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Dr. Arman Dawar
JR2, Department of Ophthalmology, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

Dr. Farhat Abrar
Associate Professor, Department of Ophthalmology, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

Dr. Charu Jain
Professor, Department of Ophthalmology, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

Corresponding Author:
Dr. Farhat Abrar
Associate Professor, Department of Ophthalmology, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India
dr.farhat.abrar@gmail.com

Serum cortisol and serum testosterone levels in idiopathic central serous chorioretinopathy

Dr. Arman Dawar, Dr. Farhat Abrar and Dr. Charu Jain

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Abstract
Aim: To analyse the serum cortisol and serum testosterone levels in idiopathic central serous chorioretinopathy.
Material and methods: The prospective interventional study was conducted in the central laboratory associated with the Department of Ophthalmology, Subharti Medical College, Meerut. A study was conducted in 30 cases of CSR. The patients were divided into two groups i.e. Group A (15 patients with unilateral sudden painless loss of vision of less than one month of duration serving as cases and Group B (15 patients with no signs and symptoms serving as control). Evaluation of Macular thickness was done using OPTOVUE RTvue 100 OCT procedure. After pupil dilation, the patient is seated at the machine, asked to fixate at the internal fixation point and scan is obtained. The macular thickness map was taken to measure the thickness of macula. Fundus Fluorescein Angiography (FFA) was done, if required. Patients of both the groups underwent investigations such as dilated fundus examination, serum cortisol and serum testosterone levels.
Results: Mean serum cortisol (µg/dL) among the case group was higher as compared to the control group with statistically significant difference as $p<0.05$. Mean serum cortisol levels compared between ink-blot pattern and smoke-stack patterns on FFA had no statistical significance. Mean serum testosterone (ngm/mL) among the case group (3.78±1.58) was lesser as compared to the control group (4.34±1.72) with statistically significant difference.
Conclusion: ICSC is highly significant and significant associated with elevated 8.00 a.m. serum cortisol and testosterone level respectively.

Keywords: ICSC, serum cortisol, serum testosterone

Introduction

Idiopathic central serous chorioretinopathy (ICSC) is characterized by accumulation of transparent fluid below the neurosensory retina causing a circumscribed macular detachment. In 94% of cases, the fluid accumulates under the neurosensory retina (Type I), in 3%, the RPE alone is detached (Type II) and in the rest both neurosensory retina and RPE are elevated (intermediate type) [1]. The overall incidence is 5.8 cases per 100,000 population. It is six times more likely to occur in males than females. Often, it affects competitive and compulsive workaholic young adults of 30–40 years [2].

Presenting symptoms are minor blurring of vision, central scotoma, metamorphopsia or micropsia, increasing hypermetropia, and dyschromatopsia. There may also be a loss of contrast sensitivity [3, 4].

The etiology of ICSC still remains unclear and numerous hypotheses have been put forward. The choriocapillaries and RPE are basically involved and various anatomical and functional changes affecting these important structures have been demonstrated. ICSC has been associated with Type A personality, elevated endogenous cortisol[5] and corticosteroid therapy in various forms [6]. This condition predominantly affects young males and its incidence declines with advancing age. As plasma testosterone levels also decline with age, it is possible that testosterone may have an important role in predisposing males to ICSC [7].

As evidenced by previous reports or studies, a relationship appears to exist between glucocorticoids and CSC [5, 8-12]. Garg *et al.* [5] found significantly higher serum cortisol levels in acute CSC cases as compared to age-matched controls. Pastor-Idoate *et al.* [8] reported high levels of serum cortisol in a case of adrenocortical adenoma. Zakir *et al.* [9] also identified elevated levels of serum cortisol but normal levels of testosterone in acute CSC cases. In contrast, Thoelen *et al.* [10] speculated that in the pathogenesis of CSC, the deregulations of sympathetic activity play a major role and elevated glucocorticosteroid levels are involved only indirectly. Chalisgaonkar *et al.* [11] found no precise correlation

between serum cortisol levels and acute cases of CSC. Similarly, Tufan *et al.* [12] reported normal levels of serum cortisol and testosterone in chronic CSC. Therefore, the association between acute or chronic CSC and serum levels of cortisol appears to be inconsistent.
Due to conflicting literature and scarce studies in the western UP, this study was planned to analyse the serum cortisol and serum testosterone levels in idiopathic central serous chorioretinopathy.

