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ENDOGENOUS CORTISOL AND TESTOSTERONE LEVEL IN CENTRAL SEROUS CHORIORETINOPATHY: A CASE CONTROL STUDY

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ABSTRACT

Central serous chorioretinopathy (CSCR) is characterized by an exudative neurosensory layer detachment of retina. Male gender, type-A personality, emotional stress, pregnancy, infections, hormonal regulatory factors and several immunological reactions have all been implicated in causing CSCR. Although several hypotheses have tried to establish a link between endocrinal abnormalities and CSCR, still none is able to explain the true etiopathogenesis of CSCR. This study was designed to estimate serum cortisol and testosterone levels in patients of CSCR and study their potential role in etiopathogenesis of the disease. In this study, 25 patients of CSCR satisfying the inclusion and exclusion criteria were enrolled as cases and 25 age and sex matched patients with an acute unilateral rhegmatogenous retinal detachment (RD) were enrolled as controls. Levels of serum cortisol and testosterone were estimated in both groups. Serum cortisol measurement was done twice, due to diurnal variation in its levels. Data analysis was done by Pearson's correlation analysis and independent student t-test. The 8:00 AM mean serum cortisol value in the cases (20.21 ± 4.86 µg/dl) was significantly ($p = 0.046$) higher than controls (17.74 ± 3.53 µg/dl). Although the 11:00 PM mean serum cortisol value of cases (8.13 ± 3.52 µg/dl)

was more than controls (6.97 ± 2.50 µg/dl) but difference was not statistically significant (p = 0.187). No statistically significant difference (p > 0.05) was observed while comparing the mean level of testosterone in both groups. Elevated cortisol level in CSCR patients strengthens the belief of its potential role in pathogenesis of disease. Also, regular posterior chamber examination can reduce the ocular morbidity in patients with exo- or endogenous hypercortisolism. It is suggested that monitoring of cortisol levels could be beneficial in deciding the outcome of CSCR.

INTRODUCTION

Central serous chorioretinopathy (CSCR), first described by Von Graefe in 1866,[1] is a disorder primarily of the choroid, or the retinal pigment epithelium (RPE), or both.[2] Choroidal hyperpermeability, in the areas of the damaged RPE cells, leads to serous pigment epithelial detachment (PED). PED may also occur in many choroidal disorders that disrupt the normal junction between the basement membrane of the RPE and the inner collagenous layer of Bruch's membrane. It leads to accumulation of serous fluid in the sub-RPE space, from the underlying choriocapillaries, causing foveal attenuation, chronic macular degeneration and damage to the photoreceptor layer leading to visual loss.[3]

The typical clinical picture is that of a male aged between 20-50 years, presenting with an acute onset of blurring of vision or painless loss of vision mostly unilateral associated with metamorphopsia, micropsia and a central scotoma.[4] The incidence is approximately six times higher in males than in women.[5] Over the years, several factors have been identified that potentiate the risk of developing CSCR, however many are very poorly understood. Infections, toxins, hormonal regulatory factors, circulatory, neuronal and immunological reactions have all been implicated in the initiation of the damaging process that leads to CSCR.[2] It has also been linked with several other risk factors including type A personality, untreated hypertension, alcohol consumption, excess use of antibiotics, organ or bone marrow transplantation, respiratory tract infection or gut infection (Helicobacter pylori) or any stressful condition, surgery and pregnancy, particularly during the third trimester[6–8] most of which are also associated with raised cortisol.

Steroid hormones play a crucial role in maintaining normal biological functions of the body and any perturbations in this complex interplay can result in disease manifestation. Cortisol and testosterone are such steroid hormones, excess levels of which have been postulated in the pathogenesis of CSCR, a clinical condition which ophthalmologists are frequently

confronted with.[4] Cortisol may directly be responsible for causing damage to RPE cells or inhibit any reparative activity in the RPE after damage by another etiological agent, by suppressing the synthesis of extracellular matrix components and inhibiting fibroblastic activity.[9] Cortisol may also potentiate capillary fragility and hyperpermeability, thereby affecting the circulation in the choroid, leading to leakage of fluid in the subretinal space.[9] In a recent study, inappropriate expression of ion channels in retina, influenced by cortisol, have also been hypothesized in the initiation of CSCR.[10] Various studies have not been able to conclusively prove[4,11,12] or disprove[9,13] the role of glucocorticoids in the development of CSCR.

