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CLINICAL STUDY

Correlation between visual function and photoreceptor inner/outer segment junction in patients with retinitis pigmentosa

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Abstract

Purpose **To determine whether a significant correlation exists between the visual acuity or foveal thickness and the status of the inner and outer segment junction (IS/OS) of the photoreceptor in patients with retinitis pigmentosa (RP).**

Methods **Three hundred eyes of 163 patients with RP were examined with the optical coherence tomography (OCT). The IS/OS appeared as a distinct, highly reflective line just vitread of the retinal pigment epithelium in the OCT3 images. The IS/OS line was graded into three groups. The correlations between the grade of the IS/OS and age, best-corrected visual acuity (BCVA), and central foveal thickness (CFT) were determined.**

Results **Grade 1 included 93 eyes (31.0%) in which an IS/OS line was not seen, Grade 2 included 67 eyes (22.3%) with an abnormal IS/OS, and Grade 3 included 140 eyes (46.7%) with a normal IS/OS. The correlation between the IS/OS grade and age was not significant ($P = 0.5536$). The IS/OS grade was significantly correlated with BCVA and CFT (both $P < 0.0001$). The BCVA was significantly better in Grade 3 eyes than Grades 1 and 2 (both $P < 0.0001$). The CFT was significantly thinner in Grade 1 eyes than in Grades 2 and 3 (both $P < 0.0001$). In Grade 3, the mean length of the IS/OS was 2.51 ± 1.42 mm ($\pm$ SD). The length of the IS/OS was significantly correlated with the BCVA ($P < 0.0001$, $r = -0.375$).**

Conclusions **The presence of the IS/OS was associated with better visual acuity and thicker fovea in RP patients. The absence of an IS/OS may reflect a foveal dysfunction in RP patients.**

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Introduction

Retinitis pigmentosa (RP) is a slowly progressive retinal disease and patients with RP show reduced visual function, mainly by degeneration of the rod and cone photoreceptors and the retinal pigment epithelium (RPE).[1–3] Several different genetic mutations have been found to be associated with RP, although RP patients can have similar symptoms and retinal histopathology.[1–3] The degeneration of the retina usually starts in the mid-periphery, leading to nyctalopia. When the disease is advanced, the retinal degeneration gives rise to a characteristic ring-shaped scotoma that expands to the periphery and macula.

The earliest histopathological changes in all forms of RP is a shortening of the photoreceptor outer segments.[3] The loss of the cones reduces central vision at the end stage of disease.[2,3] Therefore, morphological assessments of the photoreceptors in the macular area can be useful in estimating the residual central visual function in RP patients.

Optical coherence tomography (OCT) is a well-established method of examining the retinal architecture *in vivo*. Recently, a distinct, highly reflective line was detected just vitread of the RPE layer in the images obtained by the

ultrahigh-resolution OCT (UHR-OCT).[4,5] This line has been identified as the inner/outer segment junction (IS/OS) of the photoreceptor, and a distinct and continuous line indicated normal alignment of membranous discs in the photoreceptor outer segments.[6] Because the alignment of the discs is necessary for the normal functioning of the photoreceptors, the presence of a normal IS/OS line in the OCT images most likely indicates normally functioning photoreceptors. It has also been reported that the presence of the IS/OS line in the OCT images is correlated with the recovery of good vision after macular hole surgery and is essential for normal visual function.[7–9] At present, it is generally accepted that the OCT3 images correspond with the UHR-OCT images in major parts,[6,10] and the IS/OS is so distinct that it can be observed in the OCT3 images as well as in the UHR-OCT images.[6–11]

In RP patients, several OCT studies have been conducted on the correlation between the retinal structure and visual function.[11–13] Sandberg *et al*[12] examined the third high-reflectance band that represented the IS/OS in RP patients using OCT3 (Zeiss Humphrey, Sun Leandro, CA). They examined the IS/OS only in the central 1 mm area and examined the IS/OS using false-colour images in which the IS/OS line is sometimes difficult to differentiate from the RPE layer, especially in the high-signal areas of the OCT images.[14] Witkin *et al*[11] reported the central foveal thickness (CFT) and foveal outer segments thickness were associated with the visual acuity. Their OCT images were obtained with UHR-OCT, but only nine RP patients were studied.

