Int Ophthalmol (2019) 39:1323–1328
https://doi.org/10.1007/s10792-018-0950-y

ORIGINAL PAPER

Outer nuclear layer thickness at the central fovea relation with symptom duration in central serous chorioretinopathy

Ibrahim Ozdemir · Ayla Eren · Giray Ersöz

Received: 17 January 2017 / Accepted: 4 June 2018 / Published online: 18 June 2018

Abstract
Purpose To evaluate a relation between the outer nuclear layer (ONL) thickness and symptom duration in patients with central serous chorioretinopathy (CSC) using spectraldomain optical coherence tomography (SDOCT) and to compare with healthy subjects.
Methods This retrospective study included 67 CSC patients and 20 healthy subjects. The ONL thickness was measured between internal limiting membrane and external limiting membrane at central fovea using SD-OCT (Topcon 3D OCT-2000, Japan). The patients were divided into six groups based on symptom duration: group (1) contained 14 patients (symptom duration between 1 and 30 days) , group (2) contained 11 patients (symptom duration between 31 and 60 days), group (3) contained 12 patients (symptom duration between 61 and 90 days) , group (4) contained 11 (symptom duration between 91 and 120 days), group (5) contained 7 patients (symptom duration between 121 and 150 days) and group (6) contained 12 (symptom duration between 151 days and more).
Results The average ONL thickness was 76.1 ± 16.8 μm in CSC in all patients and 122.4 ± 2.8 μm in healthy subjects. The major differences were between group (3) and (4) ($p < 0.001$). The ONL thickness was negatively correlated with symptom duration ($rs = -0.918$; $p < 0.001$). In addition, the ONL thickness was positively correlated with BCVA ($rs = 0.619$; $p < 0.001$).
Conclusion Photoreceptor loss could begin within the first 3 months in CSC.

Keywords Central serous chorioretinopathy · Outer nuclear layer · Symptom duration · Eplerenone

Introduction

Central serous chorioretinopathy (CSC) is an important cause of central vision loss in young adult men, which is also characterized by serous detachment of the neurosensory retina in the macula. Decreasing visual acuity (VA), metamorphopsia and micropsia are major complaints of CSC. Although VA generally returns to normal after resolution of the subretinal fluid; metamorphopsia, micropsia and relative scotoma often persist. Prolonged subretinal fluid (SF) generally results in poor visual outcome [1].

I. Ozdemir (✉)
Department of Ophthalmology, Yenikent State Hospital, Sakarya, Turkey
e-mail: dr.ibrahimozdemir@gmail.com

A. Eren
Department of Biomedical Engineering, Sakarya University, Sakarya, Turkey

G. Ersöz
Department of Ophthalmology, Mardin Kiziltepe State Hospital, Mardin, Turkey

The primary pathology underlying in CSC is still controversial. Defective pumping function of the retinal pigment epithelium (RPE), breakdown of the barrier function of the RPE, increased vasodilation-hyperpermeability of the choriocapillaris and thickening of the choroid are among the etiologies hypothesized in the pathogenesis of CSC. Recently, the over-activation of the mineralocorticoid receptor (MR) pathway or the over-response of MR to glucocorticoids in the choroid vessels has been thought to have presumed for the pathogenesis of CSC [2].

The availability of optical coherence tomography (OCT) has vastly improved the anatomical or pathologic evaluation of CSC by providing cross-sectional imaging of the macula and the presence of the subretinal fluid [3]. Spectral-domain OCT (SD-OCT) demonstrates retinal layers and hyper-reflective lines such as the external limiting membrane (ELM), the internal limiting membrane (ILM) and the photoreceptor inner and outer segment junction (IS/OS). In CSC, microstructural changes of IS/OS, retinal pigment epithelium (RPE), choroid and retinal layers were investigated by using OCT in the recent studies [4–10].

The CSC can be classified into subtypes according to clinical and OCT findings. Acute CSC is defined as self-resolving SF within 3–4 months from the onset of symptoms. Persistent CSC is defined as acute CSC with prolonged SF for more than 4 months associated with elongated photoreceptor outer segments on SD-OCT scan. Recurrent CSC is defined as emerging of SF after resolution of the acute CSC [11].

