Dark-Field Scanning Laser Ophthalmoscopy for Prediction of Central Serous Chorioretinopathy Responsiveness to Laser Therapy

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Abstract

Purpose: To study the potential of dark-field scanning laser ophthalmoscopy (DF-SLO) for the prediction of central serous chorioretinopathy (CSC) responsiveness to laser therapy.

Methods: Fifty-two eyes of 52 patients (44 males and 8 females, mean age of 45.4 ± 8.8 years) newly diagnosed with CSC were included in this prospective cohort study. At baseline, all patients received multimodal imaging including DF-SLO and then were observed until resolution of subretinal fluid or, in nonresolving cases, treated with laser therapy. At the end of the follow-up, each case was categorized as either self-resolving, resolving after laser treatment, or nonresolving after laser treatment. Presence of granular retinal pigment epithelium (RPE) changes and lucency of RPE/choroid complex at the leak on DF-SLO images were used by two masked graders to identify cases nonresolving after laser treatment.

Results: Using DF-SLO images, the masked grader correctly classified 45 of 52 (86.5%) CSC cases. Kappa value for the classification by two graders was 0.95 (95% confidential interval [CI] 0.85–1.0). The area under the receiver operating curve, sensitivity, and specificity of DF-SLO in identifying nonresolving after laser treatment cases were 0.92 (95% CI: 0.79–0.98), 86.7% (95% CI: 59.5%–98.3%), and 96.6% (95% CI: 82.2%–99.2%), respectively.

Conclusion: DF-SLO may be a useful technique in prognostication of response to laser treatment in newly diagnosed CSC.

Keywords: Central serous chorioretinopathy, Laser photocoagulation, Micropulse laser therapy, Microsecond pulsing laser, Scanning laser ophthalmoscopy

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Introduction

Multimodal imaging provides comprehensive information about anatomical relationships in central serous chorioretinopathy (CSC). However, predicting the prognosis of the natural course or the success of laser treatment is still limited in nonresolving and chronic forms of CSC. The persistence of the leak and subretinal fluid depends on the status of the retinal pigment epithelium (RPE)/choroid complex. Therefore, if the particular area of RPE/choroid complex is irreversibly altered, its functional competence cannot be restored, even after adequate treatment. This situation clinically appears as treatment-resistant CSC and requires additional caution if the patient is referred for laser treatment. Currently available imaging modalities such as fluorescein angiography (FA) and fundus autofluorescence (FAF) help

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diagnose CSC. However, these options are unable to predict the course of newly diagnosed CSC.

Scanning laser ophthalmoscopy (SLO) is a generally well-known imaging option that is usually used as an adjunct to other imaging modalities. Infrared SLO has two modifications which are of high clinical value: dark-field SLO (DF-SLO) and retro-mode SLO (RM-SLO). RM-SLO is based on indirect illumination of the eye fundus through the side-deviated aperture and creates a pseudo-three-dimensional appearance of neurosensory and pigment epithelium detachments in CSC.[1,2] DF-SLO operates as transillumination of the eye and allows visualization of pigmented choroidal mass, including choroidal nevi.[3] The principle of DF-SLO suggests that not only the accumulation of pigment but also the loss of pigment of the RPE/choroid complex in the area of its chronic alteration will be apparent. DF-SLO could, therefore, help in the diagnosis of CSC and potentially in the prediction of its responsiveness to laser treatment.

The aim of this study was to describe changes in RPE/choroid complex using DF-SLO and to evaluate the potential of DF-SLO in differentiation of newly diagnosed CSC.

Methods

This was a single-center prospective longitudinal study. All participants were informed as to the aim and design of the study and signed informed consent for the use of the data obtained during the ophthalmic examination. The study followed the ethical standards stated in the Declaration of Helsinki and was approved by the Local Ethics Committee (extract from protocol #232 from February 18, 2020).

