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ORIGINAL ARTICLE

Morphological integrity of the outer retinal layers and visual prognosis in chronic central serous chorioretinopathy after half-dose photodynamic therapy: a qualitative SD-OCT analysis

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Abstract

The study aims to investigate the morphological integrity of the outer retinal layers (ORLs) (an ellipsoid layer (EL) + external limiting membrane) and visual prognosis in chronic central serous chorioretinopathy (CSCR) with subretinal fluid (SRF) completely resorbed after half-dose photodynamic therapy (HD PDT) using enhanced-depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT). This retrospective study included 40 eyes of 38 chronic CSCR patients treated with HD PDT between December 2012 and June 2016. However, only 34 eyes (85%) with complete SRF resorption 3 months after HD PDT had their 6th and 12th month data analyzed. Morphological integrity of the ORLs was further analyzed in relation to best-corrected visual acuity (BCVA) and disease duration. Thirty-four eyes of 34 patients (male/female: 82.35/17.65%) with mean age of 49.90 ± 7.80 (32–61) years were studied. The mean logMAR BCVA improved significantly from 0.52 ± 0.31 at baseline to 0.34 ± 0.36 and 0.26 ± 0.26 at the 6th and 12th months after HD PDT, respectively ($p < 0.001$). The proportion of eyes with completely normal morphological ultrastructural integrity of the ORLs was 44.12% at the 6th month, which increased to 64.71% at the 12th month after HD PDT. However, the EL morphological disruption was associated with significantly lower mean logMAR BCVA 12 months after HD PDT ($p = 0.029$). The disease duration had no effect on mean logMAR BCVA gain. Even after complete resorption of serous neurosensory retinal detachment after HD PDT in chronic CSCR, the ORLs, especially the EL, may not be anatomically restored. The EL morphological ultrastructural integrity seems to be the most important factor influencing visual prognosis.

Keywords Central serous chorioretinopathy · Ellipsoid layer · Photodynamic therapy · Outer retinal layers · Visual prognosis

Introduction

Central serous chorioretinopathy (CSCR) is an idiopathic disorder characterized by subretinal fluid (SRF) accumulation, leading to a serous neurosensory retinal detachment (NSRD) at the macula [1]. Males in their 20 s to 50 s are most commonly affected. While acute manifestation is usually self-limiting with spontaneous regression and vision returning to near-normal levels within 4–6 months [2], the chronic manifestation is characterized by a persistent serous NSRD for more than 6 months, which may cause retinal pigment epithelium (RPE) atrophy, cystoid retinal degeneration, and choroidal neovascularization, resulting in permanent vision loss [3, 4]. The pathophysiological mechanisms underlying CSCR are not fully understood. Nonetheless, it is thought to be associated with hyperpermeable choroidal vessels and RPE dysfunction, leading to serous NSRD [5].

Pharmacotherapy, laser photocoagulation, and photodynamic therapy (PDT) have all been investigated as possible treatments for chronic CSCR. The modulation of vascular permeability by vascular endothelial growth factor (VEGF) has

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established a logical and reasonable treatment strategy for this disorder. While targeting VEGF with a monoclonal antibody has had some success in small trials [6], other evidence suggests that anti-VEGF may not be effective for chronic CSCR [7]. Furthermore, it has been attempted to use laser photocoagulation on fluorescein angiography (FA) leakage sites. Despite this, there has been limited efficacy and unintended consequences, such as photoreceptor damage, scotomas, and SRF recurrence. Sub-threshold diode laser micropulse photocoagulation has also been investigated as a laser therapy refinement for CSCR [8]. Notwithstanding the preliminary evidence of some therapeutic potential, additional research is required.

