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CORRELATIONS BETWEEN CHANGES IN PHOTORECEPTOR LAYER AND OTHER CLINICAL CHARACTERISTICS IN CENTRAL SEROUS CHORIORETINOPATHY

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Purpose: To clarify the correlations between changes in the photoreceptor layer (PRL) and other clinical characteristics during central serous chorioretinopathy.

Methods: Patients with central serous chorioretinopathy with one eye affected were enrolled. Photoreceptor layer appearance within the detached area was evaluated, and its correlations with symptom duration, best-corrected visual acuity, and the difference in the foveal outer nuclear layer thickness between the affected and contralateral eyes were analyzed.

Results: A total of 222 patients were included. The PRL outer border appeared either smooth, granulated, or as scattered dots attached to external limiting membrane. These different appearances were associated with elongation in symptom duration (18, 180, and 1,855 days), decreases in best-corrected visual acuity (6/10, 6/15, and 6/120), and increases in the difference of foveal outer nuclear layer thickness (−16, −32, and −60 μm). Among eyes with smooth PRL outer border, which had similar symptom duration, eyes with foveal PRL defect had poorer best-corrected visual acuity and greater reduction in outer nuclear layer thickness than the other eyes (all P = 0.00).

Conclusion: Morphologic changes in PRL, best-corrected visual acuity, the reduction in foveal outer nuclear layer thickness, and symptom duration correlate closely but may behave asynchronously. These objective parameters, besides symptom duration, could be helpful when considering the timing of central serous chorioretinopathy treatment.

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Central serous chorioretinopathy (CSC) is a common macular disease and often presents with well-circumscribed serous retinal detachment in the macular region on clinical examination, with one or several leakage points at the level of the retinal pigment epithelium detectable with fluorescein angiography.[1] With the advent of optical coherence tomography (OCT), it is now possible to obtain high-resolution cross-sectional images of the retina in a noninvasive manner.[2–4] The typical pathologic changes that occur in CSC, such as serous retinal detachment and retinal pigment epithelium abnormalities, have been clearly demonstrated with OCT.[5,6] Recently, it was observed that foveal outer nuclear layer (ONL) thickness significantly decreased in active CSC eyes, which continued as the subretinal fluid persisted.[7,8] In addition, the ONL thinning was associated with vision loss in both active and resolved CSC eyes.[8–11] Moreover, the morphologic changes in the photoreceptor layer (PRL), referred to elongation, thickening, granulation, thinning, defect, or scattered dots, have been reported.[7,9,12–15]

However, the correlations between the PRL changes, the decrease of ONL thickness, and clinical characteristics, such as symptom duration and visual acuity, remain unclear. To explore the possible correlations between these features, the morphologic changes in the PRL during active CSC were studied, and the potential relationships with ONL thinning and clinical characteristics were analyzed in this study.

Methods

This prospective observational cross-sectional study was approved by the Ethics Committee of the Eye and Ear Nose Throat Hospital, Fudan University, Shanghai, China (KJ2009-16). Informed consent was obtained from each patient.

Consecutive patients with active CSC who visited the clinic of the Eye & Ear Nose Throat Hospital of Fudan University between September 2014 and June 2016 were enrolled. The clinical diagnosis of CSC was based on symptoms, reduced visual acuity with or without metamorphopsia or micropsia, and the presentation of serous retinal detachment on both fundus and OCT examinations. All subjects underwent a thorough ocular examination of both eyes, including best-corrected visual acuity (BCVA), measured with a standard Snellen chart and converted to the logarithm of the minimum angle of resolution for statistical analysis; the measurement of intraocular pressure, using a non-contact tonometer; slit-lamp biomicroscopy; an OCT examination; and the collection of data on symptom duration. The subjects included were those with one affected eye in the first episode of CSC and with a normal contralateral eye (BCVA $\geq$ 6/6, intraocular pressure $<$ 21 mmHg, and no clinical signs or history of any intraocular disease). The subjects excluded were those with either clinical signs or a history of any other intraocular disease in either eye; active CSC in both eyes; a former episode of CSC in either eye; any steroid use; or who could not define their symptom duration.