In this study, we included patients with a newly diagnosed episode of CSC. Exclusion criteria were chronic CSC, including CSC cases associated with choroidal neovascularization, posterior cystoid degeneration, gravitational tracks or substantial alteration of RPE or known duration more than 6 months, recurrent CSC (if medical history was significant for three or more episodes), previous episode of CSC within the last 6 months, history of laser treatment of previous or current episode of CSC, ongoing treatment with aldosterone receptor antagonists, and any concurrent ocular condition impeding retinal imaging.

At baseline, all patients received a comprehensive ophthalmic examination and multimodal imaging, including optical coherence tomography angiography (RTVue-XR, Optovue, Fremont, CA), FA (F-10, NIDEK, Gamagori, Japan) or/and FAF (F-10), and DF-SLO (F-10). All imaging procedures were performed after mydriasis was achieved by administering tropicamide 1%. All images captured with F-10, FA, FAF, and DF-SLO show the same area, covering 27° × 40° of the eye fundus.

After inclusion, each patient was followed up for at least 2 months. If a patient demonstrated no improvement in the status of neurosensory detachment (NSD) over 2 months or did not achieve complete resolution of NSD within 4 months, the patient was treated either using focal laser photocoagulation (in cases of focal leak) or microsecond pulsing laser therapy (in cases of diffuse leakage) and followed up for an additional 2–4 months. If no changes in the status of NSD were observed within 1 month following the first session of laser treatment, another session of microsecond pulsing laser therapy was performed, followed by observation. If no improvement of NSD status was observed after two sessions of laser treatment and 1 month of observation, the case was considered nonresolving after laser treatment. In the case of gradual resolution of subretinal fluid, the patient was followed up until complete resolution of NSD or stabilization of NSD status [Figure 1].

A case of CSC was considered self-resolving if no laser treatment was performed before the complete resolution of subretinal fluid. If a complete resolution of subfoveal fluid was achieved after one or two sessions of laser treatment, a case was considered resolving after laser treatment.

All procedures of laser treatment were performed with Navilas 577 laser system (OD-OS, Teltow, Germany), which operates with 577-nm diode yellow laser. Focal laser photocoagulation was performed in a conventional manner applying 1–3 100-μm laser spots directly at the leak using FA for treatment planning. Microsecond pulsing laser therapy was performed after the titration procedure and covered the entire area of the leakage and RPE alteration with 100-μm confluent laser spots. The duty cycle and pulse duration were 5% and 0.2 s, respectively, for all microsecond pulsing treatment procedures.

When all patients had met the study endpoint, their baseline DF-SLO images were categorized according to the outcome and analyzed using ImageJ software (NIH, Bethesda, MD). On DF-SLO images, the normalized mean gray value of the leak area was calculated and compared between the three study groups. At first, the leak area was identified on DF-SLO image by superimposition of the FA image on the DF-SLO image. Then the area of alteration of the RPE/choroid complex around the leak was manually delineated with the "freehand selection" tool, and its absolute mean gray value was measured. The reference mean gray value was then defined for a representative unaffected region within NSD. Finally, the normalized mean gray value of the leak area was calculated as the ratio of the absolute mean gray value of the leak to the reference mean gray value [Figure 2].

In addition, the total area of alteration of the RPE/choroid complex (defined as a region of the eye fundus within the NSD demonstrating granular changes of RPE with or without lucency) was measured.

Based on the characteristics of the leak, established with quantitative analysis of DF-SLO images, a masked grader categorized each case belonging to one of the three patterns: (1) having no apparent changes, presumably