In PDT, the photosensitizing medication verteporfin is infused into the patient, followed by targeted laser activation. This is one of the most effective treatments for inducing NSRD resorption by lowering choroidal vascular hyperpermeability and inducing choroidal vascular remodeling in CSCR [9, 10]. It has shown promising results in chronic CSCR therapy, both anatomically and functionally, using either standard (600 mW/cm^2) or reduced (300 mW/cm^2) fluence, and either standard (6 mg/m^2) or half (3 mg/m^2) dose [11]. Standard PDT complications have been reported, including temporary macular function loss, choroidal ischemia, RPE atrophy, and secondary choroidal neovascularization [4, 12]. By lowering the total energy delivered to the recipient tissue, the underlying normal choroidal vasculature and RPE can be protected [13]. Two methods have been used for this purpose: lowering the verteporfin dose and lowering the laser emission energy (fluence). This was accomplished by either shortening the standard laser emission irradiation time or decreasing the light intensity (power) of the laser emission while maintaining the standard laser treatment duration of 83 s [14]. Both half-dose (HD) and half-fluence (HF) PDT protocols have been shown to cause less damage to the underlying RPE and choroidal vasculature while producing results comparable to standard PDT for chronic CSCR therapy, and are thus widely used [1, 15, 16]. A complete NSRD resorption in CSCR has been reported to be approximately 90% after HD or HF PDT [1]. Though NSRD is completely resorbed after PDT, integrity and regularity of the outer retinal layers (ORLs), that is, photoreceptor inner segment/outer segment junction layer (an ellipsoid layer (EL)) and external limiting membrane (ELM), as well as RPE may not be anatomically restored in all eyes, preventing complete visual recovery.

The purpose of the present study was to qualitatively investigate the relationship between morphological ultrastructural integrity of the ORLs and visual prognosis in chronic CSCR eyes that had SRF completely resorbed after HD PDT using enhanced depth imaging (EDI) mode spectral domain optical coherence tomography (SD-OCT).

Materials and methods

Study design and participants

This retrospective clinical study included 40 eyes of 38 chronic CSCR patients treated with HD PDT at Ege University Faculty of Medicine, Department of Ophthalmology between December 2012 and June 2016. However, only 34 eyes (85%) with complete SRF resorption 3 months after HD PDT had their 6th and 12th month data analyzed for morphological ultrastructural integrity of the ORLs and RPE. This integrity was further analyzed in relation to best-corrected visual acuity (BCVA) and disease (symptom) duration.

Ethics approval

The study protocol conformed to the tenets of the Declaration of Helsinki, and was approved by the Ethics committee of Ege University Faculty of Medicine (Approval Date and Number: 02.06.2021, 21–5.1 T/55). All participants provided written informed consent to have HD PDT performed, measurements taken, and their medical records reviewed.

Diagnosis

The diagnosis of CSCR was based on fundoscopic findings, as well as imaging modalities such as EDI SD-OCT, FA, and indocyanine green angiography (ICGA). Chronic CSCR was described as a long-term serous NSRD in the central macular region that lasted for more than 6 months [17]. Treatment options and HD PDT protocol were determined by a physician, with patients being randomly selected based on the availability of verteporfin. Time between the onset of visual complaints and the initiation of HD PDT was considered as the disease duration.

Inclusion and exclusion criteria

Patients with (a) a history of visual impairment for $\geq$ 6 months, (b) eyes treated with HD PDT, and (c) a complete serous NSRD resorption after HD PDT were included in the study. Exclusion criteria included (a) prior CSCR treatment with a focal laser, standard PDT protocol, or intravitreal anti-vascular endothelial growth factors; (b) an evidence of choroidal neovascular membrane, polypoidal choroidal vasculopathy, or other retinal pathologies aside from CSCR such as diabetic retinopathy, posterior uveitis, and retinal vein occlusion; and (c) high myopia and hypermetropia defined as refractive errors (spherical

equivalent) of < -6.00 D and $> +6.00$ D, respectively, or an axial length > 26.5 mm.

Ophthalmological assessment

A comprehensive ophthalmological assessment was performed by two experienced ophthalmologists (JM&HHG) at baseline, including measurements of BCVA in logarithm of the minimum angle of resolution (logMAR), as well as dilated fundoscopy. The Heidelberg Spectralis HRA + OCT (Heidelberg, Germany) was used in multimodal imaging, including EDI SD-OCT, fundus auto-fluorescence, FA, and ICGA.