All OCT images were obtained through a dilated pupil with either a high-definition 5-line raster scan protocol (length 6 mm, spacing 0.075 mm; Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) or a line scan protocol (line scans of 30°, composed of 100 averaged images; Heidelberg Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). For each enrollee, this protocol was applied both vertically and horizontally and centered on the fovea in both eyes. The OCT images (vertical and horizontal) that passed through the central fovea were selected for the analysis of morphologic changes in the PRL and the measurement of the ONL thickness. Two authors (J.Y. and C.J.), who were masked to the information on BCVA and symptom duration, independently evaluated all the OCT images, and a senior retinal specialist (G.X.) acted as arbiter in cases of disagreement between the two authors.[14] The foveal ONL thickness was the average of the distances between the internal limiting membrane and the external limiting membrane at the center of the fovea measured from the horizontal and vertical images, respectively. The difference in the foveal ONL thickness was defined as the difference between the foveal ONL thickness of the CSC eye and that of the contralateral eye. The measurements were made manually using the supplied software (SW version 7.0.1.290; Carl Zeiss Meditec, Inc; or in 1:1 μm mode; HRA/Spectralis Viewing Module 6.0.9.0; Heidelberg Engineering).

When classifying the PRL appearance, the intragrader repeatability and intergrader reproducibility were determined for all the OCT images evaluated by 2 authors (J.Y. and C.J.), who each read all the OCT images twice, at 4-month intervals. Both intragrader repeatability and intergrader reproducibility were assessed as percentage agreement.[16,17] Kappa (κ) statistics and the corresponding 95% confidence intervals were also reported using the guidelines proposed by Koch and Landis[18,19]: $>$0.80 = near perfect agreement, 0.61 to 0.80 = substantial agreement, 0.41 to 0.60 = good agreement, and 0.21 to 0.40 = fair agreement. All the scans and measurements of foveal ONL thickness were made by J.Y. Repeatability of the foveal ONL thickness measurements was calculated from two horizontal scans taken in each eye during a single visit; 20 normal eyes and 20 CSC eyes were included. Intraclass correlation coefficients were used to assess the repeatability of measurements (intraclass correlation coefficient values of 0.81–1.00 indicated almost perfect agreement between repeated measurements; values $<$0.40 indicated poor to fair agreement).[20]

The data were analyzed with SPSS for Windows version 21.0 (SPSS, Chicago, IL). The Kolmogorov–Smirnov test was used to confirm the normality of the data. Descriptive statistics were calculated, including medians, means, proportions, and frequencies. Either the Kruskal–Wallis test or one-way ANOVA,

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followed by post hoc multiple comparisons, was used to test the differences in symptom duration, BCVA, and the foveal ONL thickness difference between the eyes classified in three or more categories, whereas either the Mann–Whitney *U* test or a *t*-test was used for these comparisons between eyes classified in two categories. Either Pearson correlation coefficient or Spearman correlation coefficient was used to examine the correlation between BCVA, symptom duration, and the difference in foveal ONL thickness. A *P* value of <0.05 was considered statistically significant.

Results

In total, 222 patients were enrolled in the study, including 167 (75.2%) men and 55 (24.8%) women. The average age was 45.16 ± 7.88 years (range, 20–67), the median symptom duration was 53 days (range, 1–3,710), the median BCVA (logarithm of the minimum angle of resolution) was 6/12, 0.3 (range, 0–1.3), and the average difference in foveal ONL thickness was -24.04 ± 18.00 μm (range, -86 to +24). Symptom duration, BCVA, and foveal ONL thickness difference were mutually correlated (all $P = 0.00$: BCVA and symptom duration, R = 0.56; foveal ONL thickness difference and symptom duration, R = -0.64; and BCVA and foveal ONL thickness difference, R = -0.55).