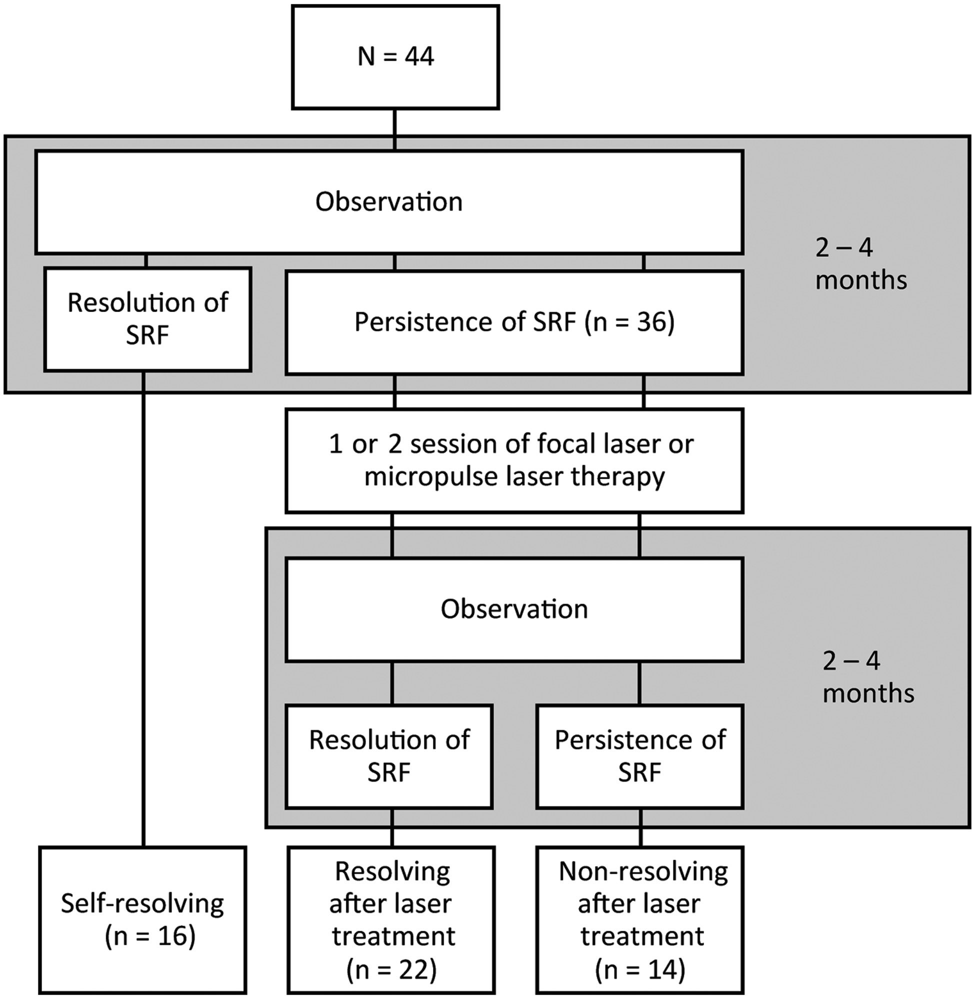

Figure 1: Flowchart showing the categorization of the patients included

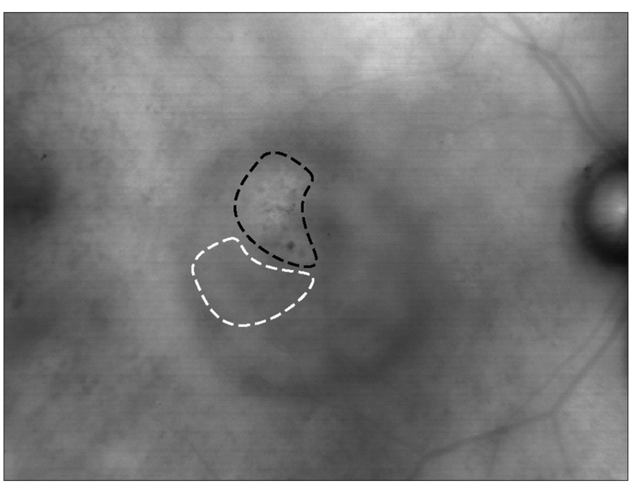

Figure 2: Measurement of the normalized mean gray value and the total area of alteration of the retinal pigment epithelium/choroid complex of the leak. The black dashed line delineates the leak area. The white dashed outlines a representative unaffected area within the neurosensory detachment

self-resolving; (2) demonstrating granular RPE changes without lucency, presumably resolving after laser treatment; and (3) while having the granular RPE changes with apparent lucency, presumably nonresolving after laser treatment [Figure 3]. Consistency between masked grading and actual clinical outcome (self-resolution, resolution after laser treatment, and nonresolution after laser treatment) was then evaluated.