Half-dose PDT protocol

All patients were treated with HD PDT. After infusing verteporfin (Visudyne; Novartis AG, Bulach, Switzerland) intravenously for 10 min, diode laser with 689 nm (Visulas 690 S, Carl Zeiss Meditec Inc., Jena, Germany) was administered 15 min after the infusion began. The HD PDT with 3 mg/m^2 verteporfin was performed for 83 s, while the duration and power of the laser application remained constant with a total light energy of 50 J/cm^2. Only localized hyperfluorescent areas on ICGA were exposed to laser irradiation. If there were multiple leaking areas on ICGA, a continuous laser spot was performed for 83 s per spot, based on the lesion size of choroidal vascular permeability. Patients were advised not to expose themselves to direct sunlight for ≥ 2 days after therapy. Consecutive ocular examinations were performed 1, 3, 6, and 12 months after therapy. During each visit, BCVA was measured and EDI SD-OCT scanning was performed.

EDI SD-OCT scanning

The SD-OCT scanning was performed using EDI technique, which included a high resolution 6-mm horizontal scan at the fovea center and a high definition 25-line raster scan through the fovea. Integrity of the ORLs, especially morphological changes in the EL and ultrastructural disturbances in the ELM, as well as RPE atrophy, was then investigated. This investigation was carried out by experienced vitreoretinal specialists (JM&SN), and any potential delineation inaccuracy of the ORLs were manually corrected as needed. The EDI SD-OCT delineation accuracy of the appropriate layer was further validated by two additional authors (HHG&ZO). Images were magnified using a built-in zoom function to perform a thorough foveal ultrastructural examination. The layers were considered physiological if they were continuous and defect-free. The absence of a back-reflection line in the ORLs was defined as a disruption in those layers.

Post-HD PDT qualitative data were then collected for analysis. This included the percentages of eyes that had (a) completely normal ORLs and RPE, (b) only EL morphological disruption, and (c) both ORLs and RPE disruption.

Data analysis

Statistical analysis was carried out using a statistical package (SPSS Inc., version 25.0, Chicago, IL, USA). Categorical data were described using observed frequencies and percentages. Continuous variables were summarized by their means and standard deviations. Non-parametric Brunner and Langer model (F1-LD-F1) was used to test group and dependent time effects by using a web-based software (R software, version 3.5.2, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org). To evaluate the effects of HD PDT, comparisons between matching variables before and after therapy were performed using either paired two-tailed *t*-test or Wilcoxon matched-pairs signed rank test. The Spearman test was used to analyze the relationship between disease duration and mean logMAR visual acuity gain. Statistical significance was defined as $p < 0.05$.

Results

In this study, 34 chronic CSCR patients with completely resorbed SRF 3 months after HD PDT were investigated retrospectively. There were 28 males (82.35%) and 6 females (17.65%). The patients' mean age at presentation was 49.90 ± 7.80 (32–61) years. The mean disease duration before HD PDT was 19.80 ± 8.80 months.

Visual acuity analysis

The mean logMAR BCVAs were 0.52 ± 0.31 at baseline, and 0.34 ± 0.36 and 0.26 ± 0.26 during the 6th and 12th months after HD PDT, respectively ($p < 0.001$). Improved mean BCVA was directly proportional to post-HD PDT duration. By the end of the 12th month, 88.24% of the eyes had improved BCVA. There was no statistically significant relationship between mean disease duration and mean logMAR BCVA gain ($r = 0.048$, $p > 0.05$).

Morphological integrity of the ORLs and RPE

Results of post-HD PDT morphological ultrastructural integrity of the ORLs (EL + ELM) and RPE in eyes with chronic CSCR during the course of the study are summarized in Table 1. Eyes with EL morphological disruption had statistically significantly lower BCVA at the end of the 12th month after HD PDT ($p = 0.029$). Accordingly, the EL

Table 1 Post-HD PDT morphological ultrastructural integrity status of the ORLs (EL + ELM) and RPE in eyes with chronic CSCR during the course of the study

Morphological integrity status	Post-PDT duration	
	6th month	12th month
Completely normal ORLs and RPE	44.12%	64.71%
Only ellipsoid layer disruption	44.12%	26.47%
Both ORLs and RPE disruption	11.76%	8.82%

HD PDT half-dose photodynamic therapy, *ORLs* outer retinal layers, *EL* ellipsoid layer, *ELM* external limiting membrane, *RPE* retinal pigment epithelium, *CSCR* central serous chorioretinopathy

morphological ultrastructural integrity was determined to be the most important morphological factor influencing visual prognosis (Fig. 1a, b).