The purpose of this study was to determine whether a significant correlation is present between the visual acuity or foveal thickness and the grade of the IS/OS line observed in the OCT3 greyscale images in a large number of RP patients. We also performed a quantitative analysis of the relationship between the length of the IS/OS and the visual acuity.

Subjects and methods

This observational, cross-sectional case study was performed on 300 eyes of 163 patients with a diagnosis of RP (81 women and 82 men). The study was conducted at Chiba University Hospital between December 2003 and April 2007. RP patients were diagnosed based on the clinical history, funduscopic appearance, visual field testing, fluorescein angiography, and full-field electroretinograms recorded under ISCEV-standardized conditions. Atypical RP cases such as sector RP and unilateral RP were excluded. Eyes with an epiretinal membrane, macular oedema, poor fixation because of extremely low visual acuity (<0.01), myopic eyes with posterior staphyloma, and eyes with opacities in the media that affected the visual acuity were excluded. All subjects underwent a standard ophthalmological examination, including best-corrected visual acuity (BCVA) measurements, applanation tonometry, slit-lamp biomicroscopy, indirect ophthalmoscopy, and colour fundus photography. The BCVA was measured with a Japanese standard Landolt visual acuity chart and converted into logarithm of the minimal angle resolution (logMAR) units for statistical analyses.

Retinal tomographic images were obtained with an OCT3 with 5-mm horizontal scans through the fovea. All OCT images were acquired through a dilated pupil. The greyscale images were used for a more precise identification and measurement of the IS/OS.[14] The appearance of the IS/OS in the OCT images at the fovea was graded from 1 to 3: Grade 1, IS/OS not visible; Grade 2, abnormal IS/OS (Figure 1); and Grade 3, normal IS/OS (Figure 2).[12] To grade the cases, we measured the length of the IS/OS, which extended from just beneath the fovea, and defined eyes as Grade 3 when the length of the continuous IS/OS line was >0.5 mm. The eyes with disruptions of the IS/OS just beneath the fovea were placed in Grade 2. The grade of the IS/OS was confirmed by two of the authors (SA and TB) who were masked to the visual acuity.

The CFT was measured manually on the horizontal OCT3 images of all eyes at the thinnest point of the fovea. The distance from the innermost layer of retina to the outer border of the RPE was measured.

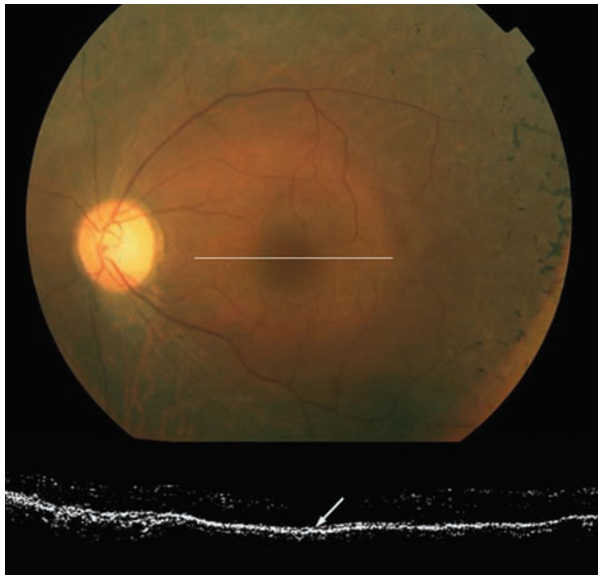

Figure 1 An eye classified as Grade 2 with an abnormal photoreceptor IS/OS. Top: fundus photograph of a 45-year-old man. The white line indicates the direction of the OCT scan. BCVA was 0.4. Bottom: greyscale OCT image of a 5-mm horizontal scan. A disrupted IS/OS line (white arrow) can be seen.