In the OCT images, all 222 eyes presented well-circumscribed serous retinal detachment in the macular region. However, the appearance of the PRL outer border varied and could be classified into three groups: smooth, with or without PRL defect; granulated, with or without protruding foveal PRL; or in the form of scattered dots attached to the external limiting membrane (Figure 1). The classification of the appearance of the PRL showed good repeatability and reproducibility. The intragrader repeatability scores for J.Y. and C.J. were similar, with 95.1% agreement ($\kappa = 0.94$, 95% confidence interval 0.89–0.98) and 96.9% agreement ($\kappa = 0.96$, 95% confidence interval 0.92–0.99), respectively. The intergrader reproducibility was also satisfactory, with an agreement rate of 91.0% ($\kappa = 0.89$, 95% confidence interval 0.82–0.95). The measurement of the foveal ONL thickness showed good repeatability, with an intraclass correlation coefficient value of 0.953 for normal eyes and 0.986 for CSC eyes.

Eyes with different PRL outer border appearances had significantly different symptom durations, BCVA, and differences in foveal ONL thickness (Tables 1–3). The eyes with a smooth PRL outer border had the shortest symptom duration, best BCVA, and lowest foveal ONL thickness difference (all $P = 0.00$, Table 1), whereas the eyes with scattered dots of PRL had the longest symptom duration, worst BCVA, and the greatest difference in foveal ONL thickness.

Some of the eyes with a smooth PRL outer border had a PRL defect involving the fovea or the extrafoveal region. The three different eye types all had similar symptom durations, whereas the eyes with a foveal PRL defect had poorer BCVA and a greater foveal ONL thickness difference than the eyes either with no PRL defect or with an extrafoveal PRL defect (all $P = 0.00$, Table 2). Eyes with a granulated PRL outer border, either with or without a protruding foveal PRL, had similar BCVAs and foveal ONL thickness differences ($P > 0.05$, Table 3), whereas those with a protruding foveal PRL had longer symptom durations ($P = 0.018$, Table 3).

Discussion

This study demonstrates that, in eyes with active CSC, the appearance of the PRL outer border can be classified into three main groups, either smooth, granulated, or in the form of scattered dots, and that these different manifestations are associated with a 10-fold difference in the median symptom duration (18, 180, and 1,855 days, respectively), a significant difference in the median BCVA (6/10, 6/15, and 6/120, respectively), and an almost 2-fold difference in the mean foveal ONL thickness difference (-16, -32, and -60 μm, respectively) (Table 1). Furthermore, eyes with a PRL defect involving the fovea had relatively poor BCVA and a notably reduced ONL thickness in the early phase of the disease (Table 2).

Besides the mutual correlations between symptom duration, BCVA, and the foveal ONL thickness difference, which are consistent with previous findings,[8–11] we also found that these parameters correlated closely with the different types of PRL appearance: smooth, granulated, or in the form of scattered dots attached to the external limiting membrane. Although the reasons for these correlations are not fully understood, they might be explained in the following way. Normally, the outer parts of the photoreceptor outer segments are phagocytized continuously by the retinal pigment epithelium, whereas the inner parts are regenerated at the junction with the inner segment.[7,10,21] However, in CSC eyes, it was speculated that a lack of phagocytosis by the retinal pigment epithelium leads to the elongation of the outer segments.[7,10] Although the PRL outer border was designated “smooth” in the first group (Table 1), the OCT images showed that the PRL layer changed slightly