Material and Method

Study Design: Prospective interventional study

Study Setting: It was conducted in the central laboratory associated with the Department of Ophthalmology, Subharti Medical College, Meerut.

Study Period: Study was conducted for a period of one year after approval from CPC and Ethics Committee.

Study Population: All patients with Central Serous Retinopathy in the Department of Ophthalmology in Subharti Medical College.

Sample Size: A study was conducted in 30 cases of CSR. The patients were divided into two groups.
An informed consent was obtained for giving blood samples for the study. The patient was prepared by explaining the patient about the procedure of the collection of the blood sample.
Patients with central serous chorioretinopathy, not on corticosteroids/sex steroids in any form (topical eye drops, skin creams, intranasal/ inhalational sprays; systemic steroids like oral, intravenous/ intramuscular) in the last one month, with no other ocular or systemic disease, who are non-alcoholic and having no history of major depression were included in the study. Patients who had taken corticosteroids/sex steroids in any form (topical eye drops, skin creams, intranasal/ inhalational sprays; systemic steroids like oral, intravenous/ intramuscular) in the last one month, any other ocular or systemic disease, any surgery or trauma within one month of presentation were excluded from our study.

Randomization and blinding of study groups: The total consented patients were divided into 2 equal groups according to computer generated random number tables i.e.
Group A consisted of minimum of 15 patients with unilateral sudden painless loss of vision of less than one month of duration serving as cases.
Group B consisted of minimum of 15 patients with no signs and symptoms serving as control.

Serum Cortisol and testosterone: Serum cortisol and testosterone levels at 9:00 am was estimated by radioimmunoassay in both groups.

Study Methodology: Patients presenting in OPD with complaint of diminution of vision was asked a detailed ocular and systemic history. Data like age, name, sex, visual disturbance, its onset, duration and progression, drug intake (especially use of corticosteroids/sex steroid hormones in any form) was elicited. Patients underwent an initial work-up *viz*. BCVA, Slit lamp examination, IOP measurement and Un-dilated fundus examination. Dilated fundus examination with 78 D was done. Evaluation of Macular thickness was done using OPTOVUE RTvue 100 OCT procedure. After pupil dilation, the patient is seated at the machine, asked to fixate at the internal fixation point and scan is obtained. The macular thickness map was taken to measure the thickness of macula. Fundus Fluorescein Angiography (FFA) was done, if required. Patients with Central Serous Retinopathy and fulfilling inclusion and exclusion criteria were included in the study and Control group containing no retinal pathology. Patients of both the groups underwent investigations such as dilated fundus examination, serum cortisol and serum testosterone levels.

Evaluation: After the initial approach and group assignment, the objective assessment of macular thickness in diabetic patients preoperatively and postoperatively was compared.
Data was collected and subjected to statistical analysis.

Statistical analysis

Data was analysed using SPSS version 24. Statistical difference between the groups was determined using chi square and t test. The level of significance was set as $p<0.05$.

Results

Male were comparatively more as compared to females among both the study groups with statistically insignificant difference as $p>0.05$. The mean age among group A and B was 37.92±8.71 and 36.02±9.30 years respectively. In group A, the subjects were suffering from visual disturbance since 3.69±1.84 weeks. 7 cases (46.67%) had a best corrected visual acuity of 6/18-6/36; 6 cases (40%) had a BCVA of 6/6-6/12, while 2 cases (13.33%) had BCVA of ≤6/60. Maximum controls (66.67%) had a BCVA of 6/18-6/36, followed by 4 patients with 6/6-6/12 (26.67%) and 1 case had a BCVA of less than 6/60 (6.67%) as shown in table 1.