Discussion

In contrast to acute CSCR, which is widely assumed to be a self-limiting process with a favorable visual prognosis, chronic CSCR leads to cumulative photoreceptor cell death-related vision loss from chronic serous NSRD [18]. The majority of chronic CSCR patients are older than those affected by acute CSCR [19], with males being roughly six times more likely than females [20]. This is consistent with the present study, in which 82.35% of the patients were males versus 17.65% of females. There was also a corresponding overall mean age of 49.90 ± 7.80 years among the patients, which, along with baseline BCVA, has been identified as a long-term determinant factor of chronic CSCR after HD PDT [21].

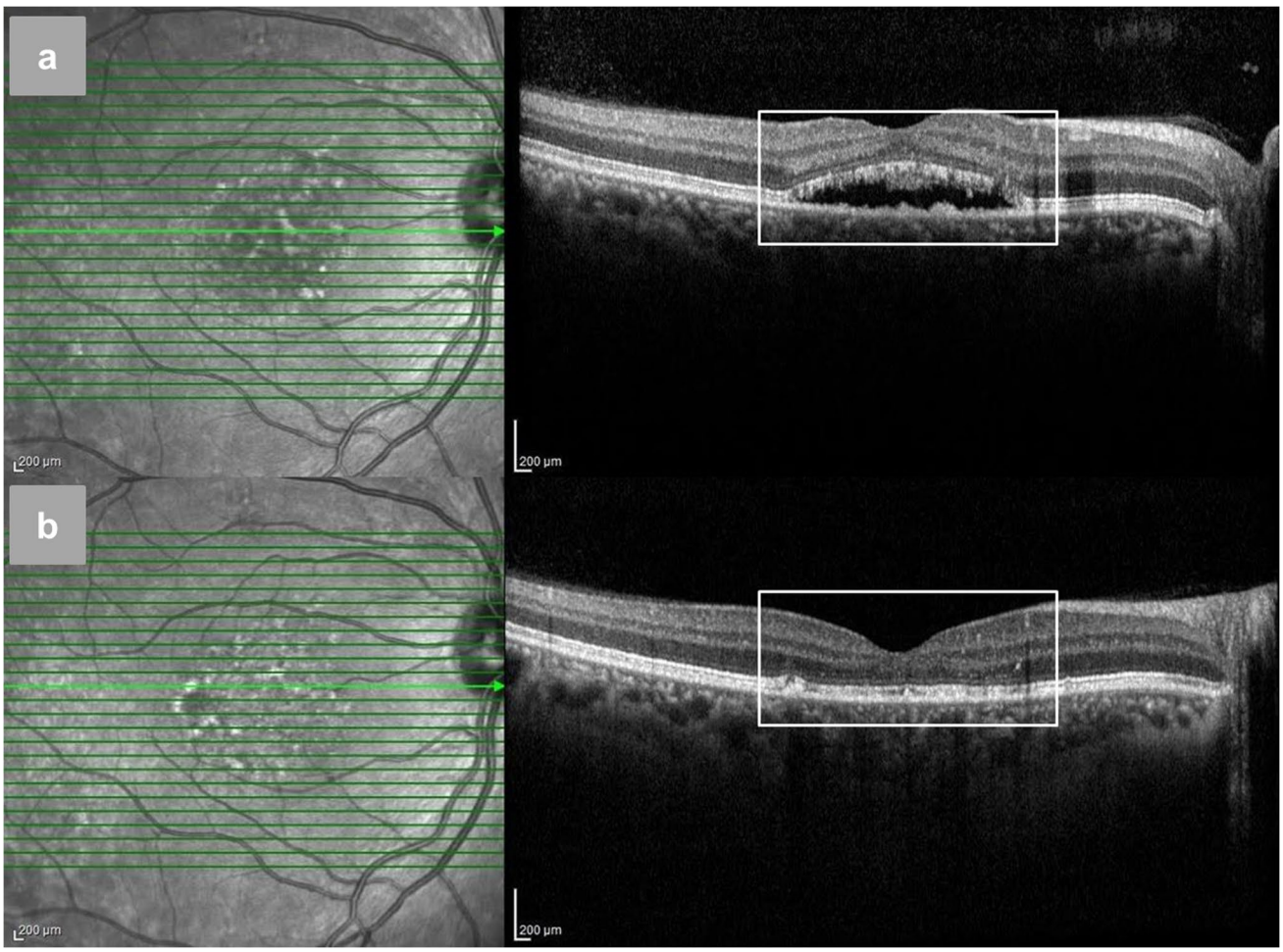

Fig. 1 A qualitative analysis of the ORLs and RPE in a central horizontal 6 mm EDI SD-OCT scan of a right eye with chronic CSCR, which included a high resolution 6 mm horizontal scan at the fovea center and a high definition 25-line raster scan through the fovea. **a** In addition to a significant SRF at the macula (white rectangle), the OCT section displays a slightly uneven outer profile of the detached neurosensory retina, with varying thickness of the ORLs as well as RPE at the fovea before PDT. **b** The SD-OCT scan of the central macula 12 months after HD PDT-induced complete SRF resorption shows a discontinuous reflective line corresponding to the EL at the fovea

Although the exact mechanism of action of PDT in chronic CSCR is currently unknown, it has been suggested that PDT could induce choriocapillary constriction. Short-term choriocapillary hypoperfusion and long-term choroidal vascular remodeling may accompany this, resulting in reduced choroidal exudation and, eventually, SRF resorption [22], as revealed in the present study. Standard PDT adverse complications are significant, especially in patients with relatively better initial BCVA. Modified PDT parameters, such as HD PDT protocol used in the present study, have been eventually adopted to improve PDT efficacy. Thus, HD PDT has emerged as an important CSCR treatment option [23].

It has recently been reported that the disease (symptoms) duration determines PDT timing [23]. Nonetheless, determining the disease duration predicated on the patient's memory is subjective and often imprecise. Besides, chronic CSCR eyes with comparable disease duration may exhibit differences in vision and ultrastructural anatomy [24]. Contrary to the disease duration, changes in morphological integrity of the ORLs and RPE on SD-OCT are objective and related directly to the EL condition. Despite the fact that the disease duration and baseline BCVA are known determinants of visual prognosis following HD PDT [23, 25], they are constant factors with undisclosed pivotal values during a CSCR incident. Morphological integrity of the ORLs and RPE, on the other hand, is a categorical factor that physicians can see and fully comprehend using SD-OCT.

