Morphological Changes of Outer Retinal Layers in Acute Central Serous Chorioretinopathy Evaluated by Spectral Domain Optical Coherence Tomography

Akut Santral Seröz Koryoretinopatide Dış Retinal Tabakaların Morfolojik Değişiminin Spektral Domain Optik Koherens Tomografi ile Değerlendirilmesi

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ABSTRACT

Objective: To evaluate changes in thickness beyond the external limiting membrane (ELM) and the photoreceptor inner and outer segment junction (IS/OS) in patients with acute central serous chorioretinopathy (CSC) and a granular (brush border) appearance of a detached posterior retina.

Material and Methods: The retinal area below the ELM at a 1,000 µm diameter zone centered on the fovea, and the greatest thickness below the IS/OS band in this area was measured by optical coherence tomography (OCT) at baseline, as well as at the 3- and 6-month visits.

Results: Sub-IS/OS thickness and the sub-ELM area did not differ statistically between baseline and month 3; however, they significantly increased from month 3 to month 6.

Conclusion: In patients with CSC and a brush appearance of the posterior border of the detached retina, sub-IS/OS thickness and sub-ELM area increased after 3 months if the retina was not reattached.

Key Words: Brush border, Central serous chorioretinopathy, Granular appearance, IS/OS; ELM

ÖZ

Amaç: Akut santral seröz koryoretinopatide (SSRP), eksternal limitan membran (ELM), fotoreseptör iç ve dış segment bileşkesi ve ayrılan retinadaki granüler fırçamsı kenar görünümünü değerlendirmek.

Gereç ve Yöntemler: Optik koherens tomografi (OKT) ile yapılan ölçümlerde fovea merkezi santral alınarak 1000 µm uzunluğundaki bölgede; ELM altında kalan retina alanı ile fotoreseptör iç ve dış segment bandı altındaki en fazla kalınlık ölçümü ilk başvuruda, üçüncü ve altıncı ayda değerlendirildi.

Bulgular: Fotoreseptör iç ve dış segment bandı altındaki kalınlık ile ELM altında kalan alan ölçümlerinde başlangıç ve üçüncü ay arasında istatistiksel olarak anlamlı fark görülmezken, üçüncü ay ile altıncı ay arasında anlamlı artış olduğu görüldü.

Sonuç: Akut SSRP hastalarında ayrılan retinadaki fırçamsı kenar görünümü, fotoreseptör iç ve dış segment bandı altındaki kalınlık ve ELM altındaki alan eğer retina tekrar yapışmazsa üçüncü aydan sonra artış göstermektedir.

Anahtar Sözcükler: Fırçamsı kenar, Santral seröz koryoretinopati, Granüler görünüm, Fotoreseptör iç/dış segment bandı, Eksternal limitan membran

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous retinal detachment (RD) and/or retinal pigment epithelial (RPE) detachment in the macula. Albrecht von Graefe described this disease in 1866 (1). Although the etiopathogenesis of CSC is unclear, the primary pathology has been thought to be an abnormality of the RPE and choroidal vasculature (2, 3).

Optical coherence tomography (OCT) findings of CSC include neurosensory RD, pigment epithelial detachment (PED), fibrinous exudates, and cystic changes of the retina (4-6). Spectral-domain OCT (Sd-OCT) has the potential to provide valuable information about additional retinal microstructural changes in CSC. Detailed images of the photoreceptor layer can be captured via Sd-OCT, and the changes in the photoreceptor layers are well described.

Recently, a granulated (brush border) appearance on the outer segment (OS) of the photoreceptor layer and accompanying changes in thickness have been described in OCT images. However, there is some controversy regarding these changes, including their precise meaning and how they change over the course of the disease. While some authors have reported that photoreceptor OS thickness increases (7), others have reported that it does not change (8), while others still have reported that it increases during the acute phase and then gradually decreases (9). Further, some authors have reported that a brush border appearance on the OS is more frequently observed in chronic or recurrent cases versus acute CSC (10, 11).

In disease-free eyes with a normal anatomy, the inner and outer segment (IS/OS) band marks the border of the photoreceptor OS. However, normal anatomy is altered in CSC patients and there is no histological evidence that an increase in thickness beyond the IS/OS band reflects an increase in photoreceptor OS thickness.

In the current study, we aimed to evaluate thickness changes beyond the external limiting membrane (ELM) and IS/OS in patients with a presumed increase in photoreceptor OS thickness with a granular (brush border) appearance, and discuss the underlying mechanisms.

