Case report

Endogenous hypercortisolism inducing reversible ocular hypertension

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ABSTRACT

Purpose: To describe the clinical findings of two patients with reversible ocular hypertension secondary to endogenous hypercortisolism.

Design: Retrospective, observational case series.

Subjects: A 65-year-old man (patient 1) and a 21-year-old woman (patient 2) were both found to have Cushing's syndrome after presentation to our clinic with elevated intraocular pressures (IOP).

Methods: Clinical histories, ophthalmic examinations including IOP measurements, optical coherence tomography of the retinal nerve fiber layer, visual field testing, magnetic resonance imaging and computerized tomography of two patients were reviewed between 2007 and 2019.

Observations: Patient 1 demonstrated elevated IOP (maximum 26 mmHg OD and 22 mmHg OS) and bilateral disc edema. Following diagnosis of Cushing's syndrome, the patient underwent two pituitary resections and bilateral adrenalectomy, with subsequent resolution of his hypercortisolism and ocular hypertension (OHT). Patient 2 presented with blurred vision and found to have OHT (maximum 32 mmHg OU). Following diagnosis of Cushing's disease and two resections of her adrenocorticotropic hormone (ACTH) producing pituitary adenoma, her IOPs normalized. Both patients maintained normal IOPs after resolution of their endogenous hypercortisolism and discontinuation of topical IOP-lowering medication.

Conclusions and Importance: Ocular hypertension induced by endogenous hypercortisolism is, in some cases, fully reversible following normalization of cortisol levels. These findings suggest that the physiologic changes to the trabecular meshwork induced by endogenous hypercortisolism may be fully reversible.

1. Introduction

Cushing's syndrome encompasses the clinical signs and symptoms resulting from exposure to excess glucocorticoids, including weight gain, hirsuitism, menstrual irregularities, hypertension, fatigability, abdominal striae, bruisability, and psychosis. Cushing's disease describes hypercortisolism resulting from excessive adrenal stimulation by an adrenocorticotropic hormone (ACTH) secreting pituitary tumor. The association between Cushing's syndrome and elevated intraocular pressure (IOP) was identified by Tartarin in 1938. Mclean in 1950 noted that exogenous intramuscularly injected ACTH also induced IOP elevation. Schwartz noted the relationship between glaucoma and the pituitary-adrenal-axis finding that free cortisol levels are higher in patients with open angle glaucoma than are those in normal subjects. In 1974, Haas published the case report of a 24-year-old patient who developed IOP as high as 41 mmHg, which normalized after removal of a benign adrenal adenoma. In addition, this patient's mother, father, and sister responded to topical dexamethasone with IOP elevations. Thus, Haas concluded that in patients with Cushing's syndrome, increased IOP likely results from genetic corticosteroid sensitivity.

Currently, the relationship between steroid-induced ocular hypertension (OHT) and glaucoma is an active area of research. Investigations into steroid-induced changes in the trabecular meshwork (TM) and steroid-responsive TM gene expression promise a deeper understanding of the mechanisms underlying glaucoma. We present two case reports of patients with elevated IOP due to endogenous hypercortisolism secondary to pituitary/adrenal masses. Both patients underwent surgical resection of the masses, resulting in normalization of their IOPs post resection.

2. Case 1

A 65-year-old man with a history of testicular cancer, suspected Parkinson's disease, and primary open angle glaucoma (POAG) was
referred to a neuro-ophthalmologist for symptoms of diplopia and intermittent tinnitus accompanied by visual aura. He had a family history of glaucoma in his mother. He exhibited abnormal weight gain, sleep apnea, hypertension, loss of balance, skin bruising, bilateral hip pain, headache, abdominal muscle weakness, visual hallucinations, and fatigue. On exam, visual acuities were 20/20 OU. His stereo vision, confrontational visual fields, and extraocular movements were intact. Gonioscopy showed open angles OU. Fundus exam revealed healthy optic discs with a cup-to-disc ratio (CDR) of 0.3 OU. Intraocular pressures were measured at 21 mmHg OD and 20 mmHg OS. At this time, he was using topical latanoprost 0.005% nightly OU. Six months after initial presentation, he was found to have optic disc edema and hemorrhages bilaterally, with IOPs at 17 mmHg OU. Fundus examination was remarkable for edematous optic discs and peripapillary retinal nerve fiber layer (RNFL) hemorrhages in both eyes (Fig. 1A). Visual field testing revealed mildly enlarged blind spots (Fig. 1B). Subsequent follow up examinations revealed IOPs of 25 mmHg OD and 22 mmHg OS, optic disc margin blurring, resolving RNFL hemorrhages, and emerging RNFL infarcts OU. Urgent lumbar puncture was ordered and opening pressure was elevated at 45 mmHg. Brain MRI revealed a nonspecific sellar hypointensity (Fig. 1C).