This was the primary drivers behind the present study, which used EDI SD-OCT to qualitatively investigate the relationship between morphological integrity of the ORLs plus RPE and visual prognosis in chronic CSCR eyes that had SRF completely resorbed after HD PDT. The EL is a key determinant of photoreceptor morphological integrity. This layer can also be used to forecast visual prognosis of patients suffering from various retinal diseases. Clinical studies have produced contradictory findings regarding significance of the EL morphological integrity in retinal functional recovery in CSCR. A PDT study of combined acute and chronic CSCR patients found that six of nine patients had EL recovery [26]. Another study of 15 CSCR patients revealed a significant relationship between EL morphological changes and retinal sensitivity after standard PDT [11]. Further, the presence of pigment epithelial detachment at baseline has been related to foveolar EL disruption [27], which has also been revealed as a factor limiting visual recovery [25, 28]. The EL morphological integrity has also been shown to be a determinant of therapeutic response in eyes with diabetic macular edema [29].

The mean disease duration in the present study was 19.80±8.80 months, which had no statistically significant relationship with mean logMAR BCVA gain. However, the mean logMAR BCVAs improved significantly during the 6th and 12th months after HD PDT ($p < 0.001$). This improvement was directly proportional to post-HD PDT duration, with 88.24% of the eyes having improved logMAR BCVA by the end of the 12th month. The lack of visual improvement in the remaining eyes could be explained by the minimal loss of cone photoreceptor cells in the EL. In eyes with active or resolved CSCR, thinning of the foveal outer nuclear layer typically starts early and continues until SRF resolves [30]. Similarly, as the present study revealed, this condition may also apply to the ORLs, particularly the EL, in chronic CSCR eyes with relatively longer disease duration prior to PDT. This ultrastructural change could be caused by photoreceptor apoptosis in the persistently detached neurosensory retina. Chronic CSCR-induced cell death is exacerbated by a disruption in photoreceptor outer segment shedding and renewal, which increases oxidative stress [31]. Likewise, studies of the determinant factors for visual acuity after PDT revealed that having longer disease duration at the start of treatment could influence its success [25].