To date, treatment options are based on the presumed CSC pathogenesis. Laser photocoagulation (LP) had been used to fix the RPE leakage points. Photodynamic therapy (PDT) with verteporfin has been used to seal the leakage on choriocapillaris [11–13]. MR antagonists have been used to block the MR pathway in the choroid vessels [2, 11–13].

In this study, we compared the thickness of the outer nuclear layer (ONL) by duration of symptoms in CSC patients who underwent SD-OCT; in order to discuss timing of treatment of CSC as a predictor of the ONL thickness at the fovea.

Materials and methods

This retrospective study consisted of 67 eyes (55 men and 12 women) with naive CSC using SD-OCT, who admitted to the Ophthalmology Outpatient Clinic in Izmir Tepecik Research Hospital between 2007 and 2015. The study followed the tenets of the Declaration of Helsinki, and it was approved by local ethical committee.

Patients with naive CSC diagnosed by the presence of subretinal fluid at the macula who had of SD-OCT B-scan images that were available were included the study. The exclusion criteria were: history of any treatment for the CSC, macular abnormality or cause of the CSC such as neovascular maculopathy (i.e., idiopathic choroidal neovascularization, polypoidal choroidal vasculopathy, age-related macular degeneration, or other secondary choroidal neovascularization), history of vitreoretinal surgery or intravitreal injection, any ocular disorder as a cause of vision loss other than CSC, evidence of glaucoma, spherical equivalent $\geq \pm$ 6D, media opacity likely to cause attenuation of signal strength in OCT.

A detailed ophthalmologic examination included the measurement of best-corrected visual acuity (BCVA) in Snellen, slit-lamp biomicroscopy, fundus examination with a non-contact lens, SD-OCT and fluorescein angiography (FA). CSC was diagnosed when focal serous retinal elevation seen in the fundus examination and serous neurosensory detachment seen in B-scan OCT image. FA (TRC 50 IX, Topcon Medical Systems, Oakland, USA) was performed in selected cases. In FA, leakage from the RPE was interpreted as CSC.

Eyes were divided into six groups by the duration of symptoms. Group (1) included patients with symptom duration of less than 1 month. Group (2) included patients with symptom duration of 1–2 months. Group (3) included patients with symptom duration of 2–3 months. Group (4) included patient with symptom duration of 3–4 months. Group (5) included patients with symptom duration of 4–5 months. Group (6) included patients with symptom duration of more than 5 months. The control group was formed by healthy subjects who admitted to the ophthalmology outpatient clinic. They had similar gender and age as the study group, and they did not have any ocular disease.

All patients underwent the 3D OCT-2000FA plus Spectral Domain (Topcon Medical Systems, Inc. Tokyo, Japan) which had 840 nm wavelength light source, 5-μm axial image resolution and a speed of 27,000 A-scans per second. The single 9 mm horizontal line scan through the center of the fovea with

1024 A-scans/B-scan was captured 50 times in the same position and overlapped the 50 B-scan image by the software of OCT. The distance between the internal limiting membrane (ILM) and the external limiting membrane (ELM) at the central fovea was measured as ONL (Fig. 1). Scans with low quality were excluded. Measurements were performed manually by the same ophthalmologist (IO) using built-in caliper in linear measuring tool of the OCT software.

The statistical analysis of the data was performed using the SPSS statistical package version 20.0 (SPSS Inc., Chicago, IL, USA). Days were used for the criterion of symptom duration for statistical purposes and transformed log MAR and also BCVA in Snellen was transform log MAR. The Kolmogorov–Smirnov test was used to check the normality of the sample distribution. Levene test was used for checking variance homogeneity. Mann–Whitney *U* test was used to evaluate the significance of differences between the groups. The relationship between the ONL thickness at the central fovea and the BCVA was evaluated using the Spearman rank correlation test as well. The level of statistical significance was set at $p < 0.05$.