A second independent masked grader repeated the measurements of the normalized mean gray value of the leak area and categorized the patterns of the changes on DF-SLO images over a different time period.

Statistical analysis was performed in MedCalc 18.4.1 (MedCalc Software, Ostend, Belgium). All data were presented as mean ± standard deviation. One-way analysis of variance was used to compare the normalized mean gray value and the entire area of alteration of the RPE/choroid complex and the age between self-resolving, resolving after laser treatment, and nonresolving after laser treatment cases with Bonferroni *post hoc* correction for multilple comparisons. The area under the receiver operating curve (ROC), sensitivity, and specificity were calculated for the ability of DF-SLO to discriminate nonresolving after laser treatment CSC cases. The interobserver reliability of the normalized gray value by the two graders was expressed as the intraclass correlation coefficient with and corresponding 95% confidence interval (CI). Kappa coefficient and 95% CI were calculated to assess the agreement between two graders regarding the classification of DF-SLO patterns. The chosen level of statistical significance was $P = 0.05$. The sample size for the ROC-analysis was calculated with type I and type II errors of 0.1 and a ratio of nonresolving after laser treatment to resolving after laser treatment cases of 0.5. With the hypothesized area under the ROC curve of 0.9, the required number of cases was found to be 39.

Results

In total, 52 eyes of 52 patients (44 males and 8 females, mean age of 45.4 ± 8.8 years) were included in this study, with baseline characteristics presented in Table 1.

There were no statistically significant differences in the male-to-female ratio and age between study groups; however, patients with self-resolving CSC were statistically significantly younger than with both resolving and nonresolving after laser treatment CSC ($P < 0.05$).

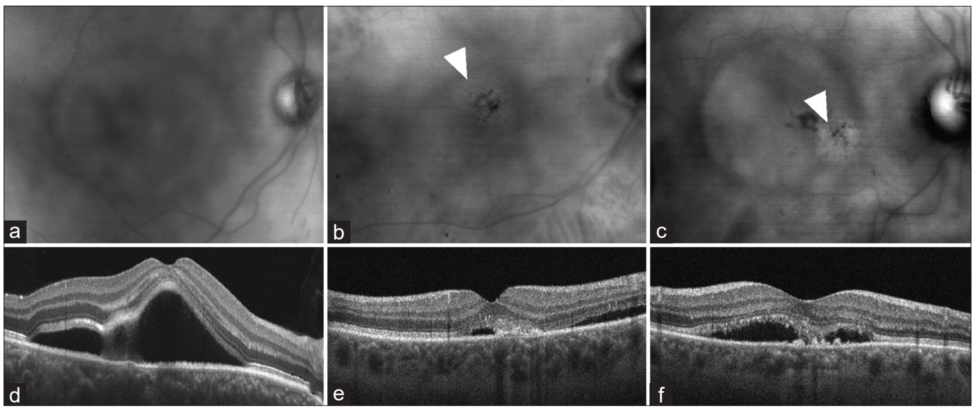

Figure 3: Representative example of the categorization of dark-field scanning laser ophthalmoscopy (DF-SLO) images. (a) Retinal pigment epithelium (RPE)/choroid changes are indistinguishable. (b) DF-SLO image demonstrating granular RPE changes (arrowhead) at the leak. (c) DF-SLO image showing granular RPE changes and the lucency (arrowhead) at the leak. (d) Optical coherence tomography shows typical acute central serous chorioretinopathy. (e) Optical coherence tomography shows flat neurosensory detachment with some RPE alterations at the leak. (f) Optical coherence tomography shows some RPE alterations at the leak

