Endogenous Hypercortisolism in recurrent Central Serous Chorioretinopathy

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ABSTRACT

Background: Central Serous Chorioretinopathy (CSCR) is an important cause of non-surgical retinopathy leading to moderate to severe visual loss. Almost 50% cases undergo recurrence, and one of the recognizable risk factors is endogenous hypercortisolism. Aims and Objective: Our study intended to its presence in recurrent CSCR patients compared to non-chorioretinal disorder. Materials and Methods: Eighteen-month cross-sectional comparative study done on recurrent CSCR patients and matched refractive error patients comprised the comparison group. Use of exogenous steroids and diagnosed conditions of hypercortisolism were excluded. Sample size for both the groups was 34 in each. After taking history and performing ocular examination, blood samples for serum cortisol estimation collected in the morning and in the evening in patients of both the groups. Results analyzed using standard statistical methods. Results: All patients of recurrent CSCR were males. The mean serum levels of cortisol were higher than laboratory reference range during both times of the day in recurrent CSCR patients, and these levels were significantly higher than those in the comparison groups. Conclusion: Recurrent CSCR patients have higher level of endogenous cortisol compared to the non-chorioretinal patients, and its early recognition and management would certainly benefit the patients.

Key words: Central Serous Chorioretinopathy; CSCR; Cortisol; Hypercortisolism

INTRODUCTION

Central Serous Chorioretinopathy (CSCR) a very common form of non-surgical retinopathy, first reported in literature by Von Graefe, and is characterized by idiopathic serous, localized detachment of the neurosensory retina at the macula due to leakage at the level of Retinal Pigment Epithelium (RPE) through one or more sites as a result of hyperpermeability of the choriocapillaris.¹ It is mostly seen in males of young or middle age (M:F 3-10:1); females suffering from CSCR are generally older.² Patients typically present with sudden painless unilateral blurring of vision, associated with metamorphopsia, micropsia, mild dyschromatopsia, and occasional paracentral scotoma. Visual loss is generally moderate to severe, and visual acuity may range from 6/9 to 6/60 in Snellen’s chart. In acute presentation, there is round or oval sensory retinal detachment at the macula involving fovea, whereas in chronic cases or in cases of recurrence, foci of depigmented RPE of variable size may be found within the neurosensory detachment. Prolonged detachment generally is associated with photoreceptor and RPE degeneration.² Optical Coherence Tomography (OCT) reveals an optically empty elevation of the neurosensory retina, with one or more smaller RPE detachments. Enhanced Depth OCT (ED-OCT) shows thickening of choroid in chronic cases.³ Fundus Fluorescein Angiography (FFA) shows a typical ‘ink blot’ or a ‘smokestack’ appearance, and Indocyanine Green (ICG), in early phase shows dilated choroid vessels, and in mid-stage there is hyperfluorescence due to choroidal hyperpermeability.⁴,⁵ Figure 1 shows OCT image of one patient from our study for illustration.

Treatment is mostly conservative, and spontaneous resolution is the norm in almost 80% cases, however, in 15% cases there may be chronicity. Treatment modalities include oral spironolactone, subthreshold diode laser, intravitreal anti-VEGF (Vascular Endothelial Growth

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Factor), and in some cases aspirin, beta-blockers, mifepristone and eplerenone. However, 50% cases may present with recurrence, and a number of risk factors has been proposed, positive family history, male gender, sleep apnea, cardiovascular disease etc. to name a few. Steroid has been considered a major risk factor, not only for acute CSCR, but chronic as well as recurrent case. Systemic steroid use (but not topical), and also endogenous hypercortisolism has been substantiated as a major determinant for recurrence by some studies. Sub fluence Photodynamic Therapy (PDT) has been used in some recurrent or chronic cases, with or without anti-VEGF with good results. But reports were lacking from our particular population, particularly, studies related to risk factors for recurrence are relatively scarce. Hence, we undertook this study to assess the presence of endogenous hypercortisolism in CSCR patients compared to non-chorioretinal pathologies.

