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High Levels of C-Reactive Protein with Low Levels of Pentraxin 3 as Biomarkers for Central Serous Chorioretinopathy

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Purpose: To investigate the association between the 2 acute phase proteins, C-reactive protein (CRP) and pentraxin 3 (PTX3) with central serous chorioretinopathy (CSCR), as PTX3 is a glucocorticoid-induced protein.

Design: Cross-sectional multicenter study.

Participants: Patients with CSCR compared with age- and sex-matched healthy participants.

Methods: Patients with CSCR from 3 centers in Europe were included in the study. The clinical form of CSCR was recorded. Blood samples from patients with CSCR and healthy participants were sampled, and high-sensitivity CRP and PTX3 levels were measured in the serum.

Main Outcome Measures: C-reactive protein and PTX3 serum level comparison between patients with CSCR with age- and sex-matched healthy participants.

Results: Although CRP levels were higher in patients with CSCR (n = 216) than in age- and sex-matched controls (n = 130) (2.2 ± 3.2 mg/l vs. 1.5 mg/l ± 1.4, respectively, $P = 0.037$), PTX3 levels were lower in patients with CSCR (10.5 ± 19.9 pg/ml vs. 87.4 ± 73.2 pg/ml, respectively, $P < 0.001$). There was no significant difference in CRP or PTX3 levels between patients with acute/recurrent and chronic CSCR.

Conclusions: In patients with CSCR, high CRP and low PTX3 levels suggest a form of low-grade systemic inflammation together with a lack of glucocorticoid pathway activation, raising new hypotheses on the pathophysiology of CSCR.

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Central serous chorioretinopathy (CSCR) is a chorioretinal disease that manifests as serous retinal detachments secondary to focal retinal pigment epithelium barrier disruption.[1] It occurs mostly in hyperopic or emmetropic middle-aged men, with a preexisting choroidal phenotype, recognized as pachychoroid because it associates an enlarged subfoveal choroid due to dilation of choroidal veins and attenuation of the overlying choriocapillaris.[2] The disease can also occur in women but at older ages and with different phenotypes including the more frequent development of macular neovascularization.[3] The exact mechanisms leading to pachychoroid and associated pathologies are not fully understood. They include possible local venous overload,[4] anatomical predisposition,[4] alteration of neural control of choroidal vasoregulation,[5] and dysmetabolism of glucocorticoids.[6] Indeed, treatment with systemic or extraocular administration of glucocorticoids not only aggravates the disease but can also favor its occurrence or recurrence.[6] Other risk factors have been recognized, such as shift work and sleep disorders or sleep apnea.[7,8] Systemic disorders have also been associated with CSCR, such as allergy, depression, anxiety, hypertension, coronaropathy, and arrythmia.[9] Various CSCR phenotypes have been largely described using multimodal imaging, showing focal or multifocal rupture of the retinal pigment epithelium barrier, choroidal vascular leakage, and choroidal and/or subretinal hyperreflective dots on spectral domain OCT that are considered as infiltrating inflammatory cells.[9] Retinal and choroidal inflammation should be considered as a mechanism involved in CSCR despite the fact that glucocorticoids aggravate the disease. Indeed, in some contexts, glucocorticoids can be proinflammatory,[10] particularly if they inappropriately activate the mineralocorticoid pathway, a mechanism that has been proposed in the pathogenesis of CSCR and pachychoroid.[11,12] Because CSCR is an ocular disease that primarily affects the choroidal vessels, which are exposed to the systemic circulation, it is most likely that systemic biomarkers of CSCR could be identified.