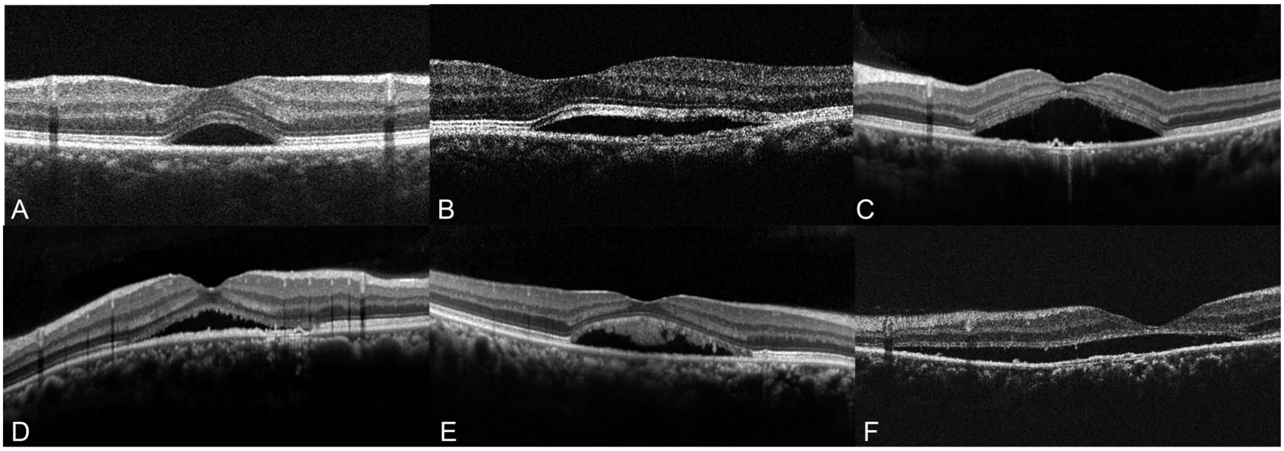

Fig. 1. Various appearances of the PRL within the detached area in active CSC (**A–F**). **A.** Line scan of a 28-year-old female patient with BCVA of 6/6 and symptom duration of 6 days; the outer border of the PRL was smooth and intact. **B.** Line scan of a 42-year-old male patient with BCVA of 6/6 and symptom duration of 14 days; the outer border of PRL was smooth and thickened, with a PRL defect involving the temporal part. **C.** Line scan of a 42-year-old male patient with BCVA of 6/30 and symptom duration of 40 days; the outer border of the PRL was smooth and thickened, with a PRL defect involving the fovea. **D.** Line scan of a 41-year-old male patient with BCVA of 6/20 and symptom duration of 91 days; the outer border of the PRL was granulated. **E.** Line scan of a 49-year-old male patient with BCVA of 6/12 and symptom duration of 540 days; the outer border of the PRL was granulated, with the foveal PRL protruding. **F.** Line scan of a 54-year-old male patient with BCVA of 6/60 and symptom duration of 1,883 days; the PRL presented as scattered dots attached to the external limiting membrane.

and, in some cases, was a little thicker than normal (Figure 1, A–C). As the retinal detachment proceeded, disintegration of the outer segments and phagocytosis by macrophages or microglial cells of the outer segments would probably lead to an inhomogeneity of the PRL and granulation of the posterior surface of the detached retina.[12,14,22] Furthermore, as the period of serous retinal detachment increased, photoreceptor cell death increased, with a corresponding reduction in ONL thickness (Table 1).[8,23–25] This would possibly lead to the reduction of PRL renewal and/or the asynchronous elongation of the outer segments, thus contributing to the uneven outer border of the granulated PRL (Figure 1, D and E). As the CSC lasted for quite a long time (median duration of the third group: 1,855 days), the foveal ONL thickness decreased significantly (Table 1), which may suggest a further increase in photoreceptor cell death.[8,23–25] Theoretically, this would inevitably lead to a marked reduction in PRL renewal. Moreover, the scattered dots, which were assumed to be phagocytes with phagocytized outer segments,[22] might indicate that macrophages or microglial cells continued to migrate and phagocytize the PRL. Both of these factors could have contributed to the near absence of PRL in the eyes with scattered dots attached to the external limiting membrane (Figure 1F).

In addition to the changes in the appearance of the PRL, the ONL thickness continued to decrease as the symptom duration increased, which is consistent with

Table 1. The Number, Symptom Duration, BCVA, and Foveal ONL Thickness Difference of Eyes With Various PRL Appearances in Active CSC

	PRL Appearance on OCT			*P*			
	Smooth Outer Border	Granulated Outer Border	Scattered Dots	All Compared	Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
	Group 1	Group 2	Group 3				
No. of eyes	128	85	9				
Symptom duration (days)	18.50 (7.00, 42.00)	180.00 (79.00, 365.00)	1,855.00 (861.00, 2,235.00)	0.000*	0.000*	0.000*	0.078*
BCVA (logMAR)	6/10, 0.20 (0.10, 0.30)	6/15, 0.40 (0.20, 0.70)	6/120, 1.30 (1.15, 1.30)	0.000*	0.000*	0.000*	0.003*
Foveal ONL thickness difference (μm)	−16.43 ± 14.12	−31.72 ± 15.33	−59.78 ± 18.24	0.000†	0.000†	0.000†	0.000†

Values are expressed either as the median (P25, P75) or the mean ± SD, according to the results of normality tests.
*Kruskal–Wallis test, followed by post hoc multiple comparisons.
†One-way analysis of variance, followed by Bonferroni comparisons.

