

To Evaluate the Association of Stress with Serum Cortisol and Serum Homocysteine Levels in Patients of Central Serous Chorioretinopathy

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Abstract

Aim: To evaluate the association of stress with serum cortisol and serum homocysteine levels in patients of CSCR and comparison with age matched controls. **Study design:** Prospective observational, single centre study. **Materials and methods:** We have evaluated stress score, serum cortisol and serum homocysteine levels in 35 patients (33 males and 2 females) of CSCR with the mean age of 33.14 ± 6.78 years and 35 age and sex matched controls. Pearson correlation coefficient (r) was calculated to correlate the stress score with levels of serum cortisol and serum homocysteine in both cases and controls. **Results:** Mean stress score in cases and controls were 13.11 ± 5.58 and 6.91 ± 4.30 respectively ($p < 0.0001$). Mean morning serum cortisol levels in patients of CSCR and controls were 12.88 ± 4.95 & 11.12 ± 3.39 ($p = 0.0872$) respectively and mean evening serum cortisol levels in patients of CSCR and controls were 11.10 ± 4.16 & 8.03 ± 1.94 respectively ($p = 0.0002$). Mean serum homocysteine levels in patients of CSCR and controls were 26.17 ± 11.52 and 13.06 ± 3.19 respectively ($p < 0.0001$). Stress score of CSCR patients found to be weakly correlated with morning and evening levels of serum cortisol ($r = 0.058, 0.084$ respectively) and strongly correlated with serum homocysteine levels ($r = 0.864$). There was no correlation between the levels of serum cortisol and serum homocysteine with the severity and duration of CSCR. **Conclusion:** CSCR is a multifactorial disorder and raised levels of stress, serum cortisol and serum homocysteine play a pivotal role in the pathogenesis.

Keywords: Central serous chorioretinopathy; Stress score; Cortisol and homocysteine.

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Introduction

Central serous chorioretinopathy (CSCR) is an idiopathic localised serous detachment of neurosensory retina involving macula, the area of most acute vision with or without focal

pigment epithelial detachment (PED).¹ It was first recognized by Albrecht von Graefe in 1866 and was named central recurrent retinitis,² later the condition was renamed as idiopathic central serous chorioretinopathy by Gass et al. in 1967.³

The overall incidence is 5.8 cases per 100,000 population.⁴ It is six times more likely to occur in males than females.⁴ Often, it affects competitive and compulsive workaholic young adults of 30-40 years.⁵ Various studies have implicated infective, vascular, toxic, immunological, allergic, mechanical, psychological and endocrinological factors in the pathogenesis of CSCR.⁵ However, the exact cause remains obscure. Many conditions including emotional stress, type A personality, pregnancy and Cushing's syndrome have been associated with an increased incidence of CSCR.⁶

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Since there are no studies on northern Indian population which have evaluated the levels of serum cortisol and serum homocysteine in CSCR patients. The current study is undertaken to give additional evidence that stress or stress related illness leads to elevation of endogenous steroids that may play a role in the pathogenesis of CSCR.

None of the previous studies done on CSCR have showed the correlation between duration of CSCR episode and levels of endogenous steroids. Herewith, by means of this study we are aiming to find out this correlation, which may help in further management of the patients.

Materials and Methods

We conducted a prospective, observational, single center study in confirmed patients with CSCR in the age group of 20–50 years (mean age of 33.14 ± 6.87 years), presenting in outpatient department and retina clinic at Regional Institute of Ophthalmology (RIO), Manohar Das Eye Hospital, Prayagraj between December 2018 and September 2019 after taking permission from ethical committee of M.L.N medical college, Prayagraj.

In this clinical study total 70 patients were included and all candidates were divided into 2 groups: Group A consisted of 38 eyes of 35 patients of confirmed cases of CSCR, out of them 33 were male and 2 were female patients. Group B included 35 patients (33 male and 2 female) who were age and sex matched controls and had presented to our outpatient department (OPD) for routine eye examination.