We previously showed that the serum levels of neutrophil-gelatinase associated Lipocalin, also referred to as Lipocalin 2, and of matrix metallopeptidase-9, which forms a complex with Lipocalin 2, were significantly lower in patients with CSCR than in age- and sex-matched control populations.[13] Other groups described that the serum

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fibrinogen/albumin ratio and interleukin (IL)-6 level were elevated in patients with CSCR.[14,15]

Pentraxins (PTXs) are an acute phase, highly conserved class of pattern recognition molecules that contribute to innate immunity. They protect against infection, help with the clearance of injured tissues, and regulate pathogenic inflammation and excessive complement activation. The short PTXs are C-reactive protein (CRP) and serum amyloid P component, and the long PTXs are neuronal PTX1, neuronal PTX2, PTX3, and PTX4. C-reactive protein is produced in the liver, whereas PTX3 is produced by a number of cell types including the retinal pigment epithelium, monocytes, macrophages, microglia dendritic cells, and neutrophils.[16] C-reactive protein, serum amyloid P component, and PTX3 activate complement by binding to C1q, but CRP and PTX3 also bind factor H (FH) to limit excessive complement activation. Unlike CRP binding to FH, PTX3 binding to FH is not affected by the FY402H age-related macular degeneration (AMD)−associated polymorphism.[17]

Under physiologic conditions, blood CRP levels remain below 10 μg/ml, but concentrations between 3 and 10 μg/ml may indicate "low-grade" infraclinical inflammation.[18] Serum PTX3 levels are very low under physiologic conditions, with higher levels measured in women and at an older age,[19] but rise rapidly up to 200 to 800 pg/ml within 6 to 8 hours in response to inflammation.[16] Although both PTXs, PTX3 and CRP, are induced by inflammation, CRP is downregulated by glucocorticoids. Pentraxin 3 is a sensitive marker of glucocorticoid receptor pathway activation, and its level is increased by glucocorticoids.[20]

In this context, we have measured the levels of CRP and PTX3 in large cohorts of patients with CSCR, a disease that is supposedly associated with glucocorticoid increase, and compared them with those of age- and sex-matched controls.

Subjects and Methods

Ethics Statement

Patients from 3 cohorts followed at the Jules Gonin Eye Hospital (Lausanne, Switzerland), the Ophtalmopôle Cochin hospital (Paris, France), and the Rotterdam Eye Hospital (Rotterdam, Netherlands) were included. This research was conducted in compliance with the tenets of the Declaration of Helsinki and was approved by the institutional review boards of each country: France (CPP Ile de France 1, C16-09 N°DC-2016-2620), Switzerland (CER-VD Eyeomics340/15), and the Netherlands (NL50816.058.14). Written informed consent was obtained for each patient and healthy participant.

Study Patients

Diagnosis criteria for CSCR were defined on multimodal imaging including spectral domain OCT (Spectralis, Heidelberg Engineering), blue-light fundus autofluorescence imaging (Spectralis), and fluorescein angiography (Spectralis), according to the CSCR study group classification as previously described.[21] Patients were divided into 2 groups based on disease history and/or presence of underlying multifocal epitheliopathy characterized by blue-light fundus autofluorescence and fluorescein angiography. Patients with epitheliopathy (total cumulated area $>$ 2 disk diameters) were classified as chronic cases, whereas patients without epitheliopathy were classified as acute/recurrent cases. Patients with any other ocular disease such as AMD (characterized by the presence of drusen), diabetic retinopathy, retinal vein occlusion, high myopia $>$ −6 diopters, or glaucoma or patients under systemic glucocorticoid treatment were excluded from the study. Comorbidities in the group of patients with CSCR are listed in Table 1. We did not have access to the full medical history of control individuals.

Serum from control participants was obtained from the French blood bank (Banque Française du Sang) under an agreement with Inserm. Blood was prospectively collected from healthy donors who had no previous history of ocular diseases or systemic diseases and were matched for age and sex with patients with CSCR. Sera were prepared and stored at −80° C in a biobank under similar conditions for individuals with CSCR and control individuals.

CRP and PTX3 Measurements

High-sensitivity CRP assays were performed using the automated BN II System nephelometer (Siemens Healthineers). Human PTX3 was quantified using the Abcam PTX3 enzyme-linked immunosorbent assay kit (ref ab214570). The test sensitivity is 3.4 pg/ml according to the manufacturer's instructions. All samples were randomized and run simultaneously in duplicate.

