Original Article

Intraocular pressure and its correlation with midnight plasma cortisol level in Cushing's disease and other endogenous Cushing's syndrome

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Purpose: The purpose of this study is to measure intraocular pressure (IOP) and evaluate the correlation between IOP and midnight plasma cortisol (MPC) level in patients with Cushing's disease (CD) and other endogenous Cushing's syndrome (ECS). **Methods:** This is a cross-sectional study from a single center including newly diagnosed patients with CD or ECS. All patients underwent detailed ophthalmological evaluation. IOP was measured by Goldmann applanation tonometry in the morning and evening on two consecutive days. MPC value was obtained for each patient. The data were compared using paired and unpaired *t*-test, Mann–Whitney U-test, and Spearman's rank correlation coefficient. **Results:** Among 32 patients, 22 were CD (68.75%) and 10 patients were other ECS (31.25%). A total of 25 patients (78.12%) in our study group had normal IOP (<22 mmHg), and seven patients (21.88%) had increased IOP (≥22 mmHg). The percentage of patients with normal IOP was found to be significantly higher compared to percentage of patients with high IOP ($P = 0.001$) using one-sample Chi-square test. Mean MPC value was 468.6 ± 388.3 nmol/L in patients having IOP ≥22 mmHg and 658.5 ± 584 nmol/L in those with IOP <22 mmHg from both CD and ECS groups, but the difference was not statistically significant. No correlation was found between IOP and MPC (Spearman's rank correlation rho = −0.16 [$P = 0.38$]). **Conclusion:** In CD and ECS patients, IOP elevation is an uncommon feature, and high IOP in either group does not correlate with MPC level.

Key words: Cushing disease, endogenous Cushing syndrome, intraocular pressure, midnight plasma cortisol

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Cushing syndrome (CS), first described by Harvey Cushing in 1910, is a condition associated with prolonged hypercortisolism of either exogenous or endogenous origin. The most common cause of this syndrome is exogenous administration of glucocorticoids (GCs) for therapeutic purpose.[1] The term "Cushing's disease" (CD) is referred to as CS that is caused by a pituitary tumor, usually an adenoma resulting in excessive secretion of adrenocorticotropic hormone (ACTH).[2] It is the most common cause of endogenous CS (ECS) and is responsible for roughly two-thirds of all cases.[1,3,4] The remainder of the endogenous cases is caused by ectopic ACTH-secreting tumors and primary adrenal neoplasms.[5]

The effect of exogenous steroid on intraocular pressure (IOP) is well known. Studies show that IOP rises in about 30%–40% of the general population due to topical or systemic GCs use.[6,7] Not many clinical studies have been done regarding IOP response to chronic excess of endogenously synthesized GC. A few published reports in this regard are contradictory to each other in their results and conclusions.[8,9]

The objective of this study is to measure IOP in newly diagnosed patients of CD and ECS and to correlate the IOP value with midnight plasma cortisol (MPC) level.

Methods

This is a cross-sectional study conducted between January 2011 and December 2011 after approval by the institutional ethics committee. The study population included all newly diagnosed patients of CD and other ECS who were admitted to the endomedicine ward of our institution. An informed consent was obtained from each participant.

All patients underwent comprehensive ophthalmological examination. Best-corrected visual acuity was documented with Snellen chart. A detailed anterior segment examination was carried out. Field of vision was assessed by automated perimetry using 30-2 SITA standard technique (Humphrey Visual Field Analyzer II-750i Carl Zeiss, USA). A single observer measured IOP on 2 consecutive days using Goldmann applanation tonometry. IO*P* values at 8 am and 4 pm on each

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day were recorded. Gonioscopy was done with Goldmann three-mirror gonioscope. A dilated fundus examination was carried out with slit lamp biomicroscopy using +90 D and indirect ophthalmoscopy using +20 D. Central corneal thickness (CCT) was measured with specular microscope (EM 3000, Tomey, Japan).

