Cerebral Neurovascular Coupling Impairment in Central Serous Chorioretinopathy

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Keywords

Central serous chorioretinopathy · CSC · Neurovascular coupling · Cerebrovascular regulation

Abstract

Background: Central serous chorioretinopathy (CSCR) is a chorioretinal disorder resulting from choroidal hyperpermeability. Its comorbidities as hypertension, coronary disease, and psychological stress, suggest that it might reflect a more generalized vascular dysfunction. **Objectives:** The aim of the study was to assess the cerebrovascular regulation integrity, using cerebral autoregulation (CA), carbon dioxide vasoreactivity (VR), and neurovascular coupling (NVC) in CSCR. **Methods:** This observational pilot study included 20 CSCR patients and 14 age- and sex-matched controls. A State-Trait Anxiety Inventory (STAI) inquiry was full-filled. Continuous measurement of cerebral blood flow velocity (CBFV), arterial blood pressure, heart rate, and end-tidal carbon dioxide was performed. VR was assessed during hypercapnia (inhaling carbogen gas) and hypocapnia (hyperventilation). For NVC, the CBFV relative increase during mental activation using

the N-Back Task was calculated. **Results:** No significant differences in systemic hemodynamic parameters, CA or VR, were found between both groups. During the NVC performance, the average CBFV rise during mental stress was significantly lower in CSCR ($p = 0.011$). A significant negative correlation was found between STAI scores and NVC. **Conclusions:** CSCR patients presented a significantly impaired cerebral NVC compared to controls, supporting the theory of a potential systemic vascular dysfunction. Stress could be related to this NVC impairment.

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Introduction

Central serous chorioretinopathy (CSCR) is a chorioretinal disorder characterized by one or multiple serous detachments of the neurosensory retina. It is more frequent among middle-aged male individuals and has been described in patients with specific psychological and personality profiles, related to stress, anxiety, and Type-A behavior [1].

Its pathophysiology remains poorly understood, but recent multimodal imaging highlighted the role of a choroidal vascular hyperpermeability. Recently the “pachy-choroid” terminology has been proposed for a spectrum of diseases, including CSCR, characterized by the presence of a thick choroid with abnormal dilated choroidal vessels in Haller’s layers (pachyvessels) and compressed choriocapillaris and Sattler’s layers [2–4].

The relation between CSCR and steroids has been widely recognized and is probably one of the most intriguing aspects of the disease [5–7]. A significant sympathetic-parasympathetic imbalance has also been described in CSCR patients, presenting an overactive sympathetic and an under-reactive parasympathetic profile, assessed by blood pressure and heart rate (HR) variability [8, 9]. Furthermore, an increased incidence of cardiovascular events has been found in these patients, presenting a higher rate of coronary heart disease [10] or ischemic stroke [11].

However, the precise mechanisms relating CSCR to anxiety-sensitive personalities, steroid biochemistry, dysautonomia, and cardiovascular risk factors are far from being elucidated, and there are probably many missing factors in this complex equation. It seems that the pathogenesis of CSCR might extend beyond a local choroidal vascular disorder and is possibly the reflection of a systemic vascular dysfunction [5]. This study aimed the assessment of the systemic hemodynamic parameters and cerebrovascular regulation in CSCR patients, comparing to controls.

Material and Methods

Study Participants

A sample of 20 consecutive patients from our retinal department with a diagnosis of CSCR was selected. Both patients with active (acute and chronic) and inactive CSCR were included. An active disease status was described for patients with a history of a serous retinal detachment on optical coherence tomography and leakage on fluorescein angiography within 3 or less months from this assessment. Patients presenting a resolution of a serous retinal detachment for more than 3 months from baseline assessment were classified as inactive CSCR.