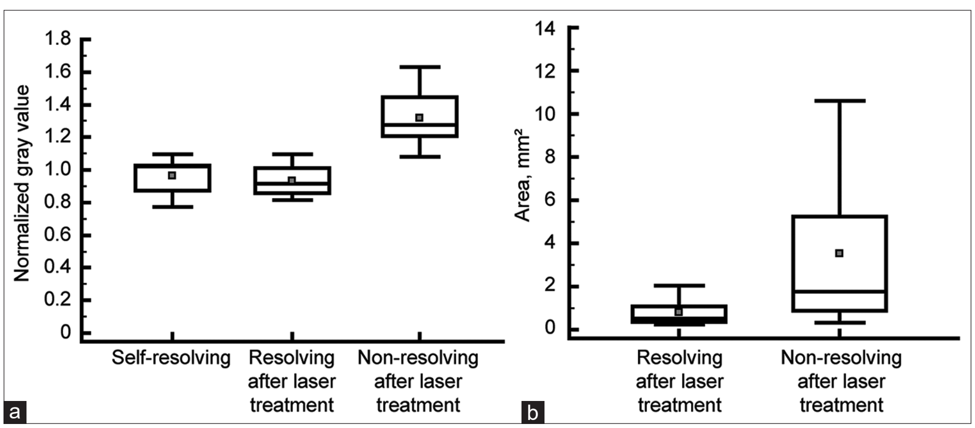

Figure 4: Box-and-whisker plots showing the distribution of the normalized gray value of the leak (a) and the area of the leak (b) on dark-field scanning laser ophthalmoscopy images

Table 1: Characteristics of study groups

	Self-resolving	Resolving after laser treatment	Nonresolving after laser treatment
Eyes	16	22	14
Male/female	14/2	17/5	13/1
Age (years)	39.2±7.5*	50.6±10.5	48.3±9.1
BCVA, logMAR (decimal equivalent)	0.08±0.08 (0.83)	0.09±0.09 (0.81)	0.1±0.1 (0.79)

*P<0.05 compared to nonresolving and persistent groups (ANOVA with Bonferroni *post hoc* test). BCVA: Best corrected visual acuity, ANOVA: Analysis of variance

In total, 14 patients (all resolving after laser treatment) received only focal laser (each patient received a single procedure); 9 patients received focal laser in the first session and microsecond pulsing laser in the second session (5 nonresolving after laser treatment and 4 resolving after laser treatment); 9 patients received two sessions of microsecond pulsing laser (8 nonresolving after laser treatment and one resolving after laser treatment); and 2 patients were resolving after a single session of microsecond pulsing laser treatment.

The mean normalized gray value of the leak in self-resolving, resolving after laser treatment, and nonresolving after laser treatment was 0.97 ± 0.12, 0.93 ± 0.09, and 1.27 ± 0.19 ($P < 0.001$, with Bonferroni *post hoc* test for nonresolving as opposed to self-resolving and resolving after laser treatment groups), respectively. There was no statistically significant difference in the mean normalized gray value of the leak between self-resolving and resolving after laser treatment cases ($P = 0.48$). The mean area of the RPE/choroid complex alteration in resolving and nonresolving after laser treatment cases was 0.79 ± 0.59 and 3.5 ± 3.95 mm^2 ($P = 0.006$), respectively [Figures 4 and 5]. The interobserver reliability of two graders who performed the measurements of the normalized gray value was excellent (0.91 [95% CI: 0.81–1.0]).

Using baseline DF-SLO images, the masked grader correctly classified 45 of 52 (86.5%) CSC cases as being self-resolving (demonstrated no changes on DF-SLO), resolving after laser treatment (demonstrated only granular RPE changes), or nonresolving after laser treatment (demonstrated RPE/choroid complex lucency). Among cases which resolved and those nonresolved after laser treatment, the grader correctly classified 33 of 36 (91.4%) of cases [Table 2]. Kappa value for the classification of the patterns of RPE changes on DF-SLO images was 0.95 (95% CI: 0.85–1.0).

The area under the ROC, sensitivity, and specificity of DF-SLO used by the masked grader to identify cases which are nonresolving after laser treatment were 0.92 (CI: 0.79–0.98), 86.7% (CI: 59.5%–98.3%), and 96.6% (CI: 82.2%–99.2%), respectively.