Results

Sixty-seven eyes of 67 patients (55 men and 12 women) and twenty healthy controls (14 men 6 women) were included to this study. The mean age ± SD of the patients was 39.3 ± 9.8 years, and the healthy controls was 35.9 ± 11.6 years (Table 1). The patients' ages ranged from 21 to 64 years. The age of healthy controls ranged from 20 to 56 years. Symptom duration ranged from 10 days to 3 years (median 90 days). The average ONL thickness at the central fovea in the patients was 76.1 ± 16.8 μm, while it was 122.4 ± 2.8 μm in the healthy controls. The average ONL at the central fovea of the patients was significantly ($p < 0.000$) thinner than the healthy controls. The average ONL at the central fovea was thickest in group 1 (94.6 ± 10.4 μm) and thinnest in group 6 (51.2 ± 5.0 μm) (Table 2). The ONL thickness was negatively correlated with symptom duration ($r_s = -0.918$; $p < 0.001$). In addition, the ONL thickness was positively correlated with BCVA ($r_s = 0.619$; $p < 0.001$).

Discussion

The ONL is contained by the nucleus of photoreceptor cell. The ELM, which is a junctional complex between photoreceptors and the Muller cell, is the outer border of the ONL. The ILM at the central fovea is the inner border of ONL with 1–3 layers of Henle fibers. SD-OCT could not notice this tiny Henle fiber layers. For this reason, we described the ONL thickness at the central fovea as the distance between the ILM and ELM.

In this study; the ONL thickness was thinner in patients (76.1 μm) than healthy controls (122.4 μm). The thickness of ONL in Group 1, which had the thickest ONL, was similar with Group 2. The major difference in ONL thickness was between groups 3 and 4. Group 3 consisted of patients in the third month of CSC. Group 4 consisted of patients in the fourth month of CSC (Graph 1). The ONL thickness was directly getting thinner as subretinal fluid duration

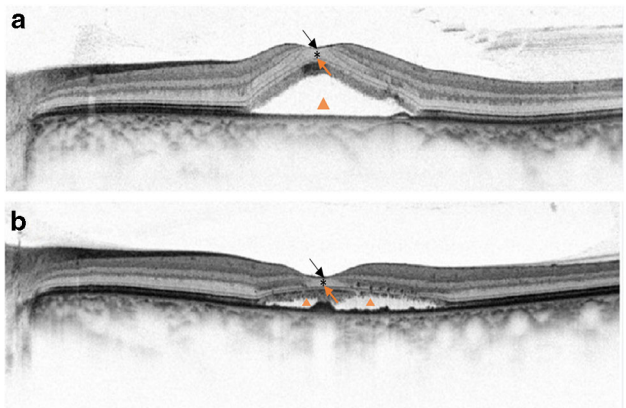

Fig. 1 OCT scans in CSC patients. Black arrow is pointing ILM, red arrow is pointing ELM. Asterisk is on ONL and red triangle is displaying SF. **a** 22-year-old man in tenth day of symptom whose ONL thickness is 94 μm. **b** 35-year-old woman in one hundredth day of symptom whose ONL thickness is 83 μm

Table 1 Demographic data of the all CSC patients and the healthy subjects

	Man		Woman	
CSC patients (67)	55 *n*	39.2 ± 10.3 years	12 *n*	39.2 ± 7.0 years
Healthy subjects (20)	14 *n*	35.0 ± 12.1 years	6 *n*	38.0 ± 11.2 years

Table 2 Distribution of average of the ONL thickness according to the groups

	Eyes (*n*)	ONL ± SD (μm)	*P**
Group 1	14	94.6 ± 10.4	
Group 2	11	88.1 ± 6.1	0.120643
Group 3	12	81.4 ± 6.5	0.044464
Group 4	11	70.5 ± 6.7	0.000967
Group 5	7	62.7 ± 2.8	0.004448
Group 6	12	51.2 ± 5.0	0.000692

*Significance of difference orderly between the groups

increased ($r_s = -0.918$) (Fig. 2). SF elongated the OS, turning the retina at the macula into a dome. Photoreceptor cells dispersed a larger area before they existed. The dispersion, could lead to the ONL being evaluated relatively thinner. Another reason could be the damage suffered by the photoreceptor cells forming the ONL. In the light of these results, the first 3 months may be the most important period in the CSC, because attenuation of the ONL accelerated after 3 months of disease.