Table 2. The Number, Symptom Duration, BCVA, and Foveal ONL Thickness Difference of Eyes With a Smooth Outer Border of the PRL in Active CSC

	Smooth PRL Outer Border Appearance on OCT			*P*			
	Without PRL Defect	With Extrafoveal PRL Defect	With Foveal PRL Defect				
	Group 1	Group 2	Group 3	All Compared	Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
No. of eyes	45	47	36				
Symptom duration (days)	7.00 (6.50, 28.50)	20.00 (10.00, 42.00)	30.00 (14.00, 57.75)	0.000*	0.059*	0.000*	0.257*
BCVA (logMAR)	6/7.5, 0.10 (0.00, 0.20)	6/10, 0.20 (0.10, 0.20)	6/12, 0.30 (0.23, 0.60)	0.000*	0.626*	0.000*	0.000*
Foveal ONL thickness difference (μm)	−12.82 ± 12.02	−12.94 ± 13.39	−25.50 ± 13.70	0.000†	1.000†	0.000†	0.000†

Values are expressed as either the median (P25, P75) or the mean ± SD, according to the results of normality tests.
*Kruskal–Wallis test followed by post hoc multiple comparisons.
†One-way analysis of variance, followed by Bonferroni comparisons.

the finding of Hata et al[8] (Table 1). It is speculated that continuous ONL thinning results from the continuation of photoreceptor cell death after retinal detachment, through apoptosis, necroptosis, autophagy, and macrophage or microglial infiltration.[8,23–25] We also found that among the eyes with a smooth PRL outer border, which had similar symptom durations, the reduction in the foveal ONL thickness in eyes with a PRL defect involving the fovea was nearly double that in eyes either with no PRL defect or with an extrafoveal PRL defect (Table 2: −26 vs. −13 μm or −13 μm, respectively). The foveal ONL thickness difference in the eyes with a foveal PRL defect (−26 μm) was close to that found in the eyes with a granulated PRL outer border (−32 μm), although the latter group had a much longer symptom duration (median duration: 30 vs. 180 days, respectively). The overlap in their location suggests that the PRL defect and the thinning of the ONL are closely related. The exact mechanism remains unknown, but the following scenario is possible. It has been reported that neuronal defects in one compartment can trigger cellular degeneration in distant parts of the neuron.[26] Similarly, the partial detachment of the PRL, which is part of the photoreceptor cell, can lead to the impairment of the cell bodies (ONL). Furthermore, when the PRL is partially pulled from the retina, which is considered to cause the PRL defect,[15] some photoreceptor cell bodies (ONL) can also be pulled from it. Moreover, the photoreceptor cell death that occurs after retinal detachment, through various mechanisms, can reduce PRL renewal, and thus contribute to different PRL changes, including PRL defects.

Photoreceptor layer defects and PRL granulation both presented with an uneven PRL outer border but differed in several respects. Although photoreceptor cell death might contribute to both changes, the PRL defect is considered to be primarily caused by subretinal exudation in the early phase of CSC,[15] whereas it is speculated that PRL granulation results from the disintegration and/or phagocytosis by macrophages or microglial cells of the photoreceptor outer segments.[12,14,22] A PRL defect can be detected much earlier than PRL granulation (median duration: 28 days for PRL defect[15] vs. 180 days for PRL granulation), and in OCT images, the PRL defect is usually focal (in our group: average 665 μm,

Table 3. The Number, Symptom Duration, BCVA, and Foveal ONL Thickness Difference of Eyes With a Granulated Outer Border of the PRL in Active CSC

