrast, evaluations in our present study were done by the LRP, which has been reported to be an objective method for the evaluation of FB[16].

There were two limitations for our current study. First, in this study we did not investigate the changes in FB over time. As the present study assessed a single measurement, it was not possible to determine whether the deviation of the FB position was due to developmental effects. Thus, it will be necessary to further examine the course of these patients over time in the future. Second, the number of subjects in the current study was quite small. There was no significant difference in the rate of nasal deviation, but it tended to be higher in the amblyopic eye than in the control eye (control eye: 3.6 %, amblyopic eye: 14.6 %). However, it was not clear from our results whether this difference in percentage reflects a tendency for specific changes in the amblyopic eye. Therefore, in the future it will be necessary to increase the number of subjects in order to verify the trend of the present results found in this study.

In conclusion, there was no significant difference among the amblyopic, fellow, and healthy control eyes with regard to the position and height of the FB relative to the FP. Our results suggest that amblyopia does not affect photoreceptor normality.

CONFLICT OF INTEREST

No conflicting relationship exists for any author.

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