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**CENTRAL SEROUS CHORIORETINOPATHY -
FUNCTIONAL, ANATOMICAL AND
PHOTORECEPTOR DENSITIES RESULTS
DETERMINED WITH
ADAPTIVE OPTICS**

ABSTRACT

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Introduction

Central serous chorioretinopathy (CSC) is the 4th most common macular pathology and affects especially young men, who did not have other ophthalmological pathologies up to that time. The main symptoms of the disease are decreased visual acuity, metamorphopsia, central scotoma and very rarely completely asymptomatic.

The most common lesions in CSC are serous detachment of the neuroepithelium and detachment of the retinal pigment epithelium (RPE). The physiopathological mechanism incriminated in this pathology is the presence of a hyperpermeability of the choriocapillaries associated with a defect in the RPE.

In most cases, CSC has a self-limiting evolution, with almost complete anatomical and functional recovery. However, there are also cases in which patients are left with sequelae after this disease, or the disease has a recurrent evolution.

Adaptive optics (AO) is a relatively new technology that allows obtaining high-resolution images by correcting optical aberrations. It is used in many fields, and in ophthalmology it is most frequently used to investigate photoreceptors, namely cones. It allows qualitative and quantitative measurements of cones, with accurate measurement of photoreceptor densities and intercellular spaces.

The main aim of this work is to compare photoreceptor densities from healthy eyes with those that have suffered from CSC. These results would demonstrate if CSC is really a disease without significant anatomical impact, if patients with CRSC should be treated or if monitoring and controlling risk factors is sufficient, and which therapeutic solutions we can use.

Methods

This paper is based on an observational case study of 44 patients who addressed to the Retina clinic between 01.2016-12.2019. Inclusion criteria were:

- treated CSC in a single eye
- at least six months of no SRF before AO examination;
- without pathologies in the fellow eye (except for small refractive errors);
- CSC in the macular area.

In all patients best-corrected visual acuity (BCVA) was measured before and after the treatment. The duration of the pathology was considered the period between the onset of symptoms and complete resorption of the SRF and was calculated in months.

The following treatment methods were used in the included patients:

- topical or systemic drug treatment;
- focal LASER photocoagulation;
- micropulse laser;
- intravitreal injections with Anti-VEGF agents.

The assessment of the SRF was made by determining the outer retinal thickness (ORT), the distance between the inner border of the RPE and the outer border of the external limiting membrane. The choroid thickness (ChT) was calculated in both eyes, before treatment and after SRF resorption, as the distance between the outer border of the RPE and the outer most visible edge of the choroid.

Cone mosaic and photoreceptor densities were obtained using AO Retinal Camera rtx1™. The following software were used for the quantitative and qualitative analysis of the photoreceptors:

- AOimage™ software;

- i2k retinaTM software;
- AOdetect mosaicTM retinaTM software.

In all patients I got cone multi-image mosaics that included $8^\circ \times 8^\circ$ from the center of the macula. Photoreceptor densities were measured from 20 points on the mosaic. The measurements were made from 1° of the fovea up to 3° from it, in all four quadrants (superior, inferior, nasal, and temporal). Each analysis of the cone mosaic provided us with the following information:

- cone density (/mm²);
- intercellular space (μm);
- dispersion (%);
- regularity (%).

Results

This study included 88 eyes (44 with CSC and 44 healthy) from 44 patients: 31 males and 13 females, mean age 39.8 ± 9.8 years (range, 21-67 years). The average BCVA was 0.6 ± 0.2 (range, 0.1-1) until treatment and 0.9 ± 0.1 (range, 0.5 -1) after the treatment. The mean duration of the disease was 5.7 ± 6.7 months (median=3; range, 1-36 months).

The mean of SRF remission was 2.5 ± 2.8 months (median=1; range, 1 – 12 months). In 25 cases (56.8%) the SRF was resorbed in less than 1 month, of which LASER photocoagulation was used in 22 cases.

In 35 cases (79.5%) the chosen treatment was Laser photocoagulation. Intraocular injections were performed in three cases, local or systemic treatment in six cases and the micropulsed LASER was used in a single patient.

Complications that have occurred in this group of patients:

- chronicity of the disease (13 cases);
- recurrence of SRF (5 cases);
- CNVM (2 cases).

The mean value of the ORT was $256.68 \pm 110.51 \mu\text{m}$ (range, 95 – 527 μm). The ChT in healthy eyes was $399.47 \pm 111.36 \mu\text{m}$ (range, 209 – 617 μm). In the eyes with CSC, until the treatment the ChT was $471.55 \pm 107.92 \mu\text{m}$ (range, 276 – 643 μm) and after resorption of the SRF it was 426.86 ± 100.43 (range, 219 – 603 μm). In 41 patients (93.18%, $p=0.03$) the ChT in the eyes with CSC was higher before treatment compared to that after SRF resorption. In 36 cases (81.81%, $p=0.0029$) the ChT in eyes with active CSC was higher than in the healthy eyes and remained higher after resorption of the SRF in 30 cases (68.18%, $p=0.17$).

The following types of anatomical changes were observed on the fundus autofluorescence images (FAF):

- intense hyperautofluorescent- most often with a dots like appearance;
- slightly increased autofluorescence- with diffuse distribution in the SRF area;
- hypoautofluorescent- most often with a dot like appearance, diffused distributed.