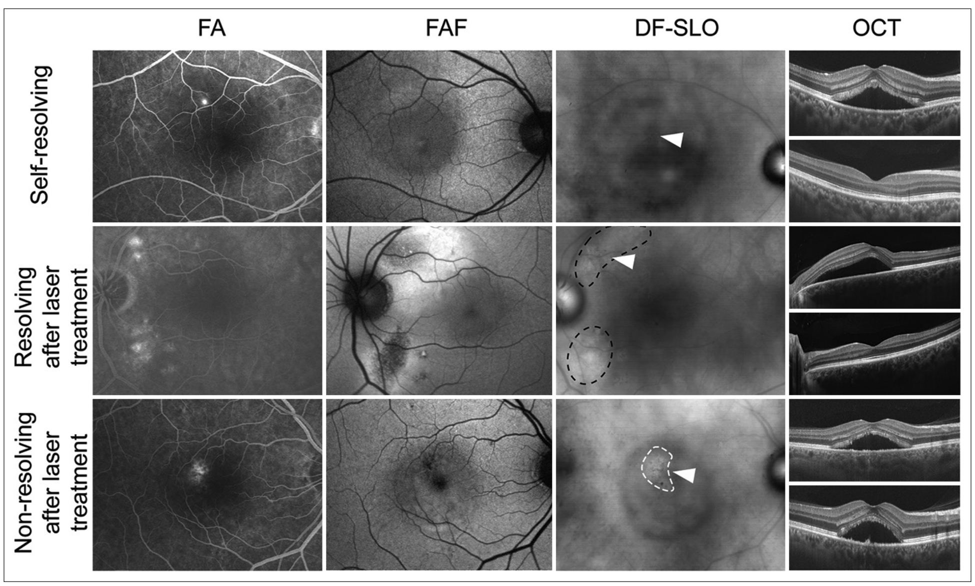

Figure 5: Multimodal imaging, including dark-field scanning laser ophthalmoscopy in self-resolving, resolving after laser treatment, and nonresolving after laser treatment central serous chorioretinopathy (CSC). Optical coherence tomography cross-sectional scans in each case show baseline status (top) and status at the end of follow-up (bottom). Both cases of resolving and nonresolving after laser treatment CSC were treated consecutively with one session of focal laser and one session of micropulse laser therapy. White arrowheads indicate the area corresponding to the leak on fluorescein angiography. The black dashed line highlights the area of lucency. The white dashed line highlights the areas of lucency and granular changes.

Table 2: Distribution of retinal pigment epithelium/choroid changes among study groups in accordance with masked grading

	Self-resolving	Resolving after laser treatment	Nonresolving after laser treatment
No changes	13	2	0
Granular RPE changes	3	18	1
Granular RPE changes with lucency	0	2	13

RPE: Retinal pigment epithelium

Discussion

In this study, DF-SLO has shown its potential to predict the natural course of newly diagnosed CSC and anticipate the response of nonresolving CSC cases to laser treatment. With DF-SLO, the leak often remains indistinguishable in self-resolving cases, while CSC cases requiring laser treatment typically demonstrate granular RPE changes and/or lucency of the RPE/choroid complex at the leak. In addition, with DF-SLO, we found a substantial difference in the quantitative characteristics of the leaks between resolving and nonresolving after laser treatment cases. With DF-SLO, laser treatment-resistant leaks are characterized by increased lucency and a wider area of RPE/choroid alteration. The graders demonstrated excellent agreement in evaluating DF-SLO images in terms of both the normalized mean gray value of the leak area and classification of the patterns of the changes on DF-SLO images. All of these suggest that for acute nonresolving CSC, DF-SLO allows accurate prediction of responsiveness to laser treatment.