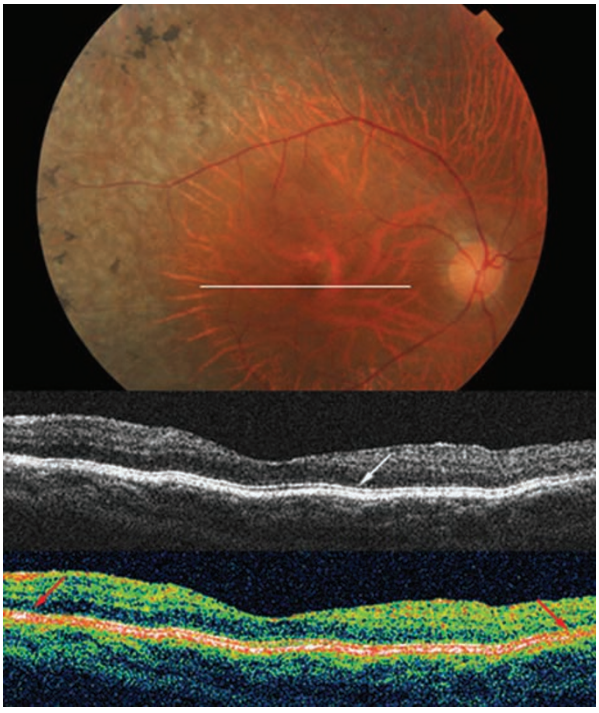

Figure 2 An eye classified as Grade 3 with a normal photoreceptor IS/OS. Top: fundus photograph of 35-year-old man. The white line indicates the direction of the OCT scan. BCVA was 1.0. Middle: greyscale OCT image of a 5-mm horizontal scan. Foveal thickness (central foveal thickness: 207 μm) was within normal limits, and the presence of a normal IS/OS line (white arrow), which covered the entire scan length, can be seen. Bottom: false-colour OCT image. The IS/OS line is difficult to differentiate from the RPE layer in some high-signal areas (red arrows).

The significance of the differences of age, BCVA, and CFT in the three IS/OS grades were tested statistically using one-factor ANOVA. When the three groups were compared independently, Fisher's protected least significant difference (PLSD) was used. The correlations between the length of the IS/OS and BCVA, age, or CFT were examined by Pearson's correlation tests. A *P*-value <0.05 was considered statistically significant.

Results

The IS/OS was not detected (Grade 1) in 93 eyes (31.0%; Table 1), an abnormal IS/OS (Grade 2) was detected in 67 eyes (22.3%), and the IS/OS was normal (Grade 3) in 140 eyes (46.7%).

The mean age of all the RP patients was 50.5 ± 13.1 (± SD) years with a range of 11–75. The mean age was 51.3 ± 12.1 years in Grade 1, 50.6 ± 14.5 years in Grade 2, and 49.4 ± 13.0 years in Grade 3 group (Table 1). The differences in the three groups were not significant ($P=0.5536$, one-factor ANOVA).

Table 1 Number of eyes, age, BCVA, and CFT in IS/OS subgroup

Grade[a]	*Number of eyes (%)*	*Age (years)*[b]	*BCVA (logMAR)*[b]	*CFT (μm)*[b]
1	93 (31.0%)	51.3 ± 12.1	0.83 ± 0.55	152 ± 40
2	67 (22.3%)	50.6 ± 14.5	0.31 ± 0.29	199 ± 42
3	140 (46.7%)	49.4 ± 13.0	0.03 ± 0.12	202 ± 34
		$P=0.5536$	$P<0.0001$	$P<0.0001$

IS/OS = photoreceptor inner and outer segment junction; BCVA = best-corrected visual acuity; CFT = central foveal thickness.
[a]The IS/OS was classified as Grade 1 (absence), Grade 2 (abnormal), and Grade 3 (normal).
[b]The data are displayed as means ± SD.