The patient’s primary care provider noted a Cushingoid appearance and ordered a dexamethasone suppression test and a 24-h urine cortisol level, which were abnormal. An abdominal CT revealed minor nodularity of both adrenal glands (Fig. 1D). The patient underwent resection of his suspected sellar tumor with a clinical context suspicious for Cushing’s disease. Analysis of the surgical specimen showed no definitive evidence of ACTH-cell adenoma tissue, and ACTH & 24-h urine cortisol levels remained elevated, so a second pituitary resection was performed. Despite medical management with cabergoline therapy, free urine cortisol levels remained elevated, and the patient underwent bilateral adrenalectomy. Post-operatively he was started on systemic hydrocortisone 20 mg BID and fludrocortisone 0.05 mg daily. The patient’s plasma ACTH levels normalized and he noted reduced leg swelling, improved energy, less agitation, and weight loss. On ophthalmic examination, his IOPs had normalized to 14 mmHg OD and 12 mmHg OS, and visual fields remained stable. Topical latanoprost was discontinued. His IOPs remained normal upon follow up, 16 months after his third surgery, at 18 mmHg OD and 16 mmHg OS.
3. Case 2

A 21-year-old woman with a history of easy bruising, multiple stress fractures, and abnormal weight gain presented to her ophthalmologist for blurry vision. Her corrected visual acuities were 20/15 in both eyes. Her intraocular pressures were 24 mmHg OD and 30 mmHg OS. Central corneal thickness measurements were 595μm OD and 600μm OS. Gonioscopy demonstrated open angles OU. Optic discs were intact with

Fig. 2. (A) Fundus photographs, including healthy appearing optic discs at baseline. (B) Optical coherence tomography thickness measurement of the peripapillary retinal nerve fiber layer show superotemporal thinning of the right eye and temporal thinning of the left eye. (C) Sagittal and coronal brain magnetic resonance images demonstrate a 6mm pituitary adenoma (arrows). (D) Tissue specimen from the pituitary adenoma stained by hematoxylin and eosin (left) and labeled by immunohistochemistry for ACTH (right). The histopathology slides confirm the presence of ACTH-producing cells within the adenoma tissue from the second resection. Scale bar = 50 μm.
a CDR of 0.35 OD and 0.4 OS (Fig. 2A). Optical coherence tomography (OCT) of the fundus showed borderline RNFL thinning super-temporally OD and temporally OS (Fig. 2B). The patient opted to defer topical IOP-lowering therapy. On a subsequent visit, the patient reported frequent headaches. Her IOPs remained elevated at 30 mmHg OD and 32 mmHg OS. Visual fields were unremarkable and RNFL OCT analysis remained stable. After consultation with a glaucoma subspecialist, the patient elected to start topical latanoprost 0.005% drops nightly OU.

Following a dual-energy X-ray absorptiometry (DEXA) scan which showed low bone density, her primary care provider noted that her history of multiple fractures and abnormal weight gain warranted investigation of Cushing’s disease. 24-hour urine cortisol levels were elevated, as was her ACTH level. The patient underwent brain MRI, which was remarkable for a 6 mm microadenoma in the left pituitary gland (Fig. 2C). Petrosal sinus sampling was performed, corroborating Cushing’s disease. Subsequent endoscopic-assisted transsphenoidal resection was performed, without neuropathological evidence of anterior pituitary tissue sampling. Her ACTH and serum cortisol levels remained elevated and the patient elected to undergo repeat pituitary resection. The second surgical specimen consisted of sheets of basophilic neoplastic cells that labeled for ACTH by immunohistochemistry (Fig. 2D). Her ACTH and serum cortisol levels normalized in the days following the procedure. Ophthalmic examination post resection showed IOPs of 16 mmHg OD and 18 mmHg OS and stable exam. Visual fields were unremarkable and latanoprost therapy was discontinued. Follow-up endocrine testing and brain MRI were consistent with remission of Cushing’s disease. Her IOPs remained normal at 16 mmHg OU three years following her second surgery and without IOP-lowering therapy.