Testosterone also may have a role in the development of the disease, as CSCR is mainly a male predominant disease. Some previous studies have tried to constitute a link between testosterone and CSCR, but with only ambiguous results.[9,14–17] The incidence of CSCR decreases as the age advances which correlates with the gradual decline in the total plasma testosterone levels with advancing age in older men,[18] which further strengthens the possibility of testosterone's involvement in the development of the disease.

With this background of conflicting reports of serum cortisol and testosterone levels in CSCR, this study was designed to gain further insight into possible role of these hormones in the etiopathogenesis of CSCR.

MATERIAL AND METHODS

This hospital based, case-control study was conducted in the Department of Biochemistry in collaboration with Regional institute of Ophthalmology, Pt B D Sharma PGIMS, Rohtak after getting ethical clearance from the institute. 25 patients aged between 20–50 years presenting with first attack of CSCR in ophthalmology OPD, clinically diagnosed by slit lamp biomicroscopy and confirmed by fundus fluorescein angiography were included in the study, as cases. Patients with any other ocular or systemic disease, any surgery or trauma prior to two weeks of presentation, receiving any form of local or systemic steroids, body mass index of more than 30, alcohol abuse or dependence and major depression (DSM-IV-TR criteria) were excluded from the study, since all these conditions can independently alter the endogenous cortisol levels.[19] 25 age and sex matched patients with an acute unilateral rhegmatogenous retinal detachment (RD) were taken as controls. The rationale for having retinal detachment patients as controls was to have a comparison group with a similar history of sudden visual loss having no endocrinal role in its pathogenesis. Elevation in cortisol level

is noted in stressful events like vision loss. The involvement of patients with retinal detachment as controls obviated the possibility of bias on this account.

Data was collected using a piloted proforma meeting the objectives of the study after an informed written consent. A systemic evaluation, comprising a complete medical history, general physical examination with height and weight measurement, measurement of routine biochemistry, serum cortisol, erythrocyte sedimentation rate and ocular examination including visual acuity, refractive status, slit-lamp biomicroscopy, indirect ophthalmoscopy, optical coherence tomography and fundus fluorescein angiography was done in cases and controls. The best-corrected visual acuity was converted to log MAR (logarithm of the minimum angle of resolution) values to allow statistical evaluation.

The patients were admitted in the Ophthalmology ward, in order to acclimatize the patients to the hospital environment. On the day of admission, 2 mL of venous blood sample was collected from the ante-cubital vein under all aseptic conditions, at 11:00 PM in a red-capped evacuated blood collection tube. After clotting, the sample was centrifuged at 2000 RPM for 10 min in emergency biochemistry laboratory. Serum was separated and stored in serum collecting tubes at 2-8ºC for subsequent cortisol estimation. Next morning, at 8:00 AM, fasting blood sample was collected from the same patient under all aseptic conditions; 2 mL in red capped, 2 mL in grey capped (containing sodium fluoride, for blood glucose estimation) and 2 mL in purple capped (containing ethylene diamine tetra acetic acid) evacuated blood collection tubes. The serum of morning sample was separated from the red-capped blood collection tube and was analyzed for the routine investigations. The serum sample for special investigations viz. cortisol and testosterone was stored at 2-8ºC in serum collecting tubes. The serum samples were shifted to -20ºC if they were not be analyzed within 7 days. Sample in purple-capped blood collection tube was estimated for ESR. Before analyzing frozen samples, proper thawing was done at room temperature. Evening and morning samples for cortisol were collected due to its diurnal variation.[20] Estimation of serum cortisol was done by solid-phase, competitive chemiluminescent enzyme immunoassay (IMMULITE® 1000 Immunoassay system) using kits manufactured by SIEMENS (USA).[21] Serum testosterone level was estimated on chemiluminescent immunoassay system (ADVIA Centaur CP) using kits manufactured by SIEMENS (USA).[22]

Data was compiled and analyzed by IBM SPSS Statistics ver. 20 using appropriate statistical methods. For comparison of mean, independent student t-test was used to determine the

significance between CSCR patients and controls. For assessment of correlation between variables, Pearson's correlation was used. P value < 0.05 was considered statistically significant. Charts and graphs were prepared using IBM SPSS Statistics ver. 20 and Microsoft Office 2007.