	Granulated PRL Outer Border Appearance on OCT		
	Without Protruding Foveal PRL	With Protruding Foveal PRL	*P*
No. of eyes	46	39	
Symptom duration (days)	95.50 (63.25, 365.00)	303.00 (133.00, 365.00)	0.018*
BCVA (logMAR)	6/15, 0.40 (0.20, 0.70)	6/20, 0.50 (0.20, 0.70)	0.901*
Foveal ONL thickness difference (μm)	−30.78 ± 15.00	−32.82 ± 15.84	0.545†

Values are expressed as either the median (P25, P75) or the mean ± SD, according to the results of normality tests.
*Mann–Whitney test.
†*t*-test.

range, 141–3,693 μm), whereas PRL granulation extends throughout the detached retina.

Symptom duration, determined from the recollection of the patient, is subjective and sometimes ambiguous in CSC.[14] Therefore, the treatment timing of CSC, which mainly depends on the duration of the symptoms, remains somewhat arbitrary.[27–30] In this study, we compared the symptom durations, BCVA ranges, and reductions in foveal ONL thickness with each type of change in the PRL. These data showed that the appearance of the PRL changed with the symptom duration increased, the BCVA decreased, and the foveal ONL thinned (Table 1). In this study, we also identified some partly inconsistent cases: eyes with similar symptom durations differed in the appearance of their PRL, their BCVA, and the reduction in their foveal ONL thickness (Table 2); or conversely, eyes with different symptom durations were similar in these parameters (Table 3). Therefore, our study suggests that, although these four aspects are closely correlated, they may not always behave in a synchronous manner. Symptom duration alone may be insufficient to indicate all the other clinical characteristics during an episode of CSC. Therefore, besides symptom duration, other objective parameters, such as the change in the PRL or the degree of ONL thinning, may be helpful when considering the timing of treatment. This study was limited by its cross-sectional design, and further longitudinal studies involving treatment might tell us more.

In conclusion, PRL appearance, BCVA, the reduction in foveal ONL thickness, and symptom duration correlated closely, but these parameters may behave asynchronously in some CSC eyes. These objective parameters could be used to complement symptom duration when considering the timing of CSC treatment.

Key words: central serous chorioretinopathy, optical coherence tomography, outer nuclear layer, photoreceptor layer.