Midnight venous sample was collected between day 1 and day 2 to determine plasma cortisol value of each patient as per routine protocol of the Endomedicine Department. MPC value of 207 nmol/L was taken as cutoff point in our patients.[10]

Exclusion criteria included the previous history of glaucoma, globe injury, ocular surgery, uveitis or any present evidence of active intraocular inflammation, significant cataract, occludable or closed angle, angle recession, retinal disorder, and optic neuropathy. Patients of pseudo-CS and ECS were not included in the study.

Statistical analysis

Normality of the data was tested using Shapiro–Wilk test. For normally distributed data, means were compared using unpaired *t*-test when groups were independent. For paired observations of a common group, the mean difference was tested using paired *t*-test. Mann–Whitney U-test was used to compare data that were not normally distributed. One-sample Chi-square test was done to compare proportions. Data were presented as a scatter diagram and error bar graph. While IOP values were normally distributed, MPC values were not distributed and we used Spearman's rank correlation coefficient to test the linear relationship between these two variables. A $P < 0.05$ has been considered statistically significant. Statistical Package for Social Science, version 22 (SPSS-22, IBM, Chicago, USA), has been used to analyze the data.

Results

A total of 35 patients of ECS were found. Three patients were excluded from the study, one with signs of intraocular inflammation, one with occludable angle, and one with a mature cataract. Of the 32 patients who were included in the study, 22 (68.75%) were CD and 10 (31.25%) were found to have other ECS. Fifteen patients were female (46.9%) and 17 male (53.1%). Age range was 24–57 years. Refractive error range was −2.5 D to +1 D OU with near correction +1 D to +2.5 D. Anterior segment and fundus examination were normal. CCT was between 530 and 550 µm. No visual field defect was noted in any case.

A total of 25 patients (78.12%) in our study group had normal IOP (<22 mmHg) and seven (21.88%) had increased IOP (≥22 mmHg), among which three (9.4%) had IOP >30 mmHg. The percentage of patients with normal IOP was found to be significantly higher as compared to percentage of patients with high IOP (one-sample Chi-square test 78.1% vs. 21.9% [$P = 0.001$]). Paired *t*-test was used to compare the mean IOP of the morning and evening time each day, but the difference was statistically insignificant [Table 1]. We calculated the mean IOP of CD and ECS group separately. Difference was compared using unpaired *t*-test but was insignificant [Table 2]. Mean MPC values in CD and ECS group were compared. No statistically significant difference was found between two groups with Mann–Whitney U-test [Table 3]. We also calculated the mean MPC value in normal and high IOP groups. Difference was found to be insignificant by Mann–Whitney U-test [Table 4]. Scatter diagram [Fig. 1] shows no correlation between IOP and MPC (Spearman's rank correlation rho = −0.16 [$P = 0.38$]).

Discussion

We found a total of 7 patients (21.88%) in our study group had increased IOP (≥22 mmHg) and 25 (78.12%) had normal IOP (<22 mmHg). The difference in proportion was statistically significant. In patients having IOP ≥22 mmHg, MPC value was 468.6 ± 388.3 nmol/L, and in patients with IOP <22 mmHg, MPC value was 658.5 ± 584 nmol/L from both CD and ECS groups. Difference was found to be statistically insignificant using the Mann–Whitney U-test.