Statistics

A descriptive analysis of the study population was performed. Categorical data were compared using the chi-square test. Quantitative data was tested for normality with the Shapiro−Wilk test. Data were compared between the 2 groups using the Student t test for normal distributions and the Mann−Whitney U test for nonnormal distributions. All P values were 2-sided, and P values ≤ 0.05 were considered statistically significant. Statistical analyzes were performed using XLstat software (version 2020; Addinsoft).

Results

CRP Serum Level in Patients with CSCR Compared with Controls

C-reactive protein was measured in 216 patients with CSCR and 130 age- and sex-matched healthy controls. The results are summarized in Table 2. The mean age did not differ statistically between the CSCR and control group (49.96 $\pm$ 8.6 years in the CSCR group vs. 49.69 $\pm$ 9.1 years in the control group, $P = 0.8$). There was no significant difference in the sex ratio between the CSCR and control group (79.6% of men in the CSCR compared with 80.8% in the control group, $P = 0.8$). C-reactive protein serum levels were higher in patients with CSCR than in age- and sex-matched controls (2.2 $\pm$ 3.2 mg/l vs. 1.5 $\pm$ 1.4 mg/l, respectively, $P = 0.037$). A CRP level $>$ 4 mg/l was detected in 14.3% of patients with CSCR and 6.9% of controls ($P = 0.038$, Table 2 and Fig 1).

Table 1. Comorbidities in the Group of Patients with CSCR

Comorbidities	Patients with CSCR (n = 216)
Familial history of CV disease	12
Personal history of CV disease	1
Sleep disorders	38
Sleep apnea	7
History of depression	42
Ongoing depression	3
Allergies	28; pollen 18, eczema 6, asthma 4
Labial herpes	1
Substance abuse	2
Past lung carcinoma	1
Arthrosis	3
Hypothyroidism	2
Kidney stones	2
Gastric ulcer	3
Past corticoid use	51
Marfan disease	1
Past pituitary adenoma	1

CSCR = central serous chorioretinopathy; CV = cardiovascular.

CRP Level in Patients with CSCR According to the Acute or Chronic Form of the Disease

Among the 216 patients with CSCR included in the study, the CSCR phenotype was ascertained in 198 patients, among whom 47.5% had an acute/recurrent form of the disease, whereas 52.5% had complex CSCR with epitheliopathy. Patients with acute/recurrent CSCR were younger than patients with chronic CSCR (46.2 ± 8.2 years vs. 53 ± 7.6 years, respectively, $P < 0.001$). There was no significant difference in CRP serum levels in the group of patients with acute/recurrent and chronic CSCR (2.6 ± 4.6 mg/l vs. 2.2 ± 2.9 mg/l, respectively, $P = 0.99$).

PTX3 Serum Levels in Patients with CSCR Compared with Controls

PTX3 levels were analyzed by enzyme-linked immunosorbent assay in 65 patients with CSCR and 44 controls. The results are summarized in Table 3. Mean age and sex ratio did not differ between CSCR and control groups ($P = 0.7$ and $P = 0.5$, respectively, Table 3). The PTX3 serum level was lower in patients with CSCR than in the control group (10.5 ± 19.9 pg/ml vs. 87.4 ± 73.2 pg/ml, respectively, $P < 0.001$; Table 3 and Fig 2A). Pentraxin 3 was below the detectable level in 70.8% of patients with CSCR and 11.4% of controls ($P < 0.001$).

PTX3 Serum Level in Patients with CSCR According to the Acute or Chronic Form of the Disease

Among the 65 patients with CSCR, 36.9% had acute/recurrent CSCR, whereas 63.1% had complex CSCR. Patients with the acute/recurrent form were younger than patients with chronic CSCR (51.2 ± 4 years vs. 54.6 ± 5.2 years, respectively, $P < 0.04$). If we considered only patients older than 50 years, there were still 30% of simple cases, suggesting that the simple form of the disease does not occur only in the younger population.

There was no significant difference in PTX3 serum levels in the group of patients with acute/recurrent and chronic CSCR (5 ± 11.2 pg/ml vs. 13.7 ± 23 pg/ml, respectively, $P = 0.35$).