Table 1: BCVA among the study groups

BCVA	Group A (Case)		Group B (Control)		p value
	N	%	N	%	
6/18-6/36	7	46.67	10	66.67	0.47
6/6-6/12	6	40	4	26.67	
≤6/60	2	13.33	1	6.67	

In this study single and multiple leak was reported among 73.33% and 26.67% of the subjects in group A respectively. Ink-blot and smoke-stack pattern was found among 80% and 20% of the subjects in group A respectively (table 2).

Table 2: Type and pattern of leak on FFA among the case group

Type of Leak	Group A (Case)	
	N	%
Single Leak	11	73.33
Multiple Leak	4	26.67
Pattern of Leak		
Ink-blot Pattern	12	80
Smoke-stack Pattern	3	20

Mean OCT among group A and B was 446.89±111.72 and 277.58±58.42 µm respectively with statistically significant difference as $p<0.05$ (table 3).

Table 3: OCT among the study groups

Groups	OCT (µm)	
	Mean	SD
Group A	446.89	111.72
Group B	277.58	58.42
t test	6.68	
p value	0.032*	

*statistically significant

Mean serum cortisol (µg/dL) among the case group was higher as compared to the control group with statistically significant difference as $p<0.05$ (table 4). Mean serum cortisol levels compared between ink-blot pattern and smoke-stack patterns on FFA had no statistical significance.

Table 4: Comparison of Serum Cortisol (µg/dL) among the study groups

Group	Serum Cortisol (µg/dL)	
	Mean	SD
Group A	21.19	2.89
Group B	18.97	2.55
t test	6.13	
p value	0.009*	

*statistically significant

Mean serum testosterone (ngm/mL) among the case group (3.78±1.58) was lesser as compared to the control group (4.34±1.72) with statistically significant difference as $p<0.05$ (table 5).

Table 5: Comparison of mean serum testosterone (ngm/mL) level among the case and study group

Group	Serum Testosterone (ngm/mL)	
	Mean	SD
Group A	3.78	1.58
Group B	4.34	1.72
t test	3.02	
p value	0.044*	

*statistically significant

Discussion

Maculopathy resembling ICSC has been reported in a patient receiving glucocorticoids for reactive arthritis. There are reports of initiation and worsening of ICSC in patients under systemic steroid treatment for other reasons. In many cases there was a close temporal relationship between use of corticosteroids and development of ICSC; exacerbations or remissions of the symptomatology correlated with the glucocorticoid levels as well [9].

Glucocorticoids promote blood coagulation causing choroidal hypoperfusion, affect the production of prostaglandins and, therefore, may affect the regulation of choroidal blood flow. Glucocorticoids inhibit collagen formation (a main component of Bruch's membrane), alter ion and water transport of epithelia primarily through the mineralocorticoid receptors. Cortisol may also directly damage the RPE cells or their tight junctions and may delay any reparative process in damaged RPE cells by suppressing the synthesis of extracellular matrix components and inhibiting fibroblastic activity [9]. In addition to glucocorticoids, androgens (testosterone) have been implicated in the pathophysiology of CSC. The incidence of CSC is much higher in males, and declines with advancing age. Plasma testosterone levels also decline with age, and present higher values in patients with type-A personality.

The present study was conducted in 30 cases of CSR. The patients were divided into two groups i.e. group A (15 patients with unilateral sudden painless loss of vision of less than one month of duration serving as cases) and group B (15 patients with no signs and symptoms serving as control). Male were comparatively more as compared to females among both the study groups with statistically insignificant difference as $p>0.05$. The mean age among group A and B was 37.92±8.71 and 36.02±9.30 years respectively in our study. ICSC frequently occurs in highly ambitious people who are stressed and overworked. Yannuzzi [13] has given a detailed description of the association of ICSC with male sex, middle age and stress, the features of which are competitive drive, a sense of urgency, an aggressive nature, a hostile temperament, intense and sustained drive to achieve, state of restlessness, perception of all responsibilities with an element of challenge, extraordinary mental and physical alertness, desire for recognition and advancement, frequent involvement with deadlines and multiple simultaneous tasks. Ruma Das *et al.* [14], Shaik M Zakir *et al.* [9] in their study reported similar male dominancy. Various studies show a higher prevalence in men ranging from 72% to 88% with a peak around 45 years in men and higher in women though no age is immune [9].