Sayegh and Weigelin[8] and Jonas *et al*.[9] studied 70 and 62 patients of ECS and CD, respectively. However, patients of both ECS and CD were not studied concurrently in either of the studies. Furthermore, they have not taken into

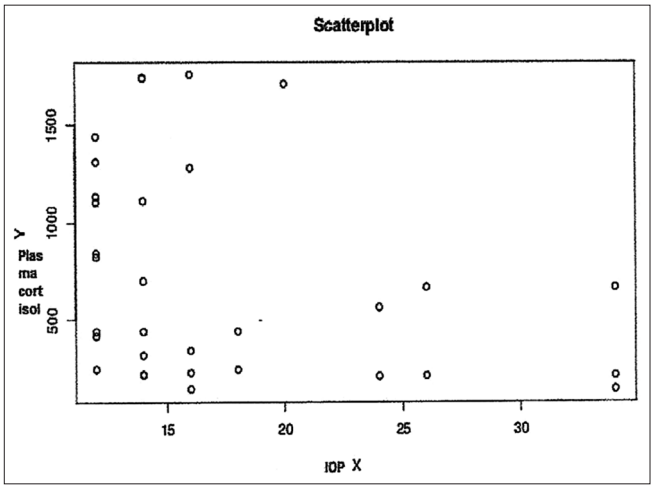

Figure 1: Data presented in scatter diagram. No correlation found between intraocular pressure and midnight plasma cortisol concentration. (Spearman's rank correlation rho = −0.16 [$P = 0.38$])

Table 1: Diurnal variation in intraocular pressure in day 1 and 2

Mean IOP±SD (mmHg)	8 am (*n*=32)	4 pm (*n*=32)	Mean difference (95% CI)	*P**
Day 1	17.7±6.7	16.6±6.5	1.1 (−1.51-3.35)	0.820
Day 2	17.6±6.4	16.9±6.5	0.7 (−1.55-2.95)	0.720
Mean difference (95% CI)	0.1 (−2.11-2.31)	0.3 (−2.55-1.95)		
*P**	0.930	0.790		

*Paired *t*-test was used to test the mean difference, $P<0.05$ significant. Mean IOP difference between 8 am and 4 pm as well as day 1 and day 2 was tested using paired sample *t*-test, result revealed that there was no significant difference in means for each of the paired groups ($P>0.05$). CI: Confidence interval, IOP: Intraocular pressure, SD: Standard deviation

Table 2: Mean intraocular pressure in Cushing's Disease and other Endogenous Cushing Syndrome groups

Study groups	CD (*n*=22)	ECS (*n*=10)	*P**
IOP (mean±SD)	16.8±6.7	18.8±7.2	0.470

*Unpaired *t*-test used, *P*<0.05 significant. Mean IOP of CD and ECS was compared using unpaired *t*-test, result revealed that there was no significant difference in means between the groups (*P*>0.05). IOP: Intraocular pressure, CD: Cushing's disease, ECS: Endogenous cushing syndrome, SD: Standard deviation

Table 3: Comparison of mean midnight plasma cortisol values in Cushing's Disease and other Endogenous Cushing Syndrome groups

Study groups	CD (*n*=22)	ECS (*n*=10)	*P**
MPC (mean±SD)	720.1±558.8	718.0±530.5	0.970

*Mann-Whitney U-test used, *P*<0.05 significant. Mean MPC of CD and ECS groups was compared using Mann-Whitney U-test as data were nonnormally distributed. Result revealed that there was no significant difference in distribution of MPC between the groups (*P*>0.05). MPC: Midnight plasma cortisol, CD: Cushing's disease, ECS: Endogenous cushing syndrome, SD: Standard deviation

Table 4: Comparison of mean midnight plasma cortisol values in high and low intraocular pressure group

Study groups	IOP		*P**
	<22 (*n*=25)	≥22 (*n*=7)	
MPC (mean±SD)	658.5±584.0	468.6±388.3	0.410

*Mann-Whitney U-test used, *P*<0.05 significant. Mean MPC values in two IOP groups were compared using Mann-Whitney U-test as data were nonnormally distributed. Result revealed that there was no significant difference in distribution of MPC between the groups (*P*>0.05). IOP: Intraocular pressure, MPC: Midnight plasma cortisol, SD: Standard deviation

consideration the levels of plasma cortisol while studying IOP in their respective analyses. Jonas *et al*. found mean IOP 14.9 ± 3.5 mmHg, and IOP of 23 and 24 mmHg was found in two patients (four eyes, 3.2%). Pre- and post-operative mean IOPs were statistically the same. Sayegh and Weigelin found IOP > 21 mmHg in 31 patients of preadrenalectomy group (41.3%) and 1 patient of postadrenalectomy group. Our results are close to the findings of Jonas *et al*.[9]

