 DOI: 10.18231/2395-1451.2017.0040

Endogenous cortisol profile in patients with central serous chorioretinopathy (CSC)

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Abstract

Context: Endogenous cortisol profile in patients with central serous chorioretinopathy (CSC) is controversial. Hence this control study was conducted to evaluate endogenous cortisol levels in CSC patients.

Aim: To evaluate endogenous cortisol levels in patients with CSC and to correlate it in different stages of the disease.

Settings and Design: Prospective, interventional case control study.

Materials and Methods: 40 cases of CSC were included in the study and 30 cases with acute, unilateral, sudden, painless loss of vision of recent onset were taken as controls. Serum cortisol estimation was done between 8am to 9am by chemiluminiscence method. Resolution of CSC was assessed based on clinical findings, Fundus fluorescence angiography (FFA), indocyanine green angiography (ICG) and optical coherence tomography (OCT).

Statistical analysis: 'Z' test was used to test the significance of the means of serum cortisol level between the control group and the CSC group on the first visit and Paired 't' test was used to test the significance for the difference of means of serum cortisol level on the 1st, 2nd and 3rd visits of the CSC group only. Regression analysis was done to test the population correlation coefficient of cortisol in the CSC group.

Results: Mean age of the cases was 35.9 + 3.77 years and all were male. Mean 8 am serum cortisol level was 12.33 + 3.87 µg/dl in cases during the first visit and 13.33 + 4.28 µg/dl in the control group. It was within normal biological range in both the groups. Difference between mean serum cortisol in each group was statistically insignificant (P = 0.83). Difference of mean of serum cortisol levels estimated during 3rd and 6th months' follow-up in cases was also not statistically significant. But population correlation coefficient detected a strong positive correlation (+0.655) between serum cortisol levels and CSC cases at each examination visits during the 3rd and 6th months' follow-up. Healing of CSC was independent of cortisol levels.

Conclusions: CSC was found to be associated with normal endogenous cortisol level. Serum Cortisol level at 8am was within the normal limit, both in the test and control groups. But a strong positive (+0.655) correlation between serum cortisol levels and CSC at each follow-up visits during the time the disease was active indicates the relationship between serum cortisol and CSC aetiopathogenesis at the biological level.

Keywords: Central serous chorioretinopathy, Endogenous serum cortisol.

Introduction

Central Serous Chorioretinopathy (CSC) is characterized by circumscribed serous detachment of neurosensory retina in the macula. It is idiopathic and is often accompanied by retinal pigment epithelial detachment (RPED), dysfunction, atrophy or choroidal circulatory disturbance. These can be demonstrated by Fundus Fluorescein Angiography (FFA) and Indocyanine Green Angiography (ICG).[1,2]

Endogenous and exogenous corticosteroids and several other risk factors have been implicated in CSC.[3,4] Development of CSC following use of exogenous corticosteroid, associated hypercortisolism and improvement of CSC following induction of cytochrome P450, 3A4 by oral rifampicin suggests cortisol might have a significant role in choroidal circulation, blood retinal barrier and CSC pathogenesis.[5]

Serum Cortisol level in CSC has been investigated by few authors but with inconclusive results.[6-12] We therefore undertook the present study to evaluate endogenous cortisol levels in patients with acute CSC and to correlate it in different stages of the disease.

Materials and Method

The general study design was an interventional and comparative case control study. A consecutive series of 40 male patients of CSC and 30 male cases of acute monocular vision loss due to any vitreoretinal cause other than CSC were included as per the study protocol. The maximum cut off age was 40 years in both the groups. The study was conducted from May 2011 to November 2012, under grant funding from the Indian Council of Medical Research (ICMR). It was approved by the Institutional Ethics Committee and was adhered to the declaration of Helsinki. Written, informed consent was taken from all the patients.

Complete ophthalmic and medical history was elicited from each subject. Ophthalmic evaluation comprised of a detailed history of visual disturbance, its onset, duration, progression, any similar past complaints, drug intake (corticosteroid, sex steroid, sympathomimetic drugs, antihistamines, decongestant nasal drops and adrenergic drugs etc). Any patient using the above drugs or had undergone any ocular surgery and / or had trauma was excluded from the test group. Patients suffering from systemic diseases or

conditions where known abnormal cortisol metabolism exists like surgery, trauma, depression, Cushing's syndrome etc were also excluded from the study, both in the case and in control groups.

Ophthalmic evaluation comprised of visual acuity, anterior segment slit lamp examination, posterior segment slit lamp biomicroscopy using +90D lens, binocular indirect ophthalmoscopy and macular function tests.