The criteria for inclusion into our study were: patients aged between 20–50 years, first attack of CSCR, visual symptoms of less than 3 months. We excluded the patients who presented to us with: chronic (>6 months duration)/recurrent episode of similar symptoms, patients with any other retinal disease (such as age related macular degeneration and retinal vein occlusion), history of steroid use in any form and systemic disease such as endogenous hypercortisolism and diabetes mellitus, alcohol abuse or dependence, major depression, history of trauma or previous treatment including intravitreal injections, laser photocoagulation, photodynamic therapy within 3 months of presentation.

As a baseline evaluation, at the time of inclusion into our study, all subjects underwent a complete systemic evaluation and detailed medical history. We evaluated stress levels in all patients (cases

and controls) using National Stress Awareness Day (NSAD) stress questionnaire, published by international stress management association UK, on 2nd November 2016.⁷ This questionnaire consisted of 25 questions related to their daily activities. We asked the patient to relax first and to answer all questions in “Yes” if any of the components of the question was true or “No” if none of the components was true.

A “Yes” answer scored 1 (one), and a “No” answer scored 0 (zero).

Patient who scored less than 4 were considered least likely to suffer from stress and patients who scored between 5 and 13 were considered as more likely to experience stress related ill health either mental, physical or both. Patients who scored more than 14 were considered as most prone to stress. Ocular examination consisted of Snellen’s visual acuity test, Slit lamp biomicroscopy and Indirect ophthalmoscopy.

OCT examination: Cirrus HD-OCT (Carl Zeiss Meditec SW: 6.5.0.772) was used to confirm our clinical diagnosis and to measure central subfield retinal thickness for further follow-up. Multiple scans were taken throughout the whole macular area (512×128), scans with strongest signal strength were selected and maximum retinal thickness was measured.

Lab investigations: Morning and evening levels of serum cortisol and serum homocysteine were advised to all patients on next day or within five days of presentation. Cortisol is best measured in the morning for possible adrenal insufficiency and best measured in the evening to differentiate normal and Cushing’s syndrome patients. Homocysteine is a sulphur containing amino acid, there is an association between elevated levels of circulating homocysteine and various vascular disorders.

In all patients, serum morning cortisol and homocysteine levels were analyzed by Carbonyl Metallo Immunoassay (CMIA) method, that uses metal carbonyl complexes as tracers and Fourier transformed infrared spectroscopy (FT-IR) as the detection method. This assay is based on the particular spectral features of these complexes, which shows very strong absorption bands in the 1,800–2,200 cm spectral range where proteins and organic molecules do not absorb. Evening cortisol levels were analyzed by Electrochemiluminescence Immunoassay (ECLIA) method.

Results

In this study, there were two groups consisting of 35 patients each, 33 (94%) were male and 2 (6%) were female in each group. Mean age of the cases (Group A) and controls (Group B) was 33.4 ± 6.87 and 32.54 ± 6.45 years, respectively. There was no significant difference in the age of cases and controls in this study ($p = 0.057$). On statistical analysis stress scores were significantly elevated in Group

A as compared to Group B ($p < 0.0001$). Morning serum cortisol levels were not significantly raised in cases in Group A as compared to controls in Group B ($p = 0.0872$). Evening serum cortisol levels were significantly raised in cases as compared to controls ($p = 0.0002$). Serum homocysteine levels were found to be significantly raised in cases in Group A as compared to controls in Group B ($p < 0.0001$) (Table 1).

Table 1: Comparison of stress score with serum cortisol and serum homocysteine in Group A and Group B (using unpaired *t*-test)

	Group A (<i>n</i> = 35)	Group B (<i>n</i> = 35)	<i>t</i> -value	<i>p</i> -value
Stress score	13.11 ± 5.58	6.91 ± 4.30	5.206	<0.0001
Serum cortisol (morning) (µg/dl)	12.88 ± 4.95	11.12 ± 3.39	1.735	0.0872
Serum cortisol (evening) (µg/dl)	11.10 ± 4.16	8.03 ± 1.94	3.956	0.0002
Serum homocysteine (µmol/L)	26.17 ± 11.52	13.06 ± 3.19	6.488	<0.0001

The maximum retinal thickness was measured on Cirrus HD-OCT and there was significant difference in the mean central retinal thickness of cases ($503.50 \pm 110.46 \mu\text{m}$) and controls ($240.48 \pm 8.54 \mu\text{m}$) at presentation and at 4 weeks ($p < 0.0001$)

but at 24 weeks due to reabsorption of sub-retinal fluid in patients of CSCR, there was no significant difference in the mean central retinal thickness of cases ($239.15 \pm 22.48 \mu\text{m}$) and controls ($240.48 \pm 8.54 \mu\text{m}$) ($p = 0.7445$) (Table 2).