The association between late morphological ultrastructural changes in the ORLs and visual prognosis after HD PDT has recently been reported with varying results. Torres-Costa et al. [32] published a recent retrospective study of 21 eyes of 15 CSCR patients, which revealed a significant long-term increase in foveal and parafoveal ORL thickness after only HD PDT. They concluded that this treatment protocol could be a reliable option for the outer retina. Another study reported achieving 100% SRF resorption in HD PDT-treated patients only [33]. Despite the findings on SRF resorption, there were no reports on morphological integrity of the ORLs and their relevance to visual acuity. In the present study, complete SRF resorption after HD PDT was associated with significantly improved mean logMAR BCVA. The EL disruption, on the other hand, was found to be associated with much worse mean logMAR BCVA after HD PDT. These findings are therefore consistent with prior reports suggesting essentially that the EL morphological integrity after HD PDT could have a significant impact on visual prognosis.

Both HD and HF PDT have been shown to be effective in CSCR treatment by improving visual acuity, reducing central macular thickness, and resolving SRF [34–36]. One study [16] reported successful treatment in 94.1% of HF PDT-treated eyes and in 100% of full-fluence PDT-treated eyes for 12 months, with no significant difference ($p = 0.493$). There was also no significant difference between the two groups in BCVA ($p = 0.603$) or central retinal thickness ($p = 0.060$). Despite this, choriocapillary perfusion in full-fluence PDT-treated eyes was significantly lower on ICGA ($p = 0.006$). Another study [33] found that HD PDT-treated eyes had relatively complete SRF resorption compared to HF PDT-treated eyes. Correspondingly, a total SRF resorption was found in 79.5% and 94.9% of HD PDT-treated eyes at 1 and

12 months, respectively, in a study published by Chan et al. [28]. Also, Erikitola et al. [37] found that HD PDT had the lowest rate of side effects and recurrence in chronic CSCR eyes. A recent study by Altinel et al. [34] found that 65.2% of HD PDT-treated eyes had complete SRF resorption and 17.4% had recurrence. However, overall success was lower than in prior reports, and recurrence was slightly greater. In general, adjusting parameters, as performed in the present study with HD PDT, could help to avoid unfavorable adverse effects of PDT [36].

Obviously, the most effective CSCR therapy should be capable of inducing both fast and long-term SRF resorption. Despite the fact that no standard treatment for chronic CSC is currently available, there have been reports that PDT can effectively induce long-term SRF resorption [38]. However, since many chronic CSCR patients have good baseline visual acuity, precautions are necessary to avoid iatrogenic visual damage as a result PDT-induced retinal toxicity. Thus, adjusting PDT parameters in chronic CSCR can improve PDT safety [23]. Although HD and HF PDT are presently widely regarded as the best treatment options for chronic CSCR, long-term research has revealed that the latter may be associated with an increased inflammatory response, which is responsible for a higher SRF recurrence rate [33, 39]. Furthermore, despite a lack of data supporting a preference for HD PDT over HF PDT, there is evidence that the former is more effective in long-term SRF resorption [33]. It should also be noted that halving the dose reduces treatment costs. As fewer retreatments may be required, HD PDT may even be more cost effective. Consequently, as previously stated, a physician determined the chronic CSCR treatment options and HD PDT protocol in the present study based on the aforementioned reports.