Discussion

In a large cohort of patients with CSCR from 3 different centers, we found that serum CRP levels were higher in patients with CSCR than in healthy age- and sex-matched controls. Higher CRP was found in both acute and chronic cases without any statistical difference between both forms of the disease. Although the mean CRP level was higher in patients with CSCR, it remains in the "normal" range (ie, < 10 mg/l) in 96.3% of CSCR and in 100% of controls. However, a higher proportion of patients with CRP levels > 4 mg/l was observed in the CSCR group, suggestive of infraclinical, low-grade inflammatory state regardless of the type of disease. This suggests that this low-grade inflammation might not be a consequence of a chronic form of CSCR but rather a favoring factor. In AMD, Mitta et al[22] showed that individuals with CRP levels > 3 mg/l had a 50% increased risk of developing the disease. Increase in CRP correlates well with the recent observation of higher IL-6 in the serum of patients with CSCR because IL-6

Table 2. CRP Serum Level of Patients with CSCR Compared with Healthy Controls

	Patients with CSCR (n = 216)	Healthy Controls (n = 130)	P
Age (yrs), mean ± SD	49.96 ± 8.6	49.69 ± 9.1	0.8*
Sex, male, n (%)	172 (79.6)	105 (80.8)	0.8†
CRP serum level (mg/l), mean ± SD	2.2 ± 3.2	1.5 ± 1.4	0.037*
CRP serum level > 4 mg/l, n (%)	31 (14.3)	9 (6.9)	0.038†
CRP serum level < 1 mg/l, n (%)	95 (44.2)	71 (54.6)	0.06†

CRP = C-reactive protein; CSCR = central serous chorioretinopathy; SD = standard deviation.
*Mann–Whitney *U* test.
†Chi-square test.

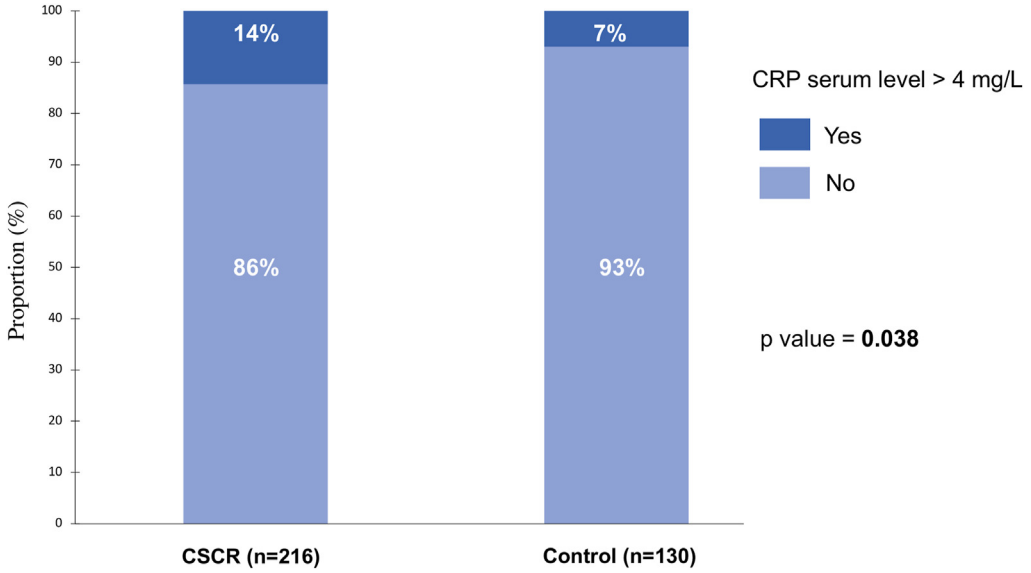

Figure 1. Graph representing the proportion of patients with a C-reactive protein (CRP) serum level > 4 mg/l in the central serous chorioretinopathy (CSCR) group compared with controls.

upregulates the expression of CRP in hepatocytes through Signal transducer and activator of transcription 3 activation.[23] Taken together, these results indicate that patients with CSCR might suffer from low-grade systemic inflammation, which agrees with systemic risk factors associated with CSCR that have been associated with high CRP, such as hypertension and coronaropathy,[24] depression,[25] and sleep apnea.[26] This low-grade inflammation might reflect comorbidity, particularly inflammatory diseases that might indicate steroids, and does not indicate any causative link with CSCR. On the other hand, in our population and probably because patients under corticoid treatments were excluded, we did not have patients with chronic inflammatory diseases.