Table 2: Comparison of mean central retinal thickness between cases and controls

	Mean central retinal thickness of cases (µm)	Mean central retinal thickness of controls (µm)	<i>t</i> -value	<i>p</i> -value
At presentation	503.50 ± 110.46	240.48 ± 8.54	14.04	<0.0001
At 4 weeks	364.13 ± 86.84	240.48 ± 8.54	8.38	<0.0001
At 24 weeks	239.15 ± 22.48	240.48 ± 8.54	0.32	0.7445

Stress scores of the patients of CSCR were correlated with the levels of serum cortisol and serum homocysteine (by calculating Pearson correlation coefficient). According to statistical analysis, there was a weak positive correlation of

the stress scores with morning and evening levels of serum cortisol ($r = 0.058$ and 0.084 respectively, Figs. 1 and 2) and strong positive correlation between stress and serum homocysteine levels ($r = 0.864$, Fig. 3) (Table 3).

Table 3: Correlation of stress scores with serum cortisol and serum homocysteine in patients of CSCR in Group A and controls in Group B

	Group A (<i>r</i>)	Group B (<i>r</i> ²)
Serum cortisol (morning) (µg/dl)	0.058	0.023
Serum cortisol (evening) (µg/dl)	0.084	0.053
Serum homocysteine (µmol/L)	0.864	0.076

(*r* - Pearson correlation coefficient of Group A, *r*² - Pearson correlation coefficient of Group B, *r* = 0 means no association, *r* < 0.5 means weak association, *r* = 0.5–0.8 means moderate association, *r* > 0.8 means strong association, *r* = 1 means perfect linear association between two variables)

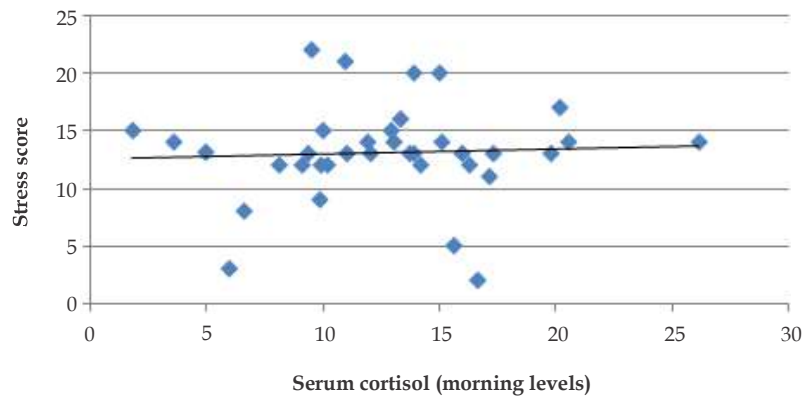


Fig. 1: Correlation between morning levels of serum cortisol and stress scores.

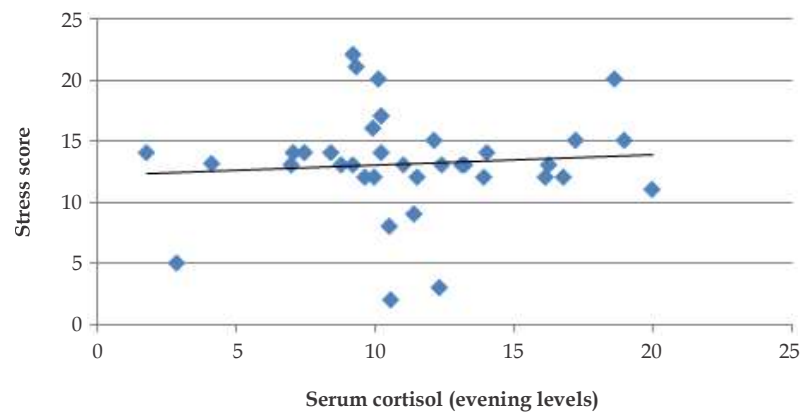


Fig. 2: Correlation between evening levels of serum cortisol and stress scores.