**MATERIALS AND METHODS**

This cross-sectional comparative study was conducted in a tertiary care hospital of Eastern India between July 2018 to December 2019. The study was pre-approved by the Institutional Ethical Committee. Consecutive sampling was done; all the patients coming to the Ophthalmology Out-patient Department (OPD) of our hospital who were diagnosed to be suffering from recurrent CSCR were included in our study. Patients with any history of exogenous steroid use, or diagnosed cases of endogenous hypercortisolism (Cushing’s syndrome, adrenal tumors, pituitary tumors etc.) were excluded from our study (to avoid selection bias). The total number of cases was 34, and informed consents were taken from them. Demographic details, clinical history was obtained from them, and ocular examinations were performed (visual acuity testing, indirect ophthalmoscopy, anterior segment examination, OCT and FFA etc.), following which, they were sent to the central laboratory of our institution for collection of blood samples for morning (8AM) and evening (4PM) cortisol level estimations.

Subsequently, 34 age and gender matched subjects were chosen for comparison from patients of refractive error coming to our OPD, who did not have any chorioretinal disease, known hypercortisolism, or history of steroid use. After obtaining informed consent from them, relevant demographic details were noted. Basic ocular examination was conducted (visual acuity testing, anterior segment examination and indirect ophthalmoscopy), following which these subjects were referred for estimation of morning and evening serum cortisol levels. Data from both the patients as well as the comparison group were charted, and analysis done using SPSS-23 software.

**RESULTS**

Table 1 shows the characteristics of the CSCR patients. All of the 34 patients with recurrence were CSCR, and their mean age was around 35 years. More than half were smokers. There was presence of moderate visual loss in most of the patients, with a median visual acuity of 6/24 in Snellen’s chart, and the mean Central Macular Thickness (CMT) as measured by OCT was around 458 μ. Almost 60% cases had recurrence in the same eye, but roughly 15% had bilateral presentation.

Serum cortisol levels were estimated at two different times of the day in both the CSCR patients as well as the comparison group consisting of refractive error patients. The levels were reported in μg/dl units, and the normal ranges for serum cortisol levels at our laboratory was performed (visual acuity testing, indirect ophthalmoscopy, anterior segment examination, OCT and FFA etc.), following which, they were sent to the central laboratory of our institution for collection of blood samples for morning (8AM) and evening (4PM) cortisol level estimations.

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**Table 1: Characteristics of the CSCR patients (n=34)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age of Patients (years)</td>
<td>35.49 ± 5.57 (Range: 27 – 54)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (100%)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Associated History</td>
<td></td>
</tr>
<tr>
<td>Family History of CSCR</td>
<td>14 (41.2%)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>7 (20.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (32.3%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (38.2%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (55.9%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
</tr>
<tr>
<td>Same eye</td>
<td>21 (61.8%)</td>
</tr>
<tr>
<td>Fellow eye</td>
<td>8 (23.5%)</td>
</tr>
<tr>
<td>Bilateral presentation</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Ocular examination</td>
<td></td>
</tr>
<tr>
<td>Mean Central Macular Thickness by OCT (μ)</td>
<td>458.37 ± 59.09 (Range: 312 – 562)</td>
</tr>
</tbody>
</table>

Figure 1: OCT image of patient
10-20 μg/dl for the morning sample (around 8AM), and 3-10 μg/dl for the evening sample (4PM). Table 2 shows the comparison of the mean cortisol levels between the CSCR patients and the comparison group.

DISCUSSION

Most of our patients were middle aged, and all were males. CSCR itself has male predilection, and additionally male gender has been proposed as a risk factor for recurrence; our study reiterates that finding. Among the proposed other risk factors for recurrence, our patients had family history of CSCR in 41% cases, Coronary Artery disease in 20% cases, 38% were diabetic and 32% were hypertensives. Almost 56% were smokers, which also poses risk for recurrence.