Following the analysis of the cone mosaic, the following phenotypes of lesions presented in the eyes with CSC were observed:

- intensely white lesions: located in the area affected by SRF; well-defined round-oval, without mosaic visible at their level; most frequently associated with increased autofluorescence on FAF.
- intensely dark lesions: located in the area affected by SRF and especially at the level of the laser scar; round-oval with diffuse distribution; most often associated with decreased autofluorescence on FAF.

- blurred mosaic: mosaic areas where photoreceptors do not look well outlined; it is often well defined and can cover the entire area that has been affected by the fluid; the density of cones is much lower in these areas.

No differences in cone mosaic phenotypes were observed between the eyes in which the laser photocoagulation was performed and the eyes in which the other types of treatments was chosen.

The lowest cone density was found in the superior quadrant at 1° from the center of the macula in an affected eye, it was 500cones/mm². The highest cone density was 37867cones/mm² found in a healthy eye also in the superior quadrant at 1° from the center of the macula.

A statistically significant difference of photoreceptor densities was observed at all distances from the center between eyes with CSC and healthy ones.

In the 21 cases in which FAF images were analyzed before treatment, an important correlation was observed between the presence of hypoautofluorescent lesions and the maximum density of photoreceptors. The presence of these lesions correlates with a greater difference in the maximum densities of photoreceptors between the sick and healthy eyes ($r^2=0.46$, $p=0.03$).

The maximum values of photoreceptors from each eye in the two groups were also analyzed. A moderate positive correlation was found between the ratio of the maximum cone densities and the duration of the pathology ($r^2 = 0.47387$, $p= 0.00116$).

Discussions

The first results of this paper showed us clearly that CSC affected especially emmetrop, young men, equally in both eyes. No correlation was observed between BCVA and duration of the pathology, SRF level or choroid thickness.

The majority of patients who have had a complete remission of SRF in a month or sooner have been treated with LASER photocoagulation. In patients who received other therapeutic solutions, SRF resorption lasted more than one month.

Despite large variations in the SRF levels, it has not been observed to correlate with visual acuity, duration or remission of the pathology, or loss of photoreceptors.

The ChT was significantly higher in eyes with CSC compared to healthy ones. The fact that with remission of the SRF the ChT decreased too, underlines the definite involvement of this structure in the pathophysiological mechanism of CSC.

The presence of hypo- autofluorescent lesions has a less favorable prognosis in CSC and changes identified on the FAF correlate with those observed on the AO images.

The extreme values of photoreceptor densities, maximum and minimum, were higher in healthy eyes. In healthy eyes, it has been observed that the trend of the average values is a curved line, with the highest values at 2° in the horizontal plane and 1.5° in the vertical plane. In the eyes of CSC the trendline of the average values was closer to a straight line, which was positioned at 15000 cones/mm^2 both vertically and horizontally.

The moderate and positive dependence of the maximum densities on the duration of the disease means that the longer the SRF resorption lasts, the more noble areas of the retina suffer. Because it has already been shown that CSC is a progressive disease and over time patients have suffered a decline in visual acuity, it is important to initiate treatment quickly to maintain a higher photoreceptor density.

Regarding the therapeutic solutions, no differences were observed in the appearance of the cone mosaic and the density of photoreceptors. It means that it would be important to choose the one that offers us the fastest resorption of the SRF.

In this paper, no attention was paid to the recurrence of CSC. What impact do these have on photoreceptors? Are photoreceptors more sensitive to fluid reappearance

and is there a more effective treatment solution to prevent relapses than another? These questions can become the objectives of the following studies.

Conclusions

1. CSC affects especially emmetrop, young men. This conclusion is already part of the definition of CSC and our results have clearly confirmed this.
2. CSC can cause a significant decrease in visual acuity, thus affecting the quality of life. Although our results show that most patients were left with good eyesight, let's not forget that all of them were treated, by one method or another.
3. Choroidal thickness shows significant changes in patients with CSC. This highlights the involvement of this tissue in the pathophysiological mechanism, making CSC part of the pachychoroid spectrum of diseases. This result we hope to bring in the future new therapeutic solutions aimed exactly at the mechanism of the disease.
4. FAF is a non-invasive investigation that allows us to visualize functional changes in the retina. It highlights invisible changes on OCT, which correlate with microscopic changes on AO high-resolution images.
5. Hypoautofluorescent lesions are a negative prognostic factor in CSC. Their presence already means a significant loss of photoreceptors.
6. AO is a modern investigation that allows us to acquire high-resolution images on which microscopic changes can be observed in the central retina.
7. By acquiring high-resolution images, AO allows tracking of cellular changes caused by CSC. These changes are framed in some typical cone mosaic phenotypes. This result can allow us to specify the diagnosis in cases when this is difficult to do. It is possible that in the future phenotypes will be described for other pathologies as well, as the diagnosis will be made on cellular changes and not only clinically.

8. CSC causes a decrease in photoreceptor densities, even in patients who remain with a good visual acuity after treatment of the disease. This is one of the main results of the study and aims to emphasize that CSC is not a benign disease and that it leaves significant sequelae.
9. The duration of the disease is a negative prognostic factor in CSC. The longer the SRF persists, the more photoreceptors will suffer. That being said, we can only understand one thing, that in a patient with CSC, treatment must be initiated as soon as possible.
10. LASER photocoagulation treatment allows a faster resorption of the subretinal fluid in CSC. Possibly due to this effect we can prevent a more harmful effect on photoreceptors.