A sample of 14 control healthy volunteers, with similar age and sex ratios, was selected. Exclusion criteria for both groups included systemic relevant cardiovascular diseases as hypertension, ischemic coronary heart disease or stroke, diabetes, neuropsychiatric disorder, use of corticosteroids or vasoactive medications, or other ocular diseases besides CSCR. The study guidelines were explained to all the participants and they were given written information explaining the study procedures. A written consent was obtained before their inclusion. All the participants initially filled in

a Portuguese-translated State-Trait Anxiety Inventory (STAI) or STAI-Y1 form to measure distress and diagnose trait and state anxiety [12–14]. The STAI S (state) form was presented first, followed by the STAI T (trait) form. An STAI Anxiety State score >47 and an STAI Anxiety Trait score >42 were considered pathological, according to the cut-offs established by the author, describing a high level of anxiety. The study design and the collection of data were approved by the Ethics Committee of our hospital. All procedures were conducted in accordance with the Declaration of Helsinki.

Monitoring Protocol

The monitoring protocol used was previously described by one of the authors [15]. Patients were evaluated in a dim-lighted room, with a temperature of around 20°C, in a supine position, with the bed head at 0°. Cerebral blood flow velocity (CBFV) was recorded bilaterally from the M1 segment of the middle cerebral artery at a depth of 50–55 mm, using 2-MHz monitoring probes properly secured by an individually fitted headband (Doppler-Box X; DWL, Singen, Germany). Continuous arterial blood pressure (ABP) was recorded using a finger cuff Finometer MIDI device (FMS, Amsterdam, The Netherlands) on the nondominant side. HR was assessed from lead II of a standard 3-lead electrocardiogram. End-tidal carbon dioxide (EtCO₂) was recorded using a nasal cannula with a capnograph (RespSense; Nonin, Amsterdam, The Netherlands). All data were synchronized and digitized at 400 Hz with PowerLab (AD Instruments, Oxford, UK) and stored for offline analysis. After a 20-min rest, a 10-min period of resting data was stored for cerebral autoregulation (CA) calculations. Afterward, carbon dioxide vasoreactivity (VR) and neurovascular coupling (NVC) protocols were performed.

CA Calculations

To assess CA, the mean values of ABP and CBFV were calculated for each heartbeat. Dynamic CA was assessed by transfer function analysis (TFA), which was done by calculating the coherence, gain, and phase parameters from beat-to-beat spontaneous oscillations in CBFV and ABP. TFA parameter settings were in compliance with standard recommendations [16]: Lower coherence (correlation coefficient), lower gain (damping of arterial BP oscillations), and higher phase (speed of the autoregulatory response) between oscillations of ABP and mean CBFV indicate more effective CA. Since vasomotor adaptation is slow and requires at least 6–10 s, CA is most likely to operate at low frequencies [17, 18]. Values were therefore reported in the 2 bands with lower frequencies: very low frequencies (VLF: 0.02–0.07 Hz) and low frequencies (LF: 0.07–0.20 Hz).

VR Protocol

On a second stage of our study, and after resting, all subjects breathed carbogen gas (Carbox 5 CO₂ 5% and O₂ 95%), delivered through a partially expanded reservoir bag at atmospheric pressure, for 2 min. After stabilization of hemodynamic parameters back to baseline, they hyperventilated to an EtCO₂ ~20 mm Hg for another 2 min. VR was calculated as the slope of the relationship between EtCO₂ plotted against relative MFV at the last 30 s of hypocapnia or hypercapnia and expressed as change % of the MFV/mm Hg of CO₂. VR was also calculated separately for hypercapnia and hypocapnia.

Table 1. Clinical and demographic characteristics of the participants

	Clinical and demographic characteristics		
	CSCR	controls	<i>p</i> value
<i>N</i>	20	14	–
Age, years	47.0±9.6	45.9±9.2	0.756 [†]
Sex male/female, <i>n</i> (%)	16 (80)/4 (20.0)	10 (71.4)/4 (28.6)	0.562 [‡]
Active CSCR, <i>n</i> (%)	10 (50)	–	–
Inactive CSCR, <i>n</i> (%)	10 (50)	–	–
STAI Anxiety State score	38.5 (±8.4)	25.0 (±4.8)	0.002 ^{§*}
STAI Anxiety Trait score	44.5 (±4.9)	32.0 (±4.6)	0.002 ^{§*}

Values are presented as mean ± standard deviation (SD). CSCR, central serous chorioretinopathy; STAI, State-Trait Anxiety Inventory. * $p < 0.05$. p value for [†] *T* test, [‡] χ^2 Test, [§] Mann-Whitney.