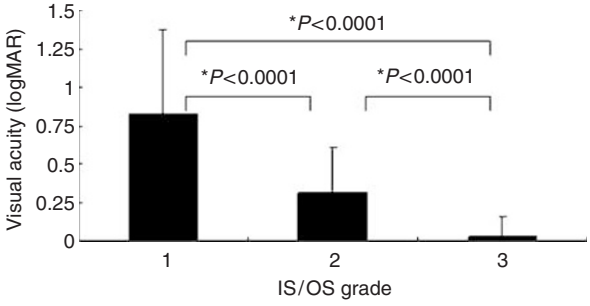

Figure 3 Mean visual acuity (logMAR units) as a function of the grade of the photoreceptor IS/OS. The difference among the three groups is statistically significant ($P<0.0001$). *P: difference between the two groups.

The mean BCVA was 0.83 ± 0.55 logMAR units in the Grade 1 group, 0.31 ± 0.29 U in Grade 2 group, and 0.03 ± 0.12 U in Grade 3 group (Table 1). The differences among the three groups were significant ($P<0.0001$, one-factor ANOVA). When the mean BCVA of the three groups was compared independently with each of the other groups, the BCVA was significantly better in Grade 3 than in Grades 1 and 2 (both $P<0.0001$, Fisher's PLSD; Figure 3). The BCVA was also significantly better in Grade 2 than in Grade 1 ($P<0.0001$, Fisher's PLSD).

The mean CFT was 152 ± 40 μm in Grade 1, 199 ± 42 μm in Grade 2, and 202 ± 34 μm in Grade 3 (Table 1). There was a significant difference among the three groups ($P<0.0001$, one-factor ANOVA). The mean CFT was significantly thinner in Grade 1 compared with the other two groups (both $P<0.0001$, Fisher's PLSD). However, the difference between Grades 2 and 3 was not significant ($P=0.6417$, Fisher's PLSD).

The length of the IS/OS line was measured in eyes in the Grade 3 group. The mean IS/OS length was 2.51 ± 1.42 mm, and the IS/OS line was detected over the entire scan length of 5 mm in 17 (12.1%) of the 140 eyes.

The correlation between the length of the IS/OS and the BCVA was significant ($r=-0.375$; $P<0.0001$,

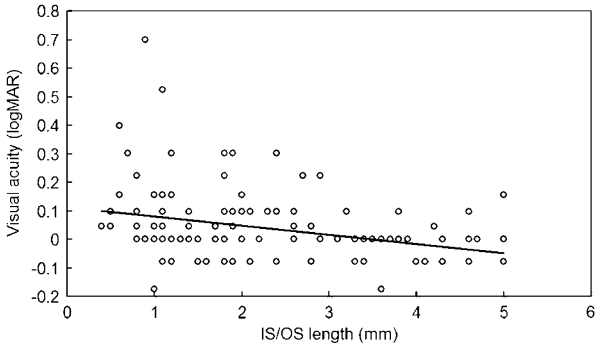

Figure 4 Correlation between the length of the photoreceptor IS/OS and visual acuity (logMAR units). The IS/OS length is significantly correlated with the visual acuity ($r=-0.375$, $P<0.0001$). The solid line represents the linear regression line; $y=0.112–0.032x$.

Pearson's correlation tests; Figure 4). However, the correlations between the IS/OS length and age or CFT were not significant ($r=0.037$, $r=0.141$, respectively; $P=0.6632$, $P=0.0968$, respectively, Pearson's correlation tests).

Discussion

RP primarily affects the photoreceptor and the RPE. The earliest histopathological change in the photoreceptors is a shortening of the rod outer segments. This is progressive and eventually results in the death of the rods. The death of the rods is usually accompanied by changes in the cones, especially a shortening of their outer segments.[2] Therefore, an assessment of the outer segment is essential in estimating the damage of the photoreceptors.