RESULTS

The study group comprised of 25 cases with CSCR, the predominant percentage being constituted by males (92%). There was no significant difference in the age (p = 0.682) in the two groups. Mean age of the CSCR patients and RD controls was 43.7 ± 6.53 years (range 23–50 years) and 43.04 ± 5.03 years (range 35-50 years) respectively (Table 1). Maximum, 56% (14) of the CSCR patients were in 45-50 years of age group while only 4% (1) were less than 25 years of age. While in controls 44% (11) subjects belonged to the age group of 45-50 years. Three out of four females in study group aged 50 years and above. The mean duration of symptoms before inclusion in the study was 10.4 ± 2.87 days in the CSCR patients and 9.56 ± 2.81 days in the controls but there was no significant difference (p = 0.302). In 14 cases, the right eye was involved, while 11 had CSCR in the left eye. In the control group, the right eye was involved in 18 patients, while the left was affected in 7 patients. The mean value of visual acuity Log MAR (Table 1) in the CSCR patient group was 0.384 ± 0.16, while in the control group was 0.500 ± 0.16, the difference was statistically significant (p = 0.015) showing worse visual acuity in the control group.

The 8:00 AM mean serum cortisol value in the patients (20.21 ± 4.86 µg/dL) was significantly (p = 0.046) higher than controls (17.74 ± 3.53 µg/dL). Figure 1 shows the 8:00 AM serum cortisol levels in cases and controls where five out of 25 cases (20%) had high cortisol value, while eight (32%) cases had high borderline level (Reference range 5 – 25 µg/dL), while there was no significant difference (p = 0.187) in 11:00 PM mean serum cortisol values of cases (8.13 ± 3.52 µg/dl) and controls (6.97 ± 2.50 µg/dL). There was no significant correlation between morning 8:00 AM serum cortisol levels and duration of symptoms (r = -0.040, p = 0.851).

The mean (±SD) level of testosterone in males was higher in cases as compared to controls, being 635.66 ± 237.56 ng/dL and 501.06 ± 246.42 ng/dL, respectively but the difference was not statistically significant (p = 0.06). Due to gender specific reference intervals and low number of female subjects (n=2) in both the groups, statistical comparison could not be performed for testosterone levels in females. So, mean level of testosterone was compared

only in males (n=23) in both the groups. Serum testosterone level exceeded the male gender specific reference interval (241-827 ng/dL) in 21.74% (5) and 8.7% (2) males in the cases and controls (males, n=23), respectively. Higher female gender specific serum testosterone level was seen in 1 (50%) of the 2 female CSCR patients (Reference interval, 14-76 mg/dL,). Both females in the control group had higher serum testosterone level. In control group 17.4% (4 out of 23) males had lower levels than gender specific reference interval (Figure 3).

Altered cortisol and testosterone levels were observed in nine cases, whose levels were higher than the reference interval. Five cases had 8:00 AM cortisol levels above the reference interval while six had serum testosterone levels higher than gender specific reference interval. Out of them, two cases had both 8:00 AM cortisol and testosterone levels higher than reference interval. While correlating serum cortisol 8:00 AM levels and VA LogMAR in the cases, a significant positive correlation was observed between the two parameters ($r = 0.477$, $p = 0.016$) (Figure 4).

DISCUSSION

There are several factors that pose a risk for initiation of CSCR. Elevated levels of the catecholamines, adrenaline and noradrenaline have been found in patients with CSCR, and strong correlation has been found between plasma concentrations of adrenaline and central macular thickness thereby laying impetus on the endocrinal contribution towards the etiopathogenesis of the disease.[7] There is extensive literature suggesting that exposure to exogenous corticosteroid administration, including oral, topical, intravenous, intranasal, intraarticular and intravitreal, is associated with increased risk of CSCR.[3,4,23–25] Studies have also linked Cushing's syndrome from endogenous causes, such as pituitary adenoma, adrenocortical adenoma and carcinoma with CSCR.[7,26,27]

Our finding of increased cortisol in CSCR is consistent with the finding of studies done by Garg et al,[4] Verma et al,[12] Zakir et al,[9] and Haimovici et al,[16] though increased 11:00 PM serum cortisol values in cases were not significant as compared to control group. This could be due to disruption of the hypothalamic pituitary- adrenal (HPA) axis, affecting the circadian rhythm of cortisol in the cases. Changes in normal functioning of HPA axis have been associated with the development of CSCR.[16]

In contrast, Dwivedi et al in their study on 47 subjects, showed no significant difference in endogenous serum cortisol profile of CSCR patients and controls.[28] Even, Tufan et al

suggested a weak association between cortisol and CSCR but this could be attributed to fairly low (six) number of subjects studied by them.[17]

The visual acuity was significantly worse in the control group and was supposedly associated with more stress in the subjects which in turn should have led to increased blood cortisol but the presence of significantly high cortisol level in the CSCR patients, all the more strengthens the belief of glucocorticoids precipitating CSCR which could be either by their effect on the RPE or the choroidal vasculature. Also, increased cortisol acting via mineralocorticoid receptor (MR) may cause inappropriate expression of various channels viz. calcium-dependent potassium channels (KCa2.3), potassium channels (Kir4.1) and aquaporin channels (AQP4) in the endothelium of choroidal vessels affecting the osmotic homeostasis,[5] in turn contributing to development of the disease.