NVC Protocol

The N-Back Task was performed and analyzed as by Sorond et al. [19]. While in supine position, a sequence of single letters was displayed onto the ceiling. Subjects were first instructed to press the mouse button each time a letter was repeated (1-Back) and then each time a letter was repeated every other letter (2-Back). A control task was performed before each task – “Identify the letter X”; NVC was calculated as the ratio of the relative MFV increase during the N-Back (MFVNB) compared with the control task of “Identify the letter X” (MFVIDX) using the following formula: $[(MFVNB - MFVIDX)/(MFVIDX)] \times 10$ [19]. Only the 2-Back Task results were reported, since they induce a higher CBFV rise and are potentially more representative for NVC assessment [20].

Statistics

For statistical analysis, SPSS software version 24.0 (SPSS Inc, Chicago, IL, USA) was used. Shapiro-Wilk test was used to assess the normality of the sample. Comparisons between groups were performed using *T* test, Mann-Whitney, and χ^2 test, as appropriate. The correlation analysis was performed using the Spearman's test.

Results

Table 1 summarizes the clinical and demographic data of the participants. Twenty patients with CSCR and 14 healthy controls were included. The mean age of the CSCR group was 47.0 ± 9.6 years and in the control group was 45.9 ± 9.2 years. The majority of the participants were male (76.5%) (26 male – 16 CSCR patients and 10 controls). Eight (23.5%) female patients were included (4 CSCR patients and 4 controls).

A significant difference was found for mean STAI scores, both for Anxiety State and Anxiety Trait, between CSCR patients and controls ($p = 0.002$) (Table 1). An STAI score >47 for the Anxiety State was found in 25% ($n = 5$) of CSCR patients and in none of the controls. An

Table 2. Baseline hemodynamics of the participants

	Baseline hemodynamics		
	CSCR patients	controls	<i>p</i> value
Mean ABP, mm Hg	88.2±14.7	79.3±9.90	0.061 [†]
HR, bpm	69.5±14.6	63.8±12.3	0.220 [‡]
ET CO ₂ , mm Hg	37.6±3.90	39.4±2.34	0.165 [†]
CBFV, cm sec ^{−1}	56.4±7.01	58.5±8.02	0.377 [‡]

Values are presented as mean ± standard deviation (SD). CSCR, central serous chorioretinopathy; BP, blood pressure; HR, heart rate; EtCO₂, end-tidal CO₂. p value for [†] *T* test, [‡] Mann-Whitney.

STAI score >42 for the Anxiety Trait was registered in 55% ($n = 11$) of the patients and only in 7% ($n = 1$) of the controls. A significant negative correlation was found between STAI scores for both groups ($r = -0.730$ $p < 0.01$).

In the resting condition (Table 2), although slightly higher in CSCR patients, no significant differences were recorded for mean ABP or HR ($p = 0.061$ and $p = 0.220$, respectively). In a subgroup analysis for the activity of disease, active CSCR patients presented a higher mean ABP than inactive patients ($p < 0.05$), but no other relevant differences were found. The EtCO₂ measurement was similar between both patients and controls ($p = 0.165$), as well as the mean CBFV ($p = 0.377$) (Table 2). Regarding CA (shown in Fig. 1; Table 3), both groups presented a similar performance in both VLF and LF average coherence, phase, and gain, meaning that the buffering of beat-to-beat spontaneous oscillation of mean ABP was preserved in CSCR patients when compared to controls.