The diagnosis was confirmed by FFA, ICG and spectral domain OCT. The presence of both demonstrable leak in FFA and neurosensory separation in OCT at the macula were considered as diagnostic criteria.

Fasting venous blood samples were collected from all subjects of the case and control groups, in the morning between 8am to 9am, on the 3rd day following a clinical examination and diagnosis of the condition. Similarly, in 22 willing patients of the study group, the 2nd and 3rd samples of venous blood were collected respectively on the 3rd and 6th months' follow up. The method of estimation of serum cortisol used was chemi-luminescent immuno – assay.

'Z' test was used to test the significance of the means of serum cortisol level between the control group and the CSC group on the first visit and Paired 't' test was used to test the significance for the difference of means of serum cortisol level on the 1st, 2nd and 3rd visits of the CSC group only. Regression analysis was done to test the population correlation coefficient of cortisol in the CSC group.

Results

The study group comprised of 40 cases with CSC and the control group had 30 male patients. All patients of the control group had acute onset vision loss due to other causes like rhegmatogenous retinal detachment, Eale's disease etc. The duration of the symptoms at the time of the presentation in both the groups was less than two weeks. The mean age was 35.9 + 3.77 years in cases and 27.5 + 6.58 years in controls. Mean body mass index in the cases was 23.95 + 3.70 and 26 (65%) of them were addicted to smoke or smokeless tobacco. FFA showed ink blot leak in 34 (85%) cases and smoke stack leak in 6 (15%) cases. 37 (92.5%) cases had single leak and 3 (7.5%) cases had multiple leaks in FFA. All cases had abnormal choroidal circulation in ICG angiography (like hyperpermeability of the choriocapillaris, filling delay and choroidal vascular dilatation). OCT showed shallow sensory retinal detachment in all cases and 8 (20%) cases had retinal pigment epithelial detachment. CSC resolved in 33 (83%) cases and remained persistent in 7 (17%) cases at 6th months' follow-up.

Except one case each in the study and the control groups, all had 8am serum cortisol level within the physiological limit. But it was in the higher normal range (15.5 µg/dl or above) in 8 (20%) CSC and 10 (25%) control subjects. The biological reference range of serum cortisol at 7am to 9am was 4.30 to 22.40 µg/dl. The mean 8am serum cortisol level was 12.33 + 3.87 µg/dl in cases during the first visit and 13.33 + 4.28 µg/dl in controls (Table 1). A 'Z' test comparing patients of control groups showed no significant difference between the mean levels in each group (P = 0.83). The mean serum cortisol levels on the 3rd and 6th months' follow up in CSC cases were 13.17 + 4.63 µg/dl and 12.8 + 4.36 µg/dl respectively. A Paired 't' test comparing the mean serum cortisol level in CSC cases between the 1st visit and 2nd visit (P = 0.96), 1st and 3rd visit (P = 0.83) and 2nd visit and 3rd visit (P = 0.65) also showed no significant difference. However, an analysis of the correlation coefficients between the CSC and serum cortisol levels showed a highly positive correlation at each follow up visit (Fig. 1, 2, 3). In resolved cases of the CSC there was a decrease in the mean serum cortisol level in comparison to the baseline value. The mean serum cortisol levels in resolved and unresolved cases at 6th months' follow-up were 12.59 + 4.14 µg/dl and 11.04 + 1.17 µg/dl respectively. Healing of the RPE defect, normalization of the choroidal circulation and absorption of subretinal fluid was observed in healed cases of CSC.

Discussion

The role of cortisol (endogenous and exogenous) has been studied in CSC. Zakir et al[8] reported a significantly higher level of serum cortisol in patients with CSC in comparison to the control group (P=0.002). The mean 8am serum cortisol levels were 495.02 + 169.47 n mol/L and 362.25 + 51.54 n mol/L in cases and controls respectively. This difference was statistically significant (P = 0.002). But only 2 out of 23 cases had serum cortisol level higher than the physiological value and 9 cases had high borderline level (normal range 193 to 690 n mol/L). This finding indicates that in their study, except a few, most of the CSC patients had serum cortisol level within the physiological limit. Serum cortisol was estimated by radioimmunoassay and there was no correlation between the duration of CSC and Cortisol level.

Ishikawa and Sugawara[11] estimated the serum cortisol and catecholamine levels in 13 patients of CSC and found elevated serum cortisol level in 15% cases only, whereas, they found elevated serum adrenaline, non-adrenaline and dopamine levels in 1(8%), 10(77%) and 6(46%) patients respectively. They suspected that the dysfunction of choroid and retina in CSC may be more related to catecholamine than cortisol.