An interesting finding of this study was that two patients who had high 8:00 AM cortisol levels also had testosterone level higher than the reference interval. Few authors suggest that increased cortisol is linked to low testosterone.[29] As stated by Dr Daniel Shokes "Association does not equal causality". Evidence suggests that some critical level of cortisol must be reached in order to substantially influence testosterone level perhaps by enzymatic inhibition of the testicular steroidogenic process in the Leydig's cell.[29] In the present study, majority (around 70%) of the patients showed testosterone within the reference interval and while correlating serum cortisol (8:00 AM and 11:00 PM) levels with serum testosterone levels in the cases, no statistical significance was found. Two of the three females showing high testosterone level were in the menopausal age group. Reproductive hormones seem to play a protective role in pre-menopausal females.

Haimovici et al estimated serum testosterone levels in the patients of CSCR. They found normal levels in 96% of their patients.[16] Zakir et al were the first to compare the levels of serum testosterone in CSCR patients with age and sex matched controls of unilateral sudden painless loss of vision. They observed mean serum level to be within the reference interval in both the cases and controls. They also found that about 32% patients of CSCR and 18% controls had lower level than the reference interval.[9] In the present study, 4% (1) of CSCR cases and 16% (4) of controls had testosterone levels lower than the reference interval. Levels of majority of our patients were within the normal range. Tufan et al analyzed serum testosterone of six CSCR patients on chemiluminescent immunoassay system and compared the results with healthy controls. They found the normal levels in their study. They stressed

on a possibility that, while the reference interval may be appropriate for most people, patients with CSCR may have an impaired response to normal levels of serum cortisol and testosterone due to faulty choroidal/RPE response.[17] These findings are in conformation with the results of the present study. On the contrary, number of case reports of CSCR after systemic testosterone therapy shows indirect evidence of the role of testosterone in CSCR.[14,15] Indirectly these case reports are emphasizing on the association between testosterone and CSCR. Except these case reports there is no conclusive study that clearly shows role of testosterone in CSCR.

Table 1: Comparison of results in CSCR patients and RD control group

Parameters	**CSCR patients (n=25) Mean ± SD**	**RD patients (n=25) Mean ± SD**	**Significance (p value)**
Age (years)	43.7 ± 6.53	43.04 ± 5.03	p = 0.682
Weight (Kg)	65.64 ± 5.43	66.64 ± 5.70	P = 0.529
Height (cm)	168.92 ± 6.31	170.68 ± 5.99	P = 0.317
Body mass index (Kg/m^2)	23.04 ± 2.04	22.86 ± 1.50	P = 0.734
Duration of symptoms (days)	10.40 ± 2.87	9.56 ± 2.81	P = 0.302
VA Log MAR	**0.384 ± 0.159**	**0.500 ± 0.163**	**p = 0.015***
Serum Cortisol level (8:00 AM) (µg/dl)	**20.21 ± 4.87**	**17.74 ± 3.53**	**p = 0.046***
Serum Cortisol level (11:00 PM) (µg/dl)	8.13 ± 3.52	6.97 ± 2.50	p = 0.187
Serum Testosterone level (Males) (ng/dL)	635.66 ± 237.56	501.06 ± 246.42	p = 0.06

(*p<0.05 is statistically significant; VA: visual acuity; Log MAR: logarithm of the minimum angle of resolution).