There are many imaging options which allow characterization of the status of RPE in CSC, including structural optical coherence tomography,[4] FAF,[5] and intravenous contrast angiography.[6] Since the RPE plays a crucial role in the pathophysiology of CSC, these options serve as the main indicator in the differentiation of chronic and acute forms of CSC. The distinction between acute and chronic CSC, particularly persistent CSC, is of high clinical importance since it defines the management of each individual case. However, until now, there is limited consensus when defining different forms of CSC.[7] This is mainly because CSC includes a phenotypically broad range of forms which do not have clearly defined borders between them. There are no difficulties in the differentiation of classical acute from chronic cases, but forms in the mid-range, namely CSC with acute manifestation but substantial RPE changes, present a greater prognostic challenge. While some of the latter cases may be successfully treated with subthreshold laser, others may require photodynamic therapy, although without the guarantee of success.[8]

FAF is a standard approach in displaying RPE alteration and can differentiate chronic from acute CSC. Based on previous studies, acute CSC eyes are usually characterized by a decrease of FAF intensity at the leakage site,[5] while in chronic CSC eyes, hyperautofluorescence or minimal changes are generally observed. In CSC, FAF generally demonstrates a high variability in patterns of autofluorescence due to the fluorescence property of subretinal fluid, alteration and loss of RPE, and loss of outer retina,[9] and therefore, it is challenging to use FAF to predict the timing for treatment. Similarly, FA demonstrates mainly local decompensation of RPE, which does not correlate with the potential of RPE to restore its functional competence after treatment.[10] Although it is intuitively reasonable to suggest that in cases where the leak area is large, the success of the subthreshold (micropulse or microsecond pulsing laser) laser is compromised, a small leak area is no guarantee of a favorable response.

DF-SLO is a less extensively studied technology. However, a previous study showed the ability of DF-SLO to detect choroidal nevi with a high degree of sensitivity, greater than that of color fundus photography or optical coherence tomography.[3] In that study, DF-SLO also showed a high intergrader repeatability in the linear measurements of the nevi. The mechanism of displaying nevi through the blockage of the light reflected by the inner sclera suggests that the areas with loss of pigmentation can be detected as well.

The main difference between DF-SLO and FAF or FA results from the high penetrative ability of infrared illumination (in contrast to the blue light using in FAF and FA)[11] and the specific technique of DF-SLO where the light backscattered from the sclera penetrates the whole RPE/choroid complex. Both features allow the extraction of information from the DF-SLO image, not only about the RPE status but also about the choroid. Granular changes that were found in cases requiring laser treatment likely represent an alteration of RPE, while the areas of the lucency found in cases nonresolved after laser treatment may reflect the loss of pigmentation in the choroidal stroma. We suggest that the lucency reflects the status of the choroid since it has never been observed without granular changes of RPE, and these two phenomena, therefore, likely represent consecutive rather than concurrent changes. Further, the correlation between the presence of the lucency at the leak area on DF-SLO and resistance to laser treatment seems to be logical because RPE and choroidal alteration combined are suggestive of more severe and, probably, less treatment-responsive CSC cases. We can suggest, therefore, that DF-SLO, which displays the loss of pigmentation in both RPE and the choroid, better reflects the status of RPE/choroid complex of a particular area of the eye fundus in contrast to FA and FAF which mainly show the status of RPE. Another point for discussion is that the loss of pigmentation in both RPE and the choroid may be associated with weaker laser-tissue interaction since yellow laser melanin is one of the main chromophores in the retina.[12] In addition, altered RPE may produce fewer biologically active molecules, which are responsible for the healing of the leak, and may have a weaker potential to repopulate the leak area after subthreshold laser therapy.

The main limitation of this study is the limited access by most retina physicians to DF-SLO. However, we suggest that other types of nonconfocal infrared imaging might have similar potential in visualization RPE/choroid complex alteration in CSC. Another potential limitation is the relatively small sample size.

In summary, DF-SLO at baseline may be a useful technique in the prediction of self-resolution and response to laser treatment in newly diagnosed CSC. Self-resolving cases typically demonstrate no changes with DF-SLO, while cases requiring laser treatment usually show granular RPE changes with or without the lucency at the leak. The presence of the lucency and the large area of granular RPE changes may indicate a higher risk of laser treatment failure.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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