MATERIAL and METHODS

We retrospectively reviewed the files of patients who were first diagnosed with CSC between 2013 and 2015. The main inclusion criteria were diagnosis of acute CSC and a brush border appearance on the photoreceptor OS in OCT images. A diagnosis of acute CSC was made based on the duration of subjective symptoms, the presence of serous detachment of the neurosensory retina in OCT, and focal dye leakage in fluorescein angiography (FA).

Only patients with a symptom duration of 1 month or less and a follow up of at least 6 months were included. Our aim was to evaluate microstructural OCT changes in the outer retinal layers in naive CSC patients during a prolonged course; thus, if patients received any treatment or if the serous RD resolved during the 6-month follow up, patients were not included. Also, chronic and recurrent cases and eyes with other accompanying retinal diseases were excluded from the study.

All participants underwent a comprehensive ophthalmic examination, including assessment of best corrected visual acuity (BCVA) with a Snellen chart, slit-lamp biomicroscopy, intraocular pressure measurement with a Goldmann applanation tonometer, and a dilated fundus examination. All patients had baseline FA and OCT images.

Included patients were observed without any intervention for 6 months. After this period, focal laser photocoagulation in eyes with extrafoveal leakage or half-dose photodynamic therapy (PDT) in eyes with juxtafoveal and subfoveal leakage was performed in patients who showed persistent subretinal fluid (SRF). The OCT images were evaluated at baseline, month 3, and month 6. All OCT images were obtained by the same experienced technician with the same spectral domain OCT instrument (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany).

In OCT images, we identified the horizontal section which passed through the foveolar depression. The thickness below the IS/OS band was measured manually. The OCT images were digitally enlarged to four times their original size, and the caliper feature of the device was used to mark the IS/OS band and the outer border of the brush border appearance (Figure 1A). If the IS/OS band was invisible, then the center of the line identified at the closest site was traced and measured. Also in this image, we measured the sub-ELM area in the central foveolar area in a 1,000 µm diameter. For this measurement, once again the OCT images were enlarged digitally to four times their original size and the caliper feature of the device was used to draw the area between the external limiting membrane and the outer border of brush border appearance. To measure this area in a 1,000 µm circle, we manually drew two lines that were 500 µm away from the center of the fovea nasally and temporally (Figure 1B). All measurements were made by the same physician (AD), who was blinded to the clinical data of the patients.

The main outcomes measured in this study were changes in sub-IS/OS thickness and sub-ELM area throughout the follow up.

Statistical methods: Mean, standard deviation, median, minimum, and maximum values, frequency, and ratio were used to describe the data set. Distribution of the data

was measured using the Kolmogorov-Smirnov test. The Wilcoxon test was used to analyze repeated measures.

RESULTS

The mean duration of patient symptoms was 19±8 days (range 10–30). Seven patients (23.3%) were female and 23 (76.7%) were male. Changes in visual acuity, sub-IS/OS thickness, and sub-ELM area are summarized in Table 1A,B and Figure 2A,B. An argon laser was used in five patients, and PDT was performed in 25 patients after 6 months of follow up. One patient from the argon laser group and two patients from the PDT group still showed active disease at the last follow-up visit.

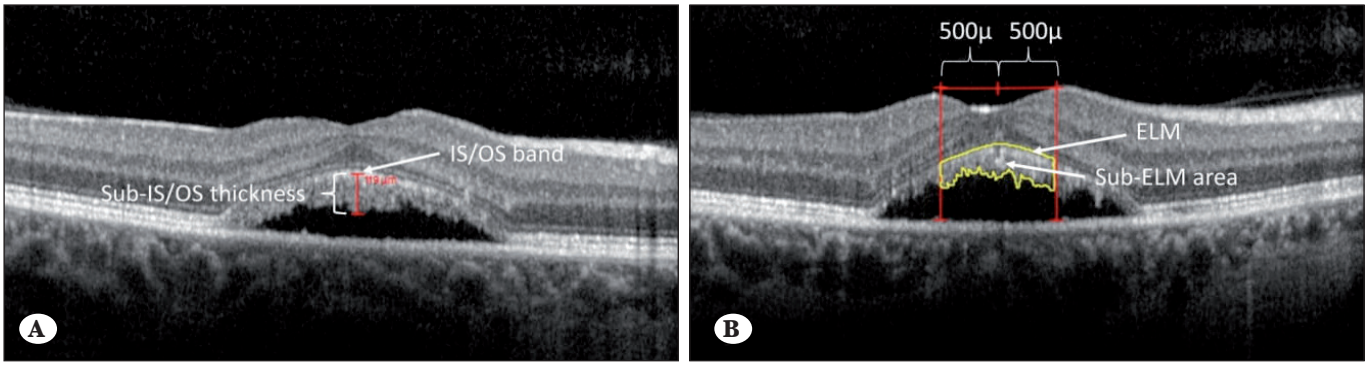

Figure 1: A) Sub-inner and outer segment (IS/OS) thickness measurement **B)** Sub-external limiting membrane (ELM) area measurement.