Moreover, the VR response (shown in Fig. 2; Table 3), both in hypercapnia (inhaling carbogen) and hypnocapnia (hyperventilation) conditions, proved to be no differ-

Fig. 1. Dynamic CA performance. Dynamic CA assessed by TFA from beat-to-beat spontaneous oscillations in CBFV (output) and ABP (input). Coherence, gain, and phase are represented along all spectrum of frequencies of oscillations. CA acts as a high-pass filter below frequencies around 0.2–0.3 Hz, at which gain is reduced (amplitude of transmission between ABP to CBFV) and phase increases (higher desynchronization between ABP and CBFV oscillations). CA in CSCR patients (thick black line) and controls (thick gray line) was not significantly different. Black and gray dotted lines represent mean $\pm$ SE in CSCR and controls, respectively. SE, standard error.

ent in CSCR versus controls ($p = 0.914$ and $p = 0.822$, respectively). Mean global VR, although higher in controls, was also similar in both groups ($p = 0.822$).

However, a significant difference between CSCR patients and controls was detected in the cerebrovascular hemodynamics assessment during NVC performance (shown in Fig. 3; Table 3). The mean CBFV gain during the 2-Back Task was significantly lower in CSCR patients ($p = 0.011$). Interestingly, this test had no different repercussion on systemic ABP, HR, and EtCO₂ across both groups. Similar NVC performances were found in both active and inactive CSCR patients ($p = 0.619$). A negative correlation was found between both the STAI scores and the NVC, more significant for the Anxiety State than the Anxiety Trait score ($r = -0.602, p = 0.002$ and $-0.442, p = 0.035$) (shown in Fig. 4).

Discussion

In our study, we found that CSCR patients presented a significantly impaired cerebrovascular regulation that affects primarily the NVC. So far to our knowledge, this is the first report on the cerebrovascular regulation performance in CSCR disease.

A competent cerebrovascular regulation is mainly conducted by three major physiological mechanisms: CA, VR, and NVC. We found baseline hemodynamic measurements to be similar in CSCR patients and controls, as well as the cerebrovascular reaction to different levels of CO₂. CSCR patients' cerebral blood vessels presented an equally efficient capacity to adapt to ABP fluctuations as controls (CA).

When submitted to a vasomotor stimulation during VR, using a vasoactive substance like CO₂, the increase in cerebral flow (or flow velocity) resulting from hypercapnia conditions and its decrease conditioned by hypocapnia was not significantly different in CSCR patients when

Fig. 2. Time course of normalized CBFV and EtCO₂ during hyper and hypnocapnia. Time course of normalized mean CBFV (**a, c**) and mean EtCO₂ (**b, d**) during the hypercapnic challenge (left) and hyperventilation-induced hypocapnia (right) of CSCR patients (thick black line) and controls (thick gray line); black and gray dotted lines represent mean $\pm$ SE, respectively. The beginning and ending of each task are marked with vertical black lines. No significant differences were found between both groups. CBFV, cerebral blood flow velocity; EtCO₂, end-tidal CO₂; CSCR, central serous chorioretinopathy; SE, standard error.

(For figure see next page.)

Table 3. Cerebrovascular regulation performance of the participants

Cerebrovascular regulation	CSCR patients	controls	<i>p</i> value
CA			
Coherence VLF, a.u	0.41±0.19	0.35±0.16	0.302 [†]
Coherence LF, a.u	0.59±0.24	0.55±0.20	0.635 [†]
Phase VLF, radians	0.95±0.38	0.98±0.48	0.248 [†]
Phase LF, radians	0.78±0.19	0.76±0.31	0.363 [†]
Gain VLF, % mm Hg ⁻¹	0.78±0.29	0.84±0.39	0.320 [†]
Gain LF, % mm Hg ⁻¹	1.31±0.38	1.07±0.52	0.277 [†]
VR			
VR in hypercapnia, % mm Hg ⁻¹	3.85±1.50	3.97±1.75	0.914 [‡]
VR in hypnocapnia, % mm Hg ⁻¹	3.28±2.67	2.85±2.21	0.822 [‡]
Global VR, % mm Hg ⁻¹	1.35±0.61	1.67±0.46	0.139 [‡]
NVC			
Relative CBFV change in 2-back task, %	3.77±3.36	7.77±4.05	0.011 ^{†*}

Values are presented as mean ± standard deviation (SD). CSCR, central serous chorio-retinopathy; a.u., arbitrary units; LF, low frequencies (0.07–0.20 Hz); VLF, very low frequencies (0.02–0.07 Hz); 2-Back gain – Increase of mean CBFV during 2-back task (%). * *p* < 0.05. *p* value for [†] *T* test, [‡] Mann-Whitney.