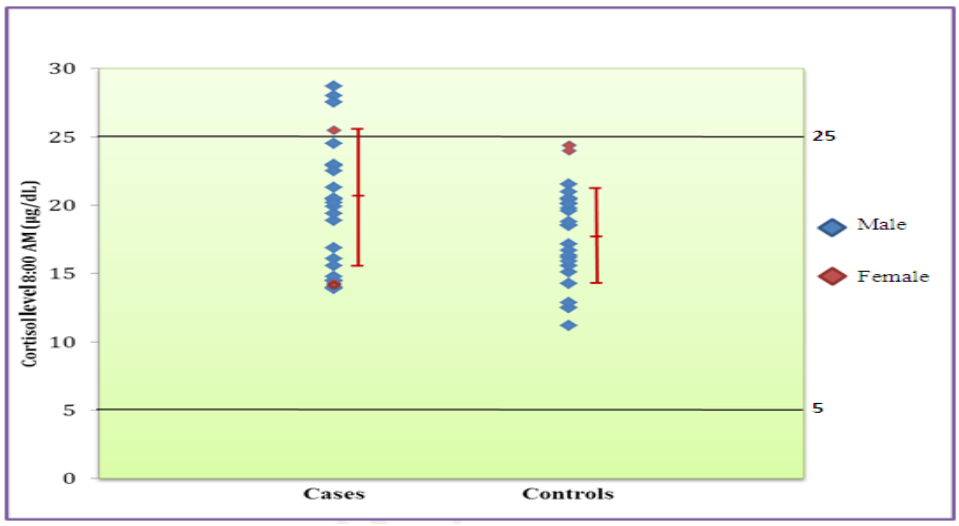

Figure 1: Stacked scatter plot of the 8:00 AM serum cortisol values in the cases and controls; Reference interval (5-25 µg/dL, depicted by horizontal lines)

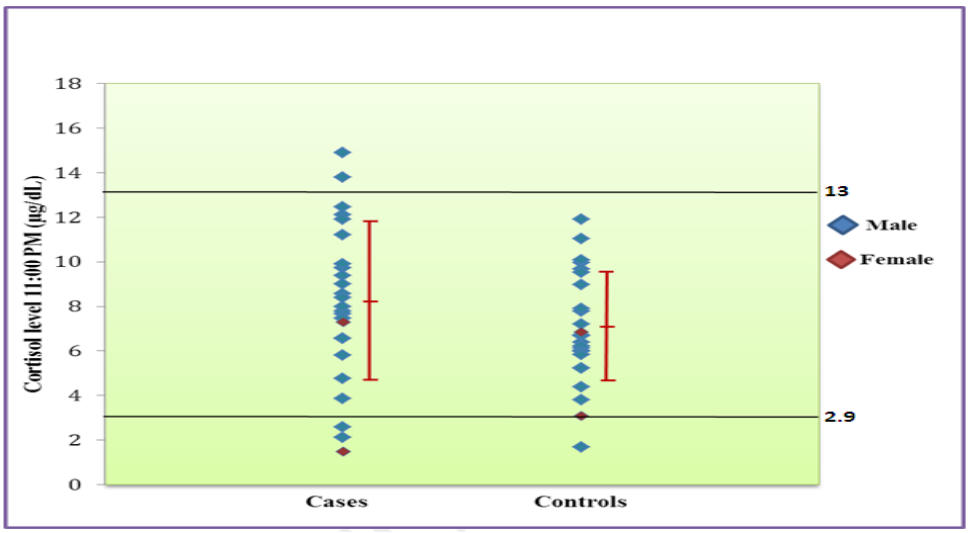

Figure 2: Stacked scatter plot of the 11:00 PM serum cortisol values in the cases and controls; Reference interval (2.9-13 µg/dL, depicted by horizontal lines)