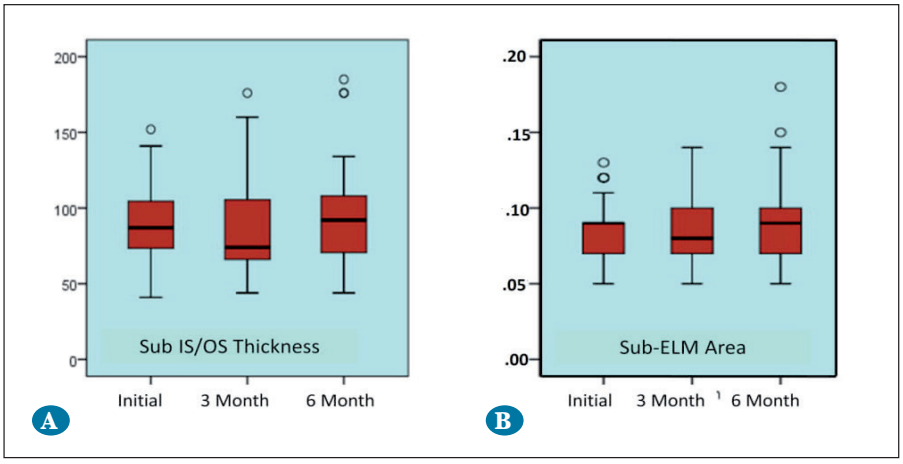

Figure 2: A) Sub-inner and outer segment (IS/OS) thickness. **B)** Sub-external limiting membrane (ELM) area.

Table I: Clinical data during follow up.

	Min-Max	Median	Mean±SD.	*P**	*P***
Visual acuity (logMAR)					
Baseline	1.3-0.1	0.3	0.3±0.5		
Month 3	1.0-0.1	0.4	0.3±0.5	0.529	
Month 6	1.0-0.1	0.3	0.2±0.5	0.168	0.773
sub-ELM area (μm^2)					
Baseline	0.05-0.13	0.09	0.09±0.02		
Month 3	0.04-0.14	0.08	0.08±0.02	0.147	
Month 6	0.04-0.18	0.09	0.09±0.03	0.621	**0.039**
Sub-IS/OS thickness(µ)					
Baseline	41-152	86	90.0±28.2		
Month 3	44-176	73	85.0±33.7	0.275	
Month 6	44-185	91	95.7±36.0	0.407	**0.022**

Wilcoxon test, ***:** compared to the first visit, ****:** compared to the previous visit, **Min:** Minimum, **Max:** Maximum, **SD:** Standard Deviation, **ELM:**External Limiting Membrane **IS/OS:** Inner and Outer Segment junction

Sub-IS/OS thickness did not differ statistically between baseline and month 3 (p=0.2); however, it significantly increased from month 3 to month 6 (p=0.02). The sub-ELM area was not statistically different between baseline and month 3 (p=0.1); however, it significantly increased from month 3 to month 6 (p<0.03).

DISCUSSION

Changes in the outer retina in CSC patients have been reported in several previous studies (7-11). In this study, we evaluated microstructural OCT changes in the outer retinal layers in naive CSC patients over a prolonged course, and mainly focused on the thickness and area of the outer retinal layer because previous reports indicate a change in the anatomy of these layers (9-11). We also focused on patients with a granular appearance of the outer border of the detached retina because the clinical significance of this appearance is not clear. As thickness changes and granularity are thought to reflect disease duration, chronicity, and recurrence of disease, we evaluated thickness changes in new-onset CSC patients with a brush border appearance during a prolonged disease course (6 months) without intervention.