The mean serum cortisol levels of the CSCR patients were higher than our laboratory cutoff values on both times of the day, whereas, the mean values of the same for the comparison group was within normal range for both the occasions. The mean morning sample cortisol value was 25.96 μg/dl for the CSCR patients, which was significantly higher than the same of the comparison group (18.02 μg/dl), p-value being 0.000. The evening sample for the patients had a mean value of 10.67 μg/dl, which was also significantly higher than the comparison group, whose mean serum level was 8.80 μg/dl (p-value 0.003).

The result of our study shows that there is increased circulating cortisol in the patients with recurrent CSCR compared to non-chorioretinal diseases (refractive error). This finding has earlier been shown in 30 patients by Garg et al. in a premier institute of our country. Interestingly, in a series of 60 patients with diagnosed Cushing's syndrome, Bouzas et al. had shown that 5% had CSCR, and that also during their period of hypercortisolism. Another case-control study on a smaller sample found similar results, but could not categorize patients according to a cut off for hypercortisolism as that would have required estimation of complete morning and evening cortisol levels, which was not feasible in OPD timings.

There exists controversy regarding the role of corticosteroids and the pathogenesis of CSCR. On one hand, steroids are said to strengthen the tight junctions and reduce blood-brain and blood-retinal barrier breakdown, and also lowers permeability of vessels. However, much evidence points towards the opposite — increased permeability of vessels with increased circulating glucocorticoids. Cortisol suppress extracellular matrix synthesis, inhibits fibroblastic activity; they cause direct damage to RPE cells and their tight junctions, and inhibits reparative activity too. Additionally, they increase capillary fragility, causes hyperpermeability, and lead to decompensation in choroidal circulation and leakage of fluid into subretinal space. Cortisol may also via reversal of polarity of the RPE cells, lead them to secrete ions into subretinal space and thereby osmotic fluid attraction and serious macular detachment. There are anecdotal evidence that systemic steroid therapy worsens CSCR.

Discriminating hypercortisolism from CSCR is associated with other hypercortisolemic states like pregnancy, stress, anxiety, type-A behavior pattern etc.

Studies on recurrent CSCR and its risk factors, particularly the association with hypercortisolism was lacking, but fortunately, a number of studies are taking place in this regard. Matet et al. in 2018 and Yu et al. in 2019 have systematically studied risk factors for recurrence, and one common finding was evidence of endogenous hypercortisolism. Also, in the management issue, stoppage of exogenous steroid therapy is part of the routine management for CSCR, and recently, Finasteride, a 5α-reductase inhibitor is being tried with some success in treatment of CSCR.

Certain limitations to our study were small sample size, and not providing a risk ratio for the association between CSCR and hypercortisolism. Small sample size was due to the factor, that the overall prevalence of CSCR in our country was low, and we additionally have excluded cases with already diagnosed hypercortisolism conditions for the sake of avoiding selection bias. Furthermore, we could not categorize patients according to a cut off for hypercortisolism as that would have required estimation of Late Night Salivary Cortisol (LNSC), or Urinary Free Cortisol (UFC), which were not feasible in OPD timings.

Despite that, we were clearly able to demonstrate the elevated level of cortisol in recurrent CSCR patients. Recurrent CSCR is associated with poorer outcome and even irreversible visual loss, and more aggressive form of treatment (lasers, PDT, anti-corticosteroids, anti-VEGF). It would certainly be beneficial to identify the risk factors for its recurrence, and hypercortisolemia is relatively cheap and easy to diagnose. Prompt diagnosis and management of endogenous hypercortisolemia would certainly benefit the patient.
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Authors Contribution:
SM- Concept and design of the study; prepared first draft of manuscript; collected data; interpreted the results; reviewed the literature and manuscript preparation; SK- Statistically analysed and interpreted the results, review of literature; preparation of manuscript; SD- Concept, coordination, review of literature and manuscript preparation and revision of the manuscript.

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