Subretinal fluid resorption does not always result in significantly improved visual acuity. Besides, the extent of prior RPE and/or photoreceptor damage, as well as PDT, are thought to influence visual acuity [40]. In the present study, the proportion of chronic CSCR patients with complete morphological disruption of the ORLs and RPE decreased from 11.76 to 8.82% between 6 and 12 months, respectively, after HD PDT. Despite the fact that this improvement was associated with a gradual but significantly increased BCVA, not all patients achieved final better vision. This could be ascribed to a chronic morphological disruption of the EL and/or RPE before treatment or to an otherwise unspecified effects of PDT itself. Likewise, in addition to the aforementioned factors, a relatively longer duration before PDT during which most chronic changes in retinal morphological ultrastructure could have occurred may explain the non-significant relationship between disease duration and mean logMAR BCVA gain revealed in the present study. On the other hand, eyes with EL or ELM defects, as well as atrophic RPE, may still have improved visual acuity. Vasconcelos et al. [11] found a significant correlation between changes in ELM and visual acuity after standard PDT. Another study found that 36% of CSCR patients had ELM disruption without associated major changes [27].

We acknowledge the drawbacks of the present study. Aside from a relatively small sample size and lack of a control group, a retrospective study design could have restricted our ability to discover chronic CSCR prospective processes with respect to long-term morphological ultrastructural changes of the ORLs and associated visual prognosis. Although there was relatively longer disease duration in the present study, this may not always be valid since patients could have been ignorant of the unilateral visual decline. Indocyanine green angiography, choroidal thickness measurement, and RPE atrophy evaluation using fundus auto-fluorescence images were not routinely conducted during follow-up. Moreover, the study was methodically manual, with the disrupted ORLs determined subjectively. It was not required to be standardized, but it was normalized through an adjudication process, as described earlier. The lack of data on central retinal thickness could also be considered a drawback; however, OCT measurements have been reported to be highly reproducible and repeatable. Further large-scale, prospective, randomized, observer-masked studies would therefore be worthwhile in investigating specific long-term clinical outcomes in relation to HD PDT in chronic CSCR patients.

Despite these drawbacks, we were able to investigate the relationship between ultrastructural integrity of the ORLs and mean logMAR BCVA after HD PDT. This was made possible by meticulously recording patients with CSCR using high-resolution EDI SD-OCT, assessing various parameters, and determining morphological integrity of the ORLs. The present study's clinical findings are critical for gaining a better understanding of the importance of HD PDT in chronic CSCR, for which there is no clinically established treatment protocol. We believe that physicians would benefit from understanding the factors that influence disruption of the ORLs and mean logMAR BCVA in chronic CSCR eyes. This could eventually help with both optimal treatment planning and visual prognosis prediction. Furthermore, after SRF resorption by the 3rd month, visual or functional improvement appears to be related to ORL morphological ultrastructural improvement, which can last as long as the 6th and 12th months after PDT. Hence, it is critical to distinguish between anatomical and functional recovery outcomes during pre-treatment conversations with chronic CSCR patients. Indeed, the most important contribution of the present study to the literature is that functional recovery is strongly related to morphological ultrastructural integrity of the ORLs, and this can last for 6 or even 12 months after PDT.

Conclusively, HD PDT was found to be effective in the treatment of chronic CSCR. The use of EDI SD-OCT to investigate chronic CSCR eyes revealed significant details regarding retinal morphological ultrastructural alterations. Long-term retinal morphological ultrastructural improvements were associated with improved visual prognosis. The EL morphological ultrastructural integrity appears to be an important factor influencing visual recovery, and it should be thoroughly examined in CSCR eyes receiving PDT.

Author contribution Study design and recruitment of participants: JM, HHG, SN, and YC; photodynamic therapy and follow-up of patients: JM and SN; data analysis: HHG, ZO, JM, and YC; reviewing, editing, and verifying the accuracy of the manuscript: HHG, JM, SN, and ZO; complete access to all study data and accountability for data integrity and accuracy of data analysis: JM, HHG, SN, ZO, and YC. HHG = Hamidu Hamisi Gobeka; JM = Jale Mentes; SN = Serhad Nalcaci; ZO = Zafer Oztas; and YC = Yigit Cay.

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Data availability Data are available from the corresponding author on reasonable request.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the principles of the Helsinki Declaration and all applicable regulations, and approved by Ege University Faculty of Medicine Ethics Committee (Approval Number: 02.06.2021: 21–5.1 T/55). Each participant signed a written informed consent form.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors note that human study participants have given informed consent to the release of the images.

Competing interests The authors declare no competing interests.

Financial interest All authors certify that they have no association or participation with any organization or individual with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

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