To compare our results with others reported in the literature, we measured sub-IS/OS thickness, which in normal eyes reflects the photoreceptor OS. Sub-IS/OS thickness increased and was very similar to the reported mean of the photoreceptor OS thickness reported by other authors. For example, Matsumoto et al. reported photoreceptor OS elongation in CSC, observing that the average thickness of the longest outer photoreceptor segment was 90 µm in CSC, which was significantly longer than that of healthy subjects with a normal value of 60 µm (7). They hypothesized that photoreceptor OS elongation in CSC may be due to a lack of photoreceptor phagocytosis by the RPE. However, we believe that one should be cautious in attributing this increase in thickness to an increase in photoreceptor OS elongation because there is no evidence that photoreceptors are the cause of this increased mass below the IS/OS band. In our study, sub-IS/OS thickness was 90, 85, and 95 µm during the initial and 3- and 6-month visits, respectively. Fujimoto et al. also reported that photoreceptor OS thickness increased in the acute phase of the CSC and then gradually decreased, while the OS appearance became granular until reattachment (9). However, they did not report thickness values or a statistical analysis of their observations. In contrast to these authors, Yu et al. reported that there was no difference between the length of the photoreceptor OS in eyes with CSC (8). In contrast to these studies, we measured thickness changes at three different timepoints during a 6-month follow up. We observed that sub-IS/OS thickness shows a statistically non-significant decrease at 3 months (85 versus 90 µm) compared with baseline, and then a statistically significant increase (85 versus 95 µm) at 6 months compared with the 3-month visit.

As the subretinal border is irregular in CSC patients, it may be misleading to compare thickness changes at just one location. In addition, the IS/OS band is not always visible in the detached retina of CSC patients. Thus, we also performed an area measurement based on a more reliable reference point that is detectable in all patients. We measured the retinal area below the ELM at a 1,000 µm diameter zone centered on the fovea. Similar to the sub-IS/OS thickness, we found that sub-ELM area shows a statistically non-significant decrease at 3 months compared with baseline, and then a statistically significant increase at 6 months compared with the 3-month visit.

A granular (brush border) appearance in the photoreceptor OS is an entity seen in some CSC patients who have a presumed increased thickness of the photoreceptor OS. Some authors reported that this appearance is seen more frequently in chronic or recurrent cases versus acute CSC. (10, 11) Fujimoto et al. indicated that this photoreceptor OS appearance developed after several weeks of acute CSC (9). However, they also indicated that patients with a granular appearance of the photoreceptor OS have a much longer mean duration of subjective symptoms when compared with patients who have a smooth appearance (42 days versus 10 days). In contrast, Ozdemir et al. stated that this appearance does not indicate evidence of CSC chronicity, and can even occur a short time after an acute attack of CSC (12). In agreement with Ozdemir et al., our study clearly shows that a granular appearance may develop within a shorter time, as all the patients in our study had a history of 1 month or less (mean, 19±8 days).

The reasons behind brush border appearance and thickness changes in CSC should be considered, and potential mechanisms may be proposed, as follows. First, the effect may be due to an accumulation of shed photoreceptor OS and a lack of phagocytosis by RPE as described previously (7). On the basis of our study, we can potentially propose that RPE cells may phagocyte the OS initially and, after a certain period such as 3 months, their phagocytosis capacity is overloaded and then the brush border appearance thickness and area may increase.

Second, Müller cells may be responsible for these changes. The only mechanism for increased OS thickness proposed so far is elongation of the photoreceptor OS. However, Fisher et al. showed that as rod photoreceptors degenerate, photoreceptor OS shorten (not elongate) and Müller cells grow into the subretinal space in the RD model of a feline retina (13). In addition, in their histologic study on human retinas, Malia et al. reported that Müller cells extend

through the ELM into the subretinal space during retinal degeneration in diseases characterized by photoreceptor degeneration (14). They assert that Müller cell protrusions may indicate the remodeling of Müller cells in response to photoreceptor damage. The absence of dramatic OS elongation or lack of a brush border appearance in serous macular detachment in diabetic retinopathy may be explained by the damage to Müller cells in diabetes. However, this is only a proposal taking into account previous findings, probable pathogenesis of the disease, and our findings.

The longitudinal design and clearly defined main outcome measures were the major strengths of this study, while the main limitations were the retrospective design and relatively low number of patients. However, we used strict inclusion criteria to create a homogenous group of patients.

CONCLUSION

In conclusion, a brush border appearance is a common finding in acute CSC patients, but does not indicate chronicity or recurrent disease. We revealed that the sub-ELM area and sub-IS/OS thickness decreased (non-significantly) during the first 3 months in new-onset CSC patients but increased over the following 3 months if the retina was not reattached and no intervention was performed. We proposed a mechanism in regard to these findings; however, these data need to be evaluated in detail in further studies.

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