References

1. Klais CM, Ober MD, Ciardella AP, Yannuzzi LA. Central serous chorioretinopathy. In: Schachat AP, ed. Retina. Vol 2. 4th ed. St. Louis, MO: Mosby; 2006:1135–1161.
2. Inoue M, Arakawa A, Yamane S, et al. Long-term outcome of macular microstructure assessed by optical coherence tomography in eyes with spontaneous resolution of macular hole. Am J Ophthalmol 2012;153:687–691.
3. Uji A, Murakami T, Unoki N, et al. Parallelism as a novel marker for structural integrity of retinal layers in optical coherence tomographic images in eyes with epiretinal membrane. Am J Ophthalmol 2014;157:227–236.e4.
4. Adhi M, Read SP, Ferrara D, et al. Morphology and vascular layers of the choroid in Stargardt disease analyzed using spectral-domain optical coherence tomography. Am J Ophthalmol 2015;160:1276–1284.e1.
5. Kamppeter B, Jonas JB. Central serous chorioretinopathy imaged by optical coherence tomography. Arch Ophthalmol 2003;121:742–743.
6. Montero JA, Ruiz-Moreno JM. Optical coherence tomography characterisation of idiopathic central serous chorioretinopathy. Br J Ophthalmol 2005;89:562–564.
7. Matsumoto H, Kishi S, Otani T, Sato T. Elongation of photoreceptor outer segment in central serous chorioretinopathy. Am J Ophthalmol 2008;145:162–168.
8. Hata M, Oishi A, Shimozono M, et al. Early changes in foveal thickness in eyes with central serous chorioretinopathy. Retina 2013;33:296–301.
9. Ojima Y, Hangai M, Sasahara M, et al. Three-dimensional imaging of the foveal photoreceptor layer in central serous chorioretinopathy using high-speed optical coherence tomography. Ophthalmology 2007;114:2197–2207.
10. Matsumoto H, Sato T, Kishi S. Outer nuclear layer thickness at the fovea determines visual outcomes in resolved central serous chorioretinopathy. Am J Ophthalmol 2009;148:105–110.e1.
11. Ohkuma Y, Hayashi T, Sakai T, et al. One-year results of reduced fluence photodynamic therapy for central serous chorioretinopathy: the outer nuclear layer thickness is associated with visual prognosis. Graefes Arch Clin Exp Ophthalmol 2013;251:1909–1917.
12. Fujimoto H, Gomi F, Wakabayashi T, et al. Morphologic changes in acute central serous chorioretinopathy evaluated by fourier-domain optical coherence tomography. Ophthalmology 2008;115:1494–1500.
13. Matsumoto H, Kishi S, Sato T, Mukai R. Fundus autofluorescence of elongated photoreceptor outer segments in central serous chorioretinopathy. Am J Ophthalmol 2011;151:617–623.e1.
14. Song IS, Shin YU, Lee BR. Time-periodic characteristics in the morphology of idiopathic central serous chorioretinopathy evaluated by volume scan using spectral-domain optical coherence tomography. Am J Ophthalmol 2012;154:366–375.e4.
15. Yu J, Jiang C, Xu G. Study of subretinal exudation and consequent changes in acute central serous chorioretinopathy by optical coherence tomography. Am J Ophthalmol 2014;158:752–756.e2.
16. Li HK, Hubbard LD, Danis RP, et al. Comparison of multiple stereoscopic and monoscopic digital image formats to film for diabetic macular edema evaluation. Invest Ophthalmol Vis Sci 2010;51:6753–6761.
17. DeCroos FC, Toth CA, Stinnett SS, et al. Optical coherence tomography grading reproducibility during the comparison of age-related macular degeneration treatments trials. Ophthalmology 2012;119:2549–2557.
18. Koch GG, Landis JR, Freeman JL, et al. A general methodology for the analysis of experiments with repeated measurement of categorical data. Biometrics 1977;33:133–158.
19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
20. Yu J, Jiang C, Wang X, et al. Macular perfusion in healthy Chinese: an optical coherence tomography angiogram study. Invest Ophthalmol Vis Sci 2015;56:3212–3217.
21. Nguyen-Legros J, Hicks D. Renewal of photoreceptor outer segments and their phagocytosis by the retinal pigment epithelium. Int Rev Cytol 2000;196:245–313.
22. Maruko I, Iida T, Ojima A, Sekiryu T. Subretinal dot-like precipitates and yellow material in central serous chorioretinopathy. Retina 2011;31:759–765.

23. Cook B, Lewis GP, Fisher SK, Adler R. Apoptotic photoreceptor degeneration in experimental retinal detachment. Invest Ophthalmol Vis Sci 1995;36:990–996.
24. Hisatomi T, Sakamoto T, Goto Y, et al. Critical role of photoreceptor apoptosis in functional damage after retinal detachment. Curr Eye Res 2002;24:161–172.
25. Matsumoto H, Kataoka K, Tsoka P, et al. Strain difference in photoreceptor cell death after retinal detachment in mice. Invest Ophthalmol Vis Sci 2014;55:4165–4174.
26. Conforti L, Adalbert R, Coleman MP. Neuronal death: where does the end begin? Trends Neurosci 2007;30:159–166.
27. Chan WM, Lai TY, Lai RY, et al. Half dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. Ophthalmology 2008;115:1756–1765.
28. Lim JI, Glassman AR, Aiello LP, et al. Collaborative retrospective macula society study of photodynamic therapy for chronic central serous chorioretinopathy. Ophthalmology 2014;121:1073–1078.
29. Fujita K, Imamura Y, Shinoda K, et al. One-year outcomes with half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy. Ophthalmology 2015;122:555–561.
30. Zhao M, Zhang F, Chen Y, et al. A 50% vs 30% dose of verteporfin (photodynamic therapy) for acute central serous chorioretinopathy: one-year results of a randomized clinical trial. JAMA Ophthalmol 2015;133:333–340.