To know why persistent high levels of endogenous GC do not elevate IOP like exogenously applied GC, we first need to understand the role of GC in IOP regulation. Previously, blood level of corticosteroids and plasma protein binding were thought to be the major determinants of corticosteroid action, aqueous humor (AH) drainage at trabecular membrane (TM) was the rate limiting step, and exogenous GC supposed to cause increase IOP by morphological TM alteration.[11-14] Now, role of GC in regulation of IOP has gone beyond this. At present, steroid action modulation at organ level is evidenced by tissue-specific enzymes and tissue-specific local metabolism. Tissue-specific modulators of corticosteroid action[15] are the enzymes 11 beta-hydroxysteroid dehydrogenase type 1 and 2 (11β-HSD 1 and 2). Physiological role 0f 11 beta HSD1 is to convert cortisone into active cortisol which occupy both glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) in the tissues.[16,17] 11β-HSD2 reconverts cortisol into cortisone and protects MR from cortisol.[18] In the eye, 11β-HSD1 and GR localized in the ciliary body (CB).[19] The presence of 11β-HSD2 is doubtful in CB and TM.[19-21] Rauz *et al*.[19] hypothesized that 11β-HSD1 have a 2-fold role within human eye, a short-term physiological role which is maintaining a normotensive, intraocular environment by nonpigmented epithelium sodium transportation and the secretion of AH, and a long-term pathological role in interaction with GR and TM contributing to outflow resistance in susceptible individuals. The relative expression could therefore represent one of the underlying pathogenic mechanisms of primary open-angle glaucoma. Experimental work has also shown that inhibition of 11β-HSD1 lowers IOP in patients with ocular hypertension.[22]

Based on above putative local GC actions, IOP regulatory mechanisms, and our observations, we put forward the following hypothesis: Exogenous steroid in the form of topical and intraocular steroids compartmentalize within ocular cavities and do not contact regulatory mechanisms in CB. Unphysiological levels of exogenous GC with normal endogenous cortisol by unaffected CB damage TM causing an increase in IOP. Absent 11β-HSD2, MR at CB, and TM give credence to our supposition. Exogenous systemic steroids cannot sustain very high and steady plasma levels round the clock, which occur in ECS, causing inconsistent blood level of GC. CB regulatory mechanisms do not respond suitably to unsteady plasma levels of exogenous GC. Intraocular GC excess at TM results in increased IOP.

In CD and ECS, rise in plasma cortisol is comparatively steady and can go up to 10 fold. It modulates local CB steroid regulatory systems. There is no intraocular cortisol excess and hence no increase in IOP.

The strength of our study remains that we have studied both CD and ECS group simultaneously, IOP and levels of MPC were evaluated concomitantly, and the treatment of naïve patients was included.

We acknowledge that our study has several limitations, including the small number of patients, and that a trend of lower plasma cortisol in IOP >20 mmHg is perceptible but not statistically significant. Patients were not followed for a prolonged period of time. It is desirable to see how patients with IOP >20 mmHg would behave after normalization of plasma cortisol.

Conclusion

We conclude that IOP does not respond to the chronic, steady excess of the endogenously synthesized GC. Large specially designed studies are needed to measure IOP responses to endo- or exo-genous GC and to explore precise molecular mechanism of IOP regulation, including the role of 11β-HSDs in ocular physiology. Still, we hope that our study will kindle new interest in this area and serve as a starting point in a quest to solve these pressing questions.

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Conflicts of interest

There are no conflicts of interest.

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