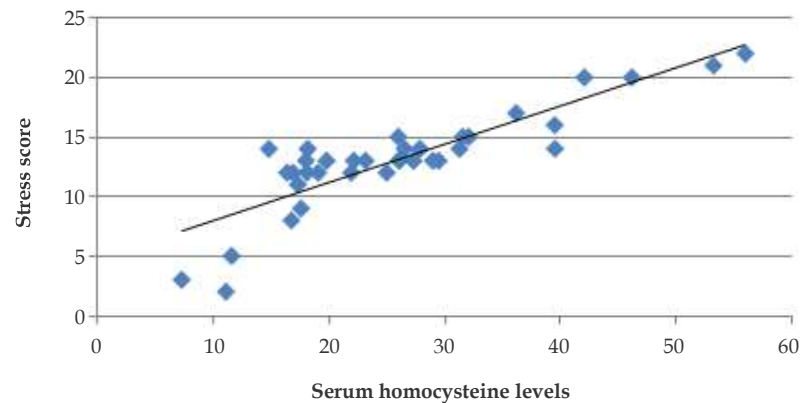


Fig. 3: Correlation between serum homocysteine levels and stress scores.

We also tried to find association between levels of endogenous cortisol and homocysteine with the severity of disease by comparing them with the presenting best Corrected visual acuity (BCVA) and central subfield retinal thickness on their first cirrus HD-OCT at the time of presentation. We did not find any association between the severity and duration of the disease with the serum cortisol and homocysteine levels.

Discussion

CSCR is the fourth most common retinopathy after age-related macular degeneration, diabetic retinopathy and retinal vein occlusion.⁸ Despite so many studies in the literature, the exact etiopathogenesis of CSCR still remains poorly understood.

It usually affects young and middle aged males between 20 and 50 years and it is more predominant in Asian population as compared to white and black races.⁵ The relative absence of the condition in females indicates that estrogen and progesterone may possibly have a beneficial role. Though no age is immune, incidence of CSCR decline with advancing age, this indicates towards the role of the male sex hormone, i.e. testosterone in the pathogenesis of CSCR. Rocha et al.⁹ reported the presence of androgen receptors in human RPE cells and mechanisms of action of androgen in various ocular factors like, aqueous outflow, intraocular pressure and vascular permeability, which could play role in pathogenesis of CSCR in young and middle aged males. However, there are various studies which reported that CSCR occurring in patients of 60 years or older. Fine SL et al.¹⁰ documented the youngest case of CSCR in a 7-year old girl. Schatz H et al.¹¹ reported idiopathic CSCR in 13 patients who were 60 or older. We also did the occupational analysis of our cases and according to their occupational status 24 out of 35 patients (65.71%) of CSCR required a high degree of competitiveness for their work, which could be said to carry a fair degree of responsibility. This could explain the fact that CSCR often affects competitive and compulsive workaholic young adults.

Active researches are going on and various studies have reported multiple risk factors for CSCR like Type A personality, emotional stress, systemic hypertension, smoking, alcohol consumption, pregnancy, organ transplantation, *H. pylori* infection, and drugs like corticosteroids, phosphodiesterase-5 (PDE-5) inhibitors (Sildenafil, Tadalafil), anti-reflux medication and few herbal medicines.¹²

Horniker¹³ was the first who related psychiatric disturbance and stress with CSCR. Conrad et al.¹⁴ reported significantly higher level of stress in patients of CSCR as measured by the global severity index. Bazzaziet al.¹⁵ reported that patients with acute or recurrent CSCR showed higher anxiety scores in Iranian population.