Fig. 3. Time course of normalized CBFV, ABP, and HR during the 2-Back Task. Group-averaged time course of normalized mean CBFV (a), mean ABP (b), HR (c) during the 2-Back Task, to assess NVC. Gray-shaded regions represent mean $\pm$ SE. The beginning and ending of the task are marked with vertical black lines. CSCR patients presented a blunted response of the mean CBFV during mental activation when compared to controls. ABP, arterial blood pressure; CBFV, cerebral blood flow velocity; HR, heart rate; SE, standard error.

compared to controls. However, while testing cerebral functional hyperemia under a mental stress task as the 2-Back Task, the average CBFV increase proved to be significantly inferior in CSCR patients. This impairment was independent of the activity state of the disease, suggesting it could be inherent to this pathological condition.

Actually, Tomasso et al. [21] have recently described an impaired retinal NVC in CSCR, presenting a decreased dynamic vasodilation in response to light stimulation. They speculated that the decreased retinal vein dilation response to flicker light stimulation could possibly be due to an increased sympathetic tone and potentially lead to venous stasis and choroidal thickening. This retinal NVC impairment in CSCR corroborates our findings of a cerebral NVC impairment in these patients, since they share the same neurochemical mechanisms.

The concept of neurovascular unit represents the intricate relationship between the brain (or its neural activity) and its vessels. In the “resting” brain, cerebrovascular flow varies in proportion to the energy consumption of each brain region. If given a specific mental stress task, as the 2-Back Task used in our study, a functional hyperemia to the activated areas is expected. This happens due to the need of a sufficient delivery of oxygen and glucose, to provide for a low energy reserve tissue as the brain, as well as the need for a quick wash-out of potential toxic by-products resulting from cell activity (as lactate, CO_2), and the need to regulate brain temperature [22]. Cerebrovascular delivery has been described to be regulated by a feedforward mechanism driven by neurovascular signaling pathways, resulting in the release of vasoactive by-products of synaptic activity such as potassium (K^+), nitric oxide, and prostanoids [23].

We believe that higher levels of stress in CSCR patients could be related to their NVC impairment. The association of CSCR to stress and anxiety has been widely recognized [1] and in our study, the STAI score proved to be significantly higher for both Anxiety State and Trait in CSCR patients when compared to controls (Fig. 4). We also found a significant negative correlation among the STAI score and NVC, meaning that individuals with a higher level of anxiety presented a worse NVC performance, supporting our theory (Fig. 4). Curiously, this does not seem to be an effect of HR or ABP surge during mental activation, which was similar between groups (Fig. 3). It has been proved that stress may influence the neurovascular unit functioning in rats, acting through a multifaceted effect [24–26]. In fact, stress can act as a negative modulator of the remodeling process involved in glial and vascular compartment [24], as well as causing a

Fig. 4. Correlation between the STAI scores and neurovascular coupling. Graphs **a, b** representing the Spearman's rho negative correlation between the Anxiety Trait (STAI-T) and Anxiety State (STAI-S) score, respectively, and CBFV change during the 2-Back Task. Patients with CSCR (black dots) presented higher STAI scores than controls (gray dots). A more significant negative correlation was found for Anxiety State than Anxiety Trait.

glucocorticoid mediated disruption of K^+ -driven vasodilation, through impaired smooth muscle inwardly rectifying K^+ channel function [25]. This ultimately renders arterioles less sensitive to small increases in local K^+ released by astrocytes, causing impairment in K^+ -mediated vasodilation during NVC, and, consequently, dampening the functional hyperemia. A NVC impairment has also recently been described in multiple pathologies with a recognized stress component, such as anxiety, depression, post-traumatic stress disorder, stroke, and Alzheimer's disease [20, 22].