Previous studies showed contradictory results regarding CRP levels in CSCR. Erol et al[27] showed increased CRP levels in acute CSCR compared with an age- and sex-matched control group, whereas 2 other studies did not show a significant difference in CRP levels in small samples of 34 and 38 patients with CSCR.[28,29] Taking into account the variability of CRP, large cohorts like the one tested in the present study might be necessary to show a significant difference. Nevertheless, repetition studies should be performed on multinational cohorts.

Surprisingly, PTX3, which is also a marker of inflammation and innate immunity and whose expression is induced by nuclear factor kB and IL-1[30] and elevated in other ocular diseases such as AMD,[31] vein occlusion,[32] and diabetic retinopathy,[33] is dramatically decreased and mostly below detectable levels in patients with CSCR. Pentraxin 3 levels did not differ in complex CSCR with epitheliopathy compared with simple CSCR, indicating that PTX3 is not correlated with the severity of the disease.

Interestingly, glucocorticoids exert inverse effects on CRP and PTX3. Indeed, glucocorticoids are known to induce PTX3 expression.[20,34] In humans, PTX3 levels are reduced in patients with iatrogenic hypocortisolemia and increased in patients with Cushing's syndrome.[20] Glucocorticoids are also known inducers of Lipocalin 2 expression, another early stress response protein, levels of which are also decreased in patients with CSCR.[13] Pentraxin 3 and Lipocalin 2 levels significantly correlate, and glucocorticoids increase the expression of both markers.[34]

Table 3. Pentraxin 3 Serum Level of Patients with CSCR and Healthy Controls Included in the Study

	Patients with CSCR (n = 65)	Healthy Controls (n = 44)	P
Age (yrs), mean ± SD	53.3 ± 5.1	53.7 ± 4.9	0.7*
Sex, male, n (%)	55 (84.6)	35 (79.6)	0.5†
Pentraxin 3 serum level, (pg/ml), mean ± SD	10.5 ± 19.9	87.4 ± 73.2	< 0.001*
Pentraxin 3 serum level below the detection threshold, n (%)	46 (70.8)	5 (11.4)	< 0.001†

CSCR = central serous chorioretinopathy; SD = standard deviation.
*Mann–Whitney *U* test.
†Chi-square test.

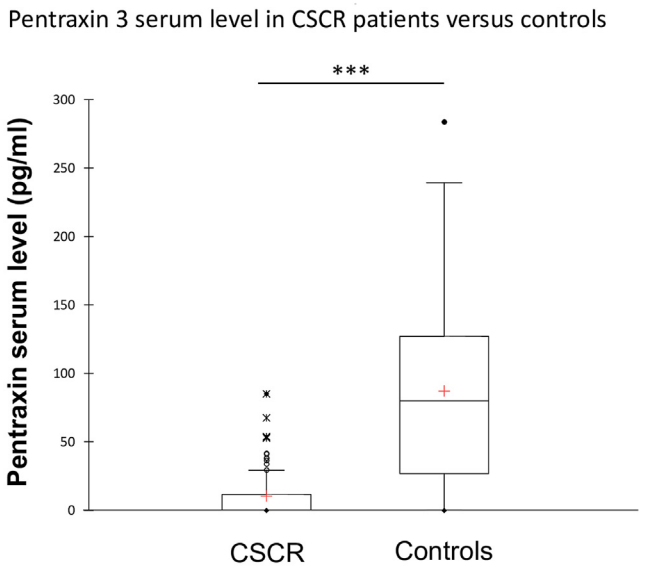

Figure 2. Graph representing the pentraxin 3 serum level in patients with central serous chorioretinopathy (CSCR) compared with controls. ***$P <$ 0.001.