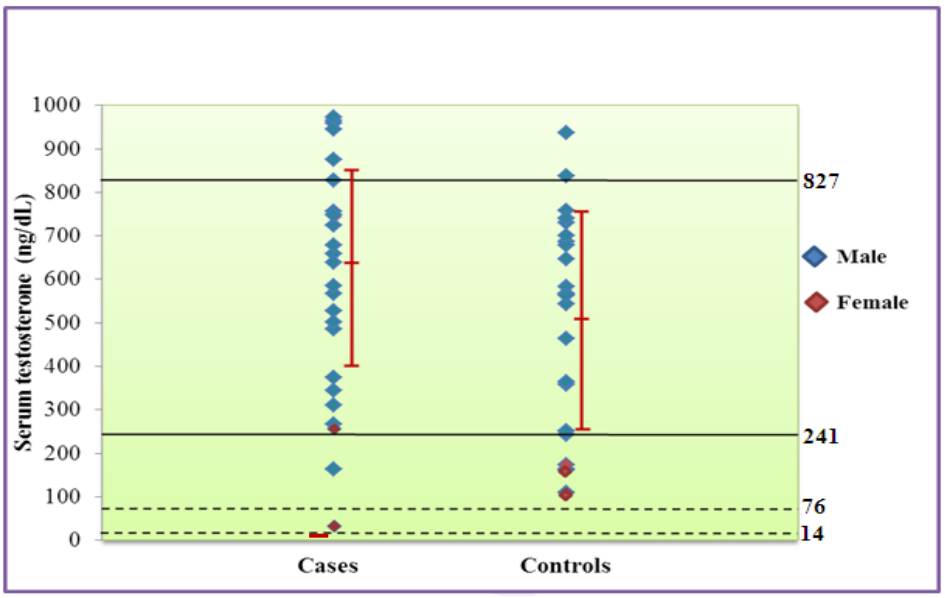

Figure 3: Stacked scatter plot of the levels of serum testosterone in the cases and controls; male gender specific reference interval (241-827 ng/dL, depicted by continuous horizontal lines) female gender reference interval, 14-76 mg/dL, depicted by broken horizontal lines

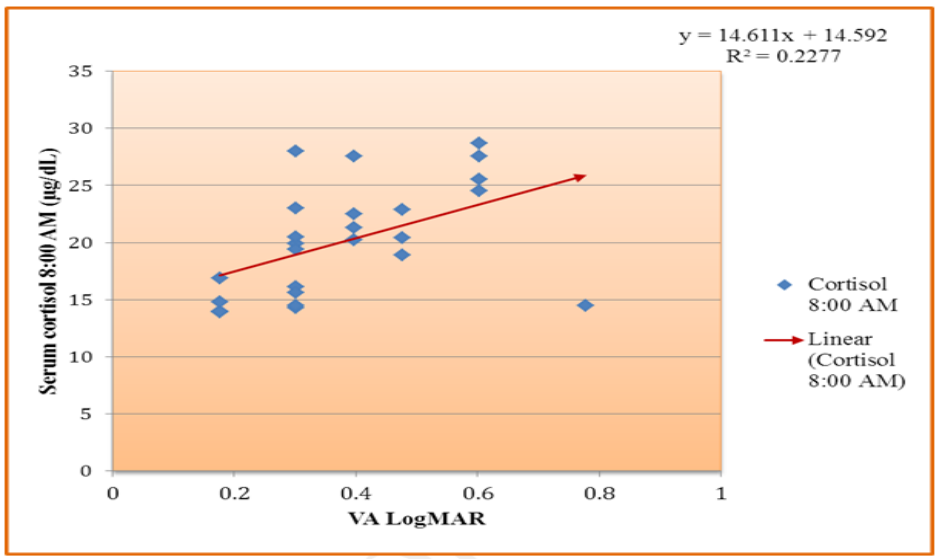

Figure 4: Correlation between serum cortisol 8:00 AM levels and VA LogMAR in the cases.

CONCLUSION

It can be concluded that serum cortisol and testosterone has some role in the development of CSCR. Other metabolic factors might also be playing a role in patients with raised corticosteroids who go on to develop CSCR. The evidence to this suspicion needs to be deciphered as well. A possibility exists that increased concentration of cortisol could cause dissociation of testosterone from its carrier proteins as the two hormones compete for the binding sites on steroid hormone binding globulin, thereby increasing the free testosterone level; estimation of which could have thrown better light on the role of the latter in CSCR.[30] In addition to the diurnal rhythm cortisol also exhibits ultradian rhythm (episodic nature of cortisol secretion) providing physiological sources of biologic variability.[16] Along with serum cortisol level we should also have measured the 24 hr urine cortisol levels to get a complete estimate of average integrated cortisol concentration during a 24 hr period. These situations bring out the limitations of our study. Further larger prospective studies are needed to understand the course and severity of the disease based on the endocrinal profile of the patients that could be of clinical importance. It would be useful to know how the human endocrinal system behaves and evolves over time in these patients.

There are various treatment modalities for CSCR available in armamentarium of an ophthalmologist. These include laser photocoagulation, photodynamic therapy, anti glucocorticoid drugs and anti-androgen therapy. The results of this study will be useful for the physician in deciding the appropriate therapy for their patients. Patients with high levels

of circulating androgenic or glucocorticoid hormones may not benefit from laser or spontaneous recovery. Similarly, institution of anti-glucocorticoid or anti-androgenic therapy may not be useful in patients with normal endocrine profile and may rather expose the patient to the unwanted deleterious side effects of these drugs. The results of this study may be used by ophthalmologists in developing targeted and individualized treatment protocols for CSCR patients instead of standard management regimen, which is widely used. The temporal evaluation of change in amount of subretinal fluid and circulating hormone levels with and without treatment still remains to be done and will further improve the understanding about this disease.

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