In the present study, 7 cases (46.67%) had a best corrected visual acuity of 6/18-6/36; 6 cases (40%) had a BCVA of 6/6-6/12, while 2 cases (13.33%) had BCVA of ≤6/60. Maximum controls (66.67%) had a BCVA of 6/18-6/36, followed by 4 patients with 6/6-6/12 (26.67%) and 1 case had a BCVA of less than 6/60 (6.67%). Ruma Das *et al.* [14] in their study reported that 24 cases (48%) had a best corrected visual acuity of 6/18-6/36; 22 cases (44%) had a BCVA of 6/6 - 6/12, while 4 cases (8%) had BCVA of ≤6/60. Maximum controls (30) had a BCVA of 6/18 - 6/36 (58%), followed by 11 patients with 6/6 - 6/12 (22%); 10 cases had a BCVA of less than 6/60 (20%). These findings are similar to our study.

Mean serum cortisol (µg/dL) among the case group was higher as compared to the control group with statistically significant difference as $p<0.05$. This throws some light on the possible effects of cortisol (on Bruch's membrane and choriocapillaries) and development of ICSC in young men. This is an interesting observation and we thought that there might be some correlation between duration of ICSC and levels of serum cortisol. Mean serum cortisol levels compared between ink-blot pattern and smoke-stack patterns on FFA had no statistical significance (p=0.11) in the present study. There are isolated reports of association of ICSC with raised serum cortisol levels. These observations assume significance and point towards a relationship between endogenous levels of cortisol and development of ICSC. In a study by Shaik M Zakir *et al.* [9], statistically significant higher mean serum cortisol levels were seen in ICSC cases than controls. Garg *et al.* [5] examined a group of 30 patients with acute CSC and age-matched controls. Mean plasma and urine cortisol levels were found to be significantly higher in patients with acute CSC compared to the controls. Kapetanios *et al.* [15] evaluated the secretion of endogenous cortisol in 16 patients affected by acute CSC, and compared it with an age- and sex-matched control group. They also reported a significant difference. Similarly Ruma Das *et al.* [14] found that when the cases and controls were compared for mean serum cortisol levels (diurnal samples), statistical significance was obtained with higher values in cases both for the morning

(p=0.001) and evening levels. Mean serum cortisol levels compared between ink-blot pattern and smoke-stack patterns on FFA had no statistical significance in either sample.

Androgens or testosterone have never been directly implicated as a factor in the pathogenesis of ICSC. The higher incidence of ICSC in young males and a gradual decline as the age advances correlates with the levels of plasma testosterone which also decline with age in older men. The female sex hormones estrogen and progesterone may possibly have a beneficial role in females. Testosterone is known to promote atherosclerosis and retain sodium. It has been shown to affect the vascular tone. Human RPE cells are found to have androgen receptors. There is therefore a possibility that testosterone is somehow related to the etiology of ICSC [16, 17]. In this study, mean serum testosterone (ngm/mL) among the case group (3.78±1.58) was lesser as compared to the control group (4.34±1.72) with statistically significant difference as $p<0.05$. There are two case reports of patients developing ICSC while on exogenous testosterone therapy. Shaik M Zakir *et al.* [9] in their study revealed that about 32% patients of ICSC and 18% controls had lower than normal levels of testosterone. Hasan Ali Tufan *et al.* [12] in their study found that serum testosterone levels were within the normal range in patients with chronic CSC.

Limitation of the present study is its small sample size in the present study, due to which we can't draw any conclusions 100% regarding the role of testosterone in the pathogenesis of ICSC. Further large-scale studies investigating the probable role of testosterone levels in ICSC need to be carried out.

Conclusion

To conclude, it may be logical to believe that ICSC remains a challenge to the ophthalmologist as the exact etiopathogenesis remains poorly understood in spite of tremendous clinical and experimental research. ICSC is highly significant and significant associated with elevated 8.00 a.m. serum cortisol and testosterone level respectively. Still studies with greater number of patients are required to fully determine the role of endogenous cortisol and testosterone in ICSC.

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