Wang et al. reported progressing of foveal attenuation when the retinal detachment (RD) is more prolonged [7]. In addition, an experimental study showed that apoptosis of photoreceptor cell started in 1–3 days in eyes with RD [14, 15]. Subretinal fluid physically separated photoreceptor cells from the RPE that disrupted the mutual metabolism including exchange of metabolites and digestion of OS's membranes. The breakdown of mutual relation could start the apoptosis. The apoptosis of photoreceptor cell or attenuation of ONL thickness could start in 1–3 days and could progress until resolution of subretinal fluid or could continue after resolution [5].

Ojima et al. [5] observed 11 eyes resolved with CSC using SD-OCT and divided the eyes according to IS/OS line defect's size. The ONL thickness was measured indirectly, and their results were similar to our study. Matsumato et al. [4] studied 67 eyes with resolved CSC using SD-OCT; they divided the eyes into two groups by VA and measured the ONL thickness. The ONL thickness was 74.6 μm in the group where VA was less than 1.0; and 103.2 μm in the other group where VA was 1.0 or better. Their results in the low VA group were similar to our study. They also demonstrated the relationship between ONL thickness and VA, but we also showed the ONL attenuation based on duration of symptoms. Vogel et al. followed 5 patients with CSC. They studied microstructural changes in ONL and photoreceptor layers using adaptive optics scanning light ophthalmoscopy and SD-OCT. They did not compare ONL with VA and had only a few cases [16].

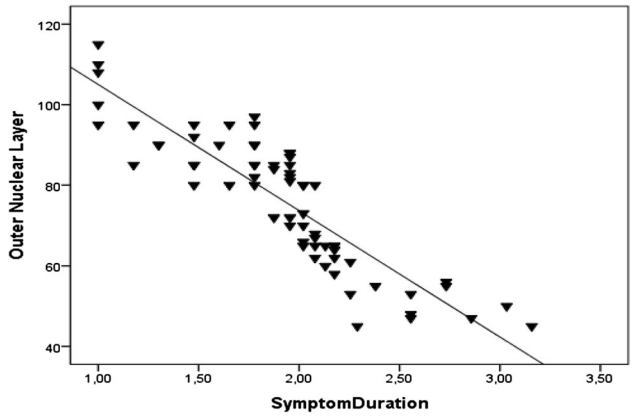

Fig. 2 Correlation between the ONL thickness at the central fovea and symptom duration

The treatment of the CSC is still controversial. Acute CSC is a self-limited disease, which can recover within 3–4 months [17]. Thus, observation could be the first-line approach. LP can be an option in acute CSC, which has single leakage at 500 mm away from the fovea, in patients with SF persisting for more than 3–4 months. Although LP seems safe, a few side effects including paracentral scotoma and iatrogenic CNV have been reported [12]. PDT with verteporfin has been used to reduce choroidal congestion, choroidal vascular hyperpermeability and choroidal leakage in the treatment of CSC [18]. However, long term prospective studies with follow-up of more than 12 months, studying visual recovery, recurrence rates, results of retreatments, rate and kinds of side effects of PDT, do not exist. Oral medications include: carbonic anhydrase inhibitor, beta-blockers, antibiotics-proton pump inhibitors (both of them used to eradicate the Helicobacter pylori) and anti-platelets [19]. But the effectiveness of these drugs in the treatment of the CSC are not analyzed with large prospective studies. MR antagonists have been used for the treatment of hypertension.

Based on the hypothesis that the over-activation of mineralocorticoid receptor (MR) pathway has presumed as a CSC pathogenesis, the MR antagonists have been suggested for treatment of the CSC. Oral administration of MR antagonists for the treatment of the CSC in small case series demonstrated reduction in the SF, reduction in choroidal thickness, anatomical recovery, and an increase in VA [20, 21].

As a result, there is no treatment option(s) within first 3–4 months of the CSC. On the other hand, according to our study, thinning of the ONL or photoreceptor damage could start in the first 3 months of the CSC. In the near future, MR antagonists could be an option if used within the first 3 months to prevent thinning of the ONL.

Author's contribution All of the authors contributed planning, conduct, and reporting of the work. All contributors are responsible for the overall content as guarantors.