Case control studies done by Garg et al,[6] Dwivedi et al,[9] Chalisgaonkar et al[10] and Haimovici et al[12] did not find any significant association between serum cortisol level, its diurnal variation and CSC. The relationship between CSC and cortisol is not consistent across all studies and the subject remains controversial. In the absence of sufficient histopathological studies,

the current understanding of pathological accumulation of subretinal fluid in CSC remains speculative based on clinical, angiographic and experimental findings.

In the present investigation, a single sample of venous blood at 8am was collected for estimation of serum cortisol levels. Because cortisol has a predictable circadian rhythm with early morning peak and gradual decline at bed time, when its level is low, a single estimation of 8am serum cortisol reflects endogenous activity of hypothalamic–pituitary-adrenal axis.[13] In accordance with studies of Dwivedi et al,[9] Ishikawa et al[11] and Haimovici et al[12] the present study also could not detect any significant difference in mean endogenous serum cortisol levels between acute CSC cases and control group. No significant difference was found between the mean serum cortisol levels measured during the 3rd and 6th months' follow- up of the test group. But a strong positive population correlation coefficient (+0.655) was found in serum cortisol levels amongst 1st, 3rd and 6th months follow-up examination visits of CSC cases. It suggests variation of cortisol levels, though within physiological limit, might have some relationship with CSC.

Glucocorticoids have direct and indirect effect on choroid, Bruch's membrane and retinal pigment epithelium.[14-16] Excessive glucocorticoids can cause disturbance in the choroidal circulation and congestion.[17-21] ICG and high resolution OCT demonstrated that disturbance in choroidal circulation and probable increase of choroidal hydrostatic pressure are the primary pathological changes in CSC.[2] It is a bilateral disease but clinical manifestations usually occur in one eye.[2,22] 5% of patients suffering from Cushing's syndrome[4] and about 52% of external steroid users[3] may develop CSC. Glucocorticoids stabilizes the blood retinal and the blood brain barrier. However, in CSC its action becomes paradoxical. All these facts suggest that possible relationship between CSC and glucocorticoids is governed by some local factors. Choroid being the most metabolically active tissue in the body, even a small variation in the local glucocorticoid metabolism may lead to changes in the choroidal circulation.

Glucocorticoids at the tissue level exert its action through genomic and non-genomic pathway.[9] The genomic action is mediated through the action of isoenzyme 11 beta hydroxy-steroid dehydrogenase (HSD) isoforms 1 and 2 at cytosolic glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). Relative deficiency of HSD 2 may lead to over expression of glucocorticoids in the affected tissue while its increase may enhance MR activity.[23] Adrenal gland derived products (endogenous) like 11-oxygenated C21 and C19- steroidal substance are likely to be the regulators of local cortisol bioactivity in humans.[24] 11 beta – HSD seems to adjust the set point of local deactivation / reactivation of glucocorticoids and mineralocorticoids in vascular and other target tissues including the eye.[24] Alteration of ocular physiology by local modulation of 11-beta HSD 1 activity has been demonstrated.[25,26] Moreover, many environmental inhibitors of 11-beta HSD 2, some of which are risk factors for CSC, have been reported.[27] Sufficient evidence suggest glucocorticoid and mineralocorticoid activity regulate the ocular fluid dynamics and maintains the blood retinal barrier. Glucocorticoid concentration is a balance between production, under negative feedback control and diurnal rhythm of the hypothalamic-pituitary-adrenal (HPA) axis, and peripheral metabolism.[28] Therefore, a local disturbance of cortisol metabolism may not have any influence on the systemic level of cortisol. On the other hand, higher or even a normal serum cortisol level may cause tissue damage due to local abnormality in 11 beta – HSD expression.

Deficient 11 beta – HSD 2 will lead to expression of exaggerated mineralocorticoid activity of cortisol, particularly at the level of RPE (apparent mineralocorticoid excess).[29] Over expression of 11 beta – HSD 1 and / or under expression of 11 beta – HSD 2 will enhance cortisol activity in the choroid and blood retinal barrier. This may be through their direct or indirect effect including immune mechanism and enhanced susceptibility of tissue to several pathogens which are not determined by circulatory level of cortisol.[30]

In the present investigation, normal serum cortisol levels were found in both the case and the control groups. The difference in the mean of serum cortisol levels between both groups was statistically insignificant. But the population correlation coefficient of serum cortisol in different stages of the disease process of CSC was strongly positive. So, local abnormality of genomic pathway of corticosteroid metabolism in the ocular tissue rather than raised serum cortisol level may be responsible for CSC. Further study on various factors having regulatory effect on cortisol bioactivity is required. Estimation of 11 beta – HSD activity in CSC by urinary gas chromatography or by mass spectrometry may also throw some light on the relationship between CSC and cortisol.

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