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## PATIENT CHARACTERISTICS OF UNTREATED CHRONIC CENTRAL SEROUS CHORIORETINOPATHY PATIENTS WITH FOCAL VERSUS DIFFUSE LEAKAGE

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### ABSTRACT

The authors are commenting on the article entitled "Patient characteristics of untreated chronic central serous chorioretinopathy patients with focal versus diffuse leakage" published by van Rijssen *et al.* in *Graefes Archive Clin Exp Ophthalmol* 2019; 257(7):1419-1425. The validation, extrapolation, and generalizability of the conclusions of this study can be made only by regression analyses including all the missing baseline potential predictive factors mentioned by us regarding the multimodal imaging of the choroid, retinal pigment epithelium, and photoreceptor cell layer in addition to the baseline characteristics already assessed.

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### INTRODUCTION

The study by van Rijssen *et al.* (2019) described the characteristics of 173 patients with untreated chronic central serous chorioretinopathy (cCSC) divided into 2 groups, namely, with focal (68 patients) and diffuse (105 patients) leakage on fluorescein angiography (FA). There was a significant difference between the focal and diffuse phenotypes regarding the mean age of patients ( $46.9 \pm 8.8$  years and  $49.7 \pm 8.3$  years, respectively) and insignificant differences with respect to the mean best-corrected visual acuity (BCVA) ( $77.1 \pm 8.1$  Early Treatment of Diabetic Retinopathy Study [ETDRS] letters and  $76.0 \pm 9.6$  ETDRS letters, respectively), the mean central foveal thickness (CFT) ( $107.1 \pm 21.3 \mu\text{m}$  and  $106.2 \pm 27.3 \mu\text{m}$ , respectively), and the mean subfoveal choroidal thickness (SFCT) ( $407.5 \pm 114.8 \mu\text{m}$  and  $419.1 \pm 113.9 \mu\text{m}$ , respectively). We would like to address several issues that have arisen from this study, which can be specifically summarized below.

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1. The abnormalities in the pachychoroid phenotype and retinal pigment epithelial band – Bruch's membrane complex (dysfunction of the choroid and retinal pigment epithelium [RPE]), which are primarily involved in the chronic CSC and have a pivotal contribution in its pathogenesis, have not been fully documented in this study using multimodal imaging (Călugăru *et al.* 2018).
2. In terms of the choroid, the increased permeability of choroidal vasculature with extravascular leakage, one of the hallmarks of cCSC imaging, was thoroughly investigated by determination the degree of hyperfluorescence in the midphase of indocyanine green angiography (ICGA) in areas correlating to atrophic or elevated RPE (hypofluorescence/mild and intense hyperfluorescence). In addition, the SFCTs ( $407.5 \mu\text{m}$  and  $419.2 \mu\text{m}$  in the focal and diffuse leakage groups, respectively) were above the normal values ( $191 - 350 \mu\text{m}$ ) (Cheung *et al.* 2019), which certify the existence of the chronic choroidal thickening (pachychoroid). However, these values are questionable taking into account that SFCTs could not be obtained in 19 patients (27.9%) with the focal phenotype and in 27 patients (25.7%) with the diffuse phenotype. Of note, the status of the choroidal abnormalities was not comprehensively

investigated in the patients of the 2 groups using the multimodal imaging. Specifically, there were no data on the assessment of the following alterations: the distribution of the pachyvessels in the Haller's layer (in a diffuse or patchy manner) localized within the areas of choroidal vascular hyperpermeability on ICGA; the focal or diffuse attenuation of the inner choroid (thinning/absence of the choriocapillaris and intermediate caliber vessels within Sattler's layer in areas overlying abnormally dilated Haller's layer vessels); and the focal choroidal excavations. Moreover, the perfusion indices (density of blood vessels and flow index) were not calculated for the choriocapillaris zone on the optical coherence (OCT) angiography. The OCT angiography, which allows detection of choroidal neovascularization (CNV) secondary to cCSC not visible with other imaging techniques (neovascular cCSC) and which seems to be helpful to show an abnormal blood flow corresponding to CNV complicating the cCSC, has not been used (Călugăru et al. 2018, 2019)

3. With reference to the retinal pigment epithelium (RPE), the diffuse atrophic RPE alterations (DARA) on FA ( $< 1/1-5/>5$  optic disc diameter), and its location (fovea/within 1 optic disc diameter of the fovea/outside the fovea) were thoroughly investigated. However, nothing was stated relating to the following alterations of the RPE in the 2 groups of patients: pigment migration within the neurosensory retina, RPE porosity, microrips or blowouts in the RPE, RPE thickening, and diffuse ooze within or adjacent to the decompensated RPE (Călugăru et al. 2019a). Likewise, there were no data regarding the existence or otherwise of the 2 OCT angiographic patterns of the pigment epithelial detachment (PED), namely, the hyperreflective irregular flat PED (undulating RPE detachment) with a double layer sign suggesting the neovascular CSC and the serous PED with internal hyporeflectivity, certifying the non-neovascular PED. The distinction should be made because neovascular CSC is associated with a worse outcome in terms of visual and reading acuity compared to non-neovascular PED.
4. There were no data referring to the multimodal imaging of the overlying photoreceptor cell layer, which may suffer progressive and irreversible damages in cases of chronic CSC because of the persistence of the subretinal fluid (SRF) caused by the pronounced dysfunctional RPE outer blood-retinal barrier with severe widespread RPE decompensation. Specifically, these alterations include: the thinning of the outer nuclear layer, the elongation of the photoreceptor outer segments, the discontinuity of the ellipsoid zone, the external limiting membrane disruption, and the hyperreflective deposits frequently accumulated in the subretinal space below the detached neurosensory retina. Furthermore, the perfusion indices for the outer retinal zone (photoreceptor) were not calculated on the OCT angiography. Of note, although the outer retina does not have vessels, the perfusion indices can be still determined (Călugăru et al. 2018, 2018a).
5. There were no comparative data in the 2 phenotype groups referring to the baseline serum potassium levels, the renal function, the level of endogenous and exogenous corticosteroids, the type personality of the patients, and the testing of patients with regard to the Helicobacter pylori infection (Călugăru et al. 2018b).

6. Thorough investigation of the fellow eye using the multimodal imaging revealed an obvious difference between the focal and diffuse leakage groups regarding the proportions of patients with SRF (16.2% and 29.1%, respectively) and a significant difference with respect to the proportions of patients without DARA (49.3% and 28.2%, respectively) suggesting that patients with diffuse leakage have a functionally more aggressive phenotype (more severe and extensive disease) compared to patients with focal leakage of the CSC. These findings might represent the early-phase abnormalities of the same condition, involving a primary choroidal vasculopathy, which tends to be bilateral.

Altogether, the authors of this study concluded that BCVA, CFT, and SFCT did not differ significantly between the focal and diffuse leakage groups, which may indicate that patients with diffuse leakage do not necessarily have a more severe phenotype in comparison to patients with focal leakage. However, the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing baseline factors mentioned by us in addition to the baseline characteristics already assessed.

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