Considering the intricate relation of stress with autonomic nervous system activity, we could also speculate if the autonomic imbalance described in CSCR could have influenced our findings. An impaired NVC in the brain of patients with dysautonomia has been previously described by our investigation team [26]. Nevertheless, very little is known about the influence of autonomic imbalance in cerebrovascular regulation, rendering all the hypothetical attempts highly speculative.

There is nowadays a suspicion that CSCR may be associated with a more generalized vascular systemic dys-

function, rather than just a localized choroidal malfunctioning [5, 27]. An endothelial dysfunction could potentially be present in CSCR, since it has been described in several cardiovascular diseases such as coronary heart disease and stroke, also reported in CSCR patients [5, 10, 11, 27, 28]. More recently, the recognition of an association between the aldosterone/mineralocorticoid receptor pathway and CSCR has encouraged the use of mineralocorticoid receptors (MRs) antagonist in its treatment [5]. Increasing evidence suggests that blocking MR activation can have therapeutic value for endothelial dysfunction, atherosclerosis, hypertension, heart failure, and chronic kidney disease [5]. Inappropriate or overactivation of the MRs in ocular cells and other tissues, such as brain, heart, and systemic vessels, could relate CSCR pathology with its known comorbidities including hypertension, coronary disease and psychological stress. However, the VICI trial, a large randomized placebo controlled double-blinded trial surprisingly showed that eplerenone was not superior to placebo for chronic CSCR [29, 30], proving that there must be other missing factors involved in the intricate equation of CSCR pathogenesis. A more recent

study reported an impaired peripheral endothelial dysfunction in CSCR patients, revealing that it shares the feature of endothelial dysfunction that is common to many cardiovascular diseases [27]. Nevertheless, the precise way this endothelial dysfunction relates to CSCR needs further investigation. Future directions in CSCR etiology should aim at identifying genetic risk factors, high resolution choroidal phenotyping, choroidal, and peripheral endothelial function and cell biology research [31]. Nevertheless, we have to acknowledge some limitations in our study, including a reduced sample of participants, the lack of alcohol and caffeine restraining before their assessment, as well as the lack of control for menstrual cycle and hormonal therapy, although only 8 female patients were evaluated.

Conclusions

Patients with CSCR presented a significantly impaired neurovascular coupling in their brain, when compared to controls. This finding supports the theory that the pathogenesis of CSCR might supersede a local choroidal vascular disorder and is possibly the reflection of a broader vascular dysfunction. Nevertheless, several questions remain unsolved, rendering the need for further investigation on local and systemic hemodynamics in this pathology.

Statement of Ethics

Published research complies with the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Participants gave their written informed consent (as described on the

manuscript body) and the study protocol was approved by the Ethics Committee for Health of Centro Hospitalar Universitário de São João, EPE/Faculty of Medicine of University of Porto, Portugal (project approval number: 52/2016).

Conflict of Interest Statement

Angela Carneiro: participation in advisory boards for Allergan, Alimera, Bayer, Novartis, and Roche. The other authors have no financial disclosures or conflicts of interest to declare.

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Author Contributions

Susana Penas – protocol design and conception; acquisition, analysis, and interpretation of data; and manuscript draft. Pedro Castro – protocol design and conception; acquisition, analysis, and interpretation of data; and manuscript draft. Gilberto Pereira – acquisition of data. Ana Marta Oliveira – protocol design and conception. Angela Carneiro – critical review of the manuscript. Amândio Sousa – critical review of the manuscript. Elsa Azevedo – analysis and interpretation of data; critical review of manuscript. Fernando Falcão-Reis – analysis and interpretation of data, and critical review of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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