4. Discussion

The diagnosis of Cushing’s syndrome requires extensive evaluation. Patients with Cushing’s disease are treated for common conditions like hypertension, diabetes, and osteoporosis for an average of 6 years before full diagnosis is made, similar to the cases presented here. In the two cases presented, endogenous hypercortisolism induced reversible ocular hypertension. It has been shown that IOP elevation can persist for 4–8 hours after exposure to exogenous glucocorticoids, although IOP generally normalizes after a brief lag time following steroid cessation. In the two cases presented here, despite prolonged endogenous hypercortisolism, OHT was reversible and normalized after correction of hypercortisolism. Physiologic cortisol has long been suspected to play a role in controlling IOP.

The correlation between the diurnal fluctuations in IOP and plasma cortisol concentrations further strengthens the assertion that endogenous glucocorticoids continuously modulate eye pressure. Patients with Cushing’s and resultant IOP elevations represent an extreme of endogenous cortisol-induced OHT occurring more insidiously in patients with various forms of glaucoma. Glucocorticoid-induced TM changes cause aqueous humor outflow resistance. Patients with POAG demonstrate greater IOP elevations in response to application of topical steroids and steroid-responsive individuals are more likely to develop POAG. The degree of the IOP elevation varies based on the potency of steroid therapy, and the responsiveness of the individual; individuals are either high, medium, low, or non-responders. Although, elevated cortisol is a known risk factor for the development of glaucoma, the intricacies of the function of cortisol are not fully understood.

Unlike the IOP elevation observed in endogenous hypercortisolism, exogenous steroid-induced OHT has been extensively studied in animal and human subjects. Glucocorticoids alter TM cellular replication, phagocytosis of pigment granules and other debris, cellular activation, and extracellular matrix expression. Glucocorticoids are known to increase mRNA transcription leading to increased collagen IV and elastin in the TM of mouse models. Exposure to dexamethasone causes TM cells to upregulate genes for alpha-1-antichymotrypsin, pigment epithelium-derived factor, cornea-derived transcription factor 6, and prostaglandin D2 synthase.

Myocilin has been studied as an important protein related to steroid-induced OHT. Glucocorticoids induce myocilin protein expression through the TM inducible glucocorticoid response gene MYOC. Although myocilin expression increases in response to glucocorticoids, mice lacking the MYOC gene demonstrate OHT to a similar degree as do wild-type mice in response to exogenous glucocorticoids. Furthermore, mice overexpressing MYOC do not demonstrate consequent defects in the TM or resultant IOP elevation, undermining the causal role of MYOC in steroid-induced OHT.

One confounding factor to consider is the relationship between intracranial pressure (ICP) and IOP. While ICP is low in patients with POAG, it is elevated in those with OHT. In light of this relationship, it is important to consider the effect of pituitary surgery on IOP in these two cases (Fig. 3). The significantly elevated opening pressure measured in Patient 1 before his first pituitary resection must also be taken into account. However, the relationship between ICP and IOP is complex. High IOP may lead to a decrease in ICP through feedback mechanisms influencing cerebrospinal fluid dynamics. High ICP may also protect against optic nerve damage by counterbalancing IOP elevation and thereby lowering the pressure differential experienced by the optic nerve.

The IOP elevation in Cushing’s syndrome represents an in vivo example of the link between endogenous hypercortisolism and OHT, which may further our understanding and treatments of steroid-induced glaucoma. If, as is suggested by two cases presented here, OHT induced by endogenous hypercortisolism is fully reversible with normalization of cortisol levels, then the physiologic changes induced by cortisol which give rise to OHT may be reversible as well. Investigations into the interaction between steroids, the TM, and OHT may lead to novel therapies including glucocorticoid receptor blockers and the use of cortisol metabolites shown to lower IOP.
Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patients. Furthermore, OHSU’s Institutional Review