Compliance with ethical standards

Conflict of interests All of the authors have no conflict of interest.

Ethical approval Author has taken these ethical rules by İzmir Katip Çelebi University at 20.02.2016, number of Ethical rules: 1029.

References

1. Iida T, Hagimura N, Sato T, Kishi S (2000) Evaluation of central serous chorioretinopathy with optical coherence tomography. Am J Ophthalmol 129:16–20
2. Behar-Cohen F, Zhao M (2016) Corticosteroids and the retina: a role for the mineralocorticoid receptor. Curr Opin Neurol 29:49–54
3. Spaide RF, Koizumi H, Pozzoni MC (2008) Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 146:496–500
4. Matsumoto H, Sato T, Kishi S (2009) Outer nuclear layer thickness at the fovea determines visual outcomes in resolved central serous chorioretinopathy. Am J Ophthalmol 148:105–110
5. Ojima Y, Hangai M, Sasahara M, Gotoh N, Inoue R, Yasuno Y, Makita S, Yatagai T, Tsujikawa A, Yoshimura N (2007) Three-dimensional imaging of the foveal photoreceptor layer in central serous chorioretinopathy using high-speed optical coherence tomography. Ophthalmology 114:2197–2207
6. Piccolino FC, de la Longrais RR, Ravera G et al (2005) The foveal photoreceptor layer and visual acuity loss in central serous chorioretinopathy. Am J Ophthalmol 139:87–99
7. Wang MS, Sander B, Larsen M (2002) Retinal atrophy in idiopathic central serous chorioretinopathy. Am J Ophthalmol 133:787–793
8. Eandi CM, Chung JE, Cardillo-Piccolino F, Spaide RF (2005) Optical coherence tomography in unilateral resolved central serous chorioretinopathy. Retina 25:417–421
9. Schocket LS, Witkin AJ, Fujimoto JG et al (2006) Ultrahigh-resolution optical coherence tomography in patients with decreased visual acuity after retinal detachment repair. Ophthalmology 113:666–672
10. Drexler W, Sattmann H, Hermann B et al (2003) Enhanced visualization of macular pathology with the use of ultrahigh-resolution optical coherence tomography. Arch Ophthalmol 121:695–706
11. Daruich A, Matet A, Dirani A et al (2015) Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. Prog Retin Eye Res 48:82–118
12. Verma L, Sinha R, Venkatesh P et al (2004) Comparative evaluation of diode laser versus argon laser photocoagulation in patients with central serous retinopathy: a pilot, randomized controlled trial. BMC Ophthalmol. 4:15
13. Chan WM, Lim T-H, Pece A et al (2010) Verteporfin PDT for non-standard indications a review of current literature. Graefes Arch Clin Exp Ophthalmol 248:613–626
14. Cook B, Lewis GP, Fisher SK et al (1995) Apoptotic photoreceptordegeneration in experimental retinal detachment. Invest Ophthalmol Vis Sci 36:990–996
15. Hisatomi T, Sakamoto T, Goto Y et al (2002) Critical role of photoreceptor apoptosis in functional damage after retinal detachment. Curr Eye Res 41:1542–1545

16. Vogel RN, Langlo CS, Scoles D et al (2017) High-resolution imaging of intraretinal structures in active and resolved central serous chorioretinopathy. Invest Ophthalmol Vis Sci 58(1):42–49
17. Yannuzzi LA (2010) Central serous chorioretinopathy: a personal perspective. Am J Ophthalmol 149:361–363
18. Chan WM, Lam DSC, Lai TYY et al (2003) Treatment of choroidal neovascularization in central serous chorioretinopathy by photodynamic therapy with verteporfin. Am J Ophthalmol 136:836–845
19. Nicholson B, Noble J, Forooghian F, Meyerle C (2013) Central serous chorioretinopathy: update on pathophysiology and treatment. Surv Ophthalmol 58:103–126
20. Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Behar-Cohen F (2013) Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: a pilot study. Retina 33:2096–2102
21. Pichi F, Carrai P, Ciardella A, Behar-Cohen F, Nucci P (2016) Comparison of two mineralcorticosteroids receptor antagonists for the treatment of central serous chorioretinopathy. Int Ophthalmol 16:377–382