The increase in CRP together with a reduction in PTX3 and Lipocalin 2[13] is an indicator that patients with CSCR may suffer from a form of infraclinical adrenal insufficiency or from insufficient glucocorticoid receptor pathway activation. This hypothesis is reinforced by the observation that exogenous glucocorticoids are a well-known risk factor of CSCR,[6] whereas prolonged and significant intraocular glucocorticoid levels that are noted with glucocorticoid implants do not cause the disease. Indeed, contrary to intraocular glucocorticoids, which do not diffuse in the systemic circulation, extraocular corticosteroids, even at low doses, can induce a braking of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent adrenal insufficiency that can persist months after glucocorticoid intake. After systemic exposure to glucocorticoids, HPA axis suppression is highly variable among individuals and can be drastic or moderate and last long after corticoid arrest in sensitive patients, even at a low dose. About 10% to 50% of patients treated with systemic glucorcorticoids and 2% to 6% of patients using topical glucocorticoids[35] develop HPA axis suppression, which may last over 6 months and may influence their future response to glucocorticoid treatment or stress.[36] Secondary adrenal insufficiency that develops as a result of HPA axis suppression can take years to fully recover, as it was demonstrated in patients treated for Cushing's syndrome but also in patients treated with exogenous glucocorticoid. Even low doses (5 mg prednisone/day) may precipitate relative adrenal insufficiency that may last up to 2 to 4 years after glucocorticoid withdrawal or could rarely not be reversible.[37,38] The diagnosis of such infraclinical adrenal insufficiency might be very difficult to detect.[39] It can therefore not be excluded in those patients with CSCR who have been treated even several months or years ago with glucocorticoids and might present with relative adrenal insufficiency.

The potential pathogenic consequences of PTX3 deficiency in the occurrence of CSCR have not been studied specifically. However, it is interesting to recall that PTX3 is produced by retinal pigment epithelial cells and secreted at their apical side,[40,41] where it plays a role in the inhibition of proliferation and epithelial-mesenchymal transition.[42] In addition, PTX3 is an important player in the regulation of the complement pathway because it promotes the inhibitory activity of FH and its protective effects against oxidative stress and inflammasome activation.[43] In the central nervous system, PTX3 promotes the restoration of cerebral blood flow after ischemia and favors neural survival.[44] Deficiency in PTX3 promotes vascular inflammation,[45] which could be a feature in pachychoroid eyes. Overall, PTX3 is an important regulator of inflammation, contributing to the clearance of apoptotic cells and restoration of vascular barriers.

In patients with CSCR showing systemic signs of inflammatory status such as elevated IL-6 and CRP, PTX3 deficiency could contribute to choroidal vascular pathology and retinal pigment epithelial cell disruption. Thus, PTX3 is a potential new therapeutic target, regulated by glucocorticoids, for the treatment of CSCR.

The strength of this study is the inclusion of a large cohort of patients with CSCR. Limitations include the cross-sectional design and the fact that PTX3 was measured in a subset of patients with CSCR and healthy participants. However, all the results were highly statistically significant. We also recognize no control on systemic medications taken by the individuals in this study.

In summary, a high CRP level indicates that patients with CSCR may suffer from a specific form of low-grade systemic inflammation, possibly due to a lack of glucocorticoid pathway activation because 2 inflammatory mediators known to be increased by glucocorticoids, PTX3 and Lipocalin 2, are strikingly decreased in the serum of patients with CSCR. Increased CRP together with reduced PTX3 and Lipocalin 2 could serve as a systemic biomarker for CSCR.

These results should be confirmed in independent, large, multinational cohorts. Further studies are also required to correlate CRP, PTX3, and Lipocalin 2 in the same individuals and determine whether one or both molecules could be predictive of the evolution and/or severity of the disease.

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Overall responsibility: Behar-Cohen

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CRP** = C-reactive protein; **CSCR** = central serous chorioretinopathy; **FH** = factor H; **HPA** = hypothalamic-pituitary-adrenal; **IL** = interleukin; **PTX** = pentraxin.

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