Gelber GS et al.⁶ found that very disturbing psychological event had preceded the loss of vision due to CSCR in 91% patients of the total of 33 cases. Yannuzi et al.¹² reported that patients with type A behaviour pattern were significantly more prone to develop CSCR. In accordance with the previous studies, this study also shown that stress scores were significantly elevated in patients of CSCR as compared to controls.

There is an inconsistent relationship between raised levels serum cortisol and incidence of CSCR. Corticosteroid related CSCR can develop because of multifactorial effects leading to increased RPE leakage, RPE cell apoptosis and alteration in ion transport across RPE cells. Till now, so many studies have shown that etiopathogenesis of CSCR is strongly associated with raised levels of serum cortisol. This study had shown that morning cortisol was normal and evening serum cortisol was significantly raised in patients of CSCR (reason could not be explained). But, there was a weak correlation of stress levels with both morning and evening levels of serum cortisol. Tufan et al.¹⁶ and Aggarwal et al.¹⁷ could not identify precise correlation of the serum cortisol with CSCR. In contrast to this Garg et al.¹⁸ found that the cortisol levels were significantly higher in patients with acute CSCR. Zakir et al.,¹⁹ Liang et al.²⁰ concluded that increased morning cortisol level was associated with increased risk of CSCR.

As per the literature, there have been studies of the influence of mental stress on the total serum homocysteine levels but the findings were inconsistent. In our study, serum homocysteine levels were found to be significantly elevated in patients of CSCR and there was a strong positive correlation of the stress with serum homocysteine levels. In accordance with our study, Sawaiet al.²¹ documented significant relation between stress and increased levels of total serum homocysteine. Agarwal A et al.²² reported that stress scores strongly correlated with serum homocysteine and serum cortisol morning and evening levels and systolic and diastolic blood pressure.

We thought that there might be some correlation between the severity and duration of CSCR with increased levels of serum cortisol and serum homocysteine. However, no significant correlation between the two was observed.

On the basis of results of our study, we believe that stress indirectly plays an important role in precipitating CSCR by increasing the levels of serum homocysteine, which in turn leads to various changes in the RPE and the choroidal vasculature resulting in osmotic fluid accumulation in the subretinal space and the serous retinal detachment. Association of increased levels of homocysteine in serum and eye diseases such as glaucoma, maculopathy, cataract, optic nerve damage, and retinal vessel atherosclerosis is established by Ramakrishnan S et al.²³ and Ranimenon et al.²⁴ The metabolism of homocysteine requires enzymes with vitamins such as folic acid, vitamin B₁₂ and B₆.

So, we believe that levels of homocysteine, folate, vitamin B₁₂ and B₆ should be evaluated in all young-middle aged patients of CSCR with complaints of visual impairment.

The Present Study has Several Limitations

Firstly, the small sample size limited us to fully investigate the relationship of stress between the levels of serum cortisol and homocysteine and does not permit us to draw any conclusion regarding their role in the pathogenesis of CSCR. Secondly, the blood samples were taken only once i.e. at the time of presentation of the patients to our hospital after evaluating the stress scores, but the levels of serum cortisol and serum homocysteine is likely to fluctuate throughout the period of stress. Further prospective studies in larger groups of subjects along with longer duration of follow-up period are needed.

Conclusion

To conclude it may be logical to believe that CSCR remains a challenge to the Ophthalmologist as the exact etiopathogenesis remains poorly understood in spite of tremendous clinical and experimental researches.

On the basis of results of our study, we strongly believe that CSCR is a multifactorial disorder which shares a definite link with stress, evening levels of serum cortisol and serum homocysteine levels.

However, we did not observe any significant correlation of serum cortisol and serum homocysteine levels with duration and severity of the CSCR. But, it will be interesting to find out this correlation in further large scale studies in the future which could help in prevention of disease and its treatment to shorten the duration of symptoms in patients who required a high degree of visual discrimination for their work, and who have strong desire for early recovery.

It will be interesting to study in future to evaluate the beneficial role of folate, vitamin B₁₂ and B₆ in patients of CSCR with increased homocysteine levels in order to neutralize the cytotoxic and inflammatory response of homocysteine-thiolactone and prevent ocular damage.

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Conflicts of interest: We declare that there are no potential conflicts of interest relevant to this study.

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