The IS/OS line was clearly delineated in the OCT3 greyscale images in this study. An OCT image is usually examined with false-colour images, but the IS/OS line is sometimes difficult to differentiate from the RPE layer, especially in high-signal OCT images (Figure 2). In such cases, greyscale images are better because they can enhance each layer, and a distinct image of the IS/OS line separated from the RPE layer can be seen.[14] Ishikawa *et al*[14] examined eyes with cystoid macular oedema using both false-colour and greyscale OCT images and concluded that greyscale images showed a finer gradation of signal reflectance. This finer gradation of greyscale images is mainly because the false-colour algorithm converts tissue reflectivity into intensity in an abrupt, linear, and stepwise fashion, whereas the greyscale algorithm uses a smooth curved line (square root) for conversion.[14] Thus, we recommend that the greyscale image should be used as a standard method to identify and study the IS/OS line.

We were not able to detect an IS/OS line in 31.0% of the eyes, able to detect an abnormal IS/OS in 22.3% of the eyes, and a normal IS/OS in 46.7% in the OCT3 greyscale image in the 163 RP patients. On the other hand, Sandberg *et al*[12] detected no IS/OS (third high-reflectance band) line in 29.5%, an abnormal IS/OS in 56.6%, and a normal IS/OS in 13.9% in OCT3 false-colour images of 162 RP patients. Because of the differences in age, gender, duration of disease, and type of RP between the two studies, the results of these two studies cannot be simply compared. However, there is a possibility that our higher detection rate was due to the use of greyscale images.

Our results showed that the IS/OS grade was highly correlated with the BCVA in our RP patients. These findings are in agreement with the report by Sandberg *et al*[12] that shows that the IS/OS grade was significantly correlated with the visual acuity and with the CFT. On the other hand, Witkin *et al*[11] reported that the foveal outer segment/pigment epithelium thickness was highly correlated with the visual acuity in RP patients. Considering these results, we suggest that the presence of the IS/OS indicates a preservation of foveal function.

Ergun *et al*[15] quantified the transverse photoreceptor loss at the level of the photoreceptor outer segments, that is, a disruption in the length of the IS/OS line, in patients with Stargardt's disease using UHR-OCT. They reported that the transverse photoreceptor loss was significantly correlated with the visual acuity, central atrophy determined by fluorescein angiography, and the degree of autofluorescence. In our study, we examined IS/OS length or transverse photoreceptor presence in RP patients. Our finding that the IS/OS length was correlated with the BCVA is in agreement with their findings. Together, these results suggest that examining the IS/OS length is a useful way to assess the visual function of photoreceptor diseases such as Stargardt's disease and RP.

The presence of the IS/OS line was not correlated with patient's age. This does not mean that the degenerative changes were not related to the duration of the disease. We suggest that our results were obtained from different types of RP patients, at different stages, and with different rates of degeneration, and these differences accounted for the nonsignificant correlation between the presence of the IS/OS and age.

We found a significant difference in the CFT between Grades 1 and 2 and between Grades 1 and 3, but not between Grades 2 and 3. It has been reported that a foveal thinning measured with the OCT was correlated with the visual acuity in patients with RP and Stargarrt's disease.[11,12,15] Witkin *et al*[11] reported that the foveal thinning might be primarily due to photoreceptor loss. In our RP patients, Grade 2 eyes had a fovea as thick as that of eyes in Grade 3, and we assumed that the damage of

the photoreceptor in Grade 2 eyes was partial, and that the length of the outer segments was preserved. It should be noted that OCT3 has an axial imaging resolution of approximately 10 μm, whereas the UHR-OCT has an axial imaging resolution of approximately 3 μm. This difference may be another reason why we were not able to find a difference in the CFT between eyes in Grades 2 and 3 using the OCT3 images.

One of the limitations of this study was its cross-sectional design. We were not able to determine the time course of the changes in the IS/OS. To determine this, a follow-up longitudinal study will be required.

We conclude that the presence of the IS/OS is associated with better visual acuity and normal foveal thickness in RP patients. Our findings show that OCT can assess the photoreceptor cells *in vivo*, and the significant correlation between the visual acuity and presence or length of the IS/OS indicates that the IS/OS line may be an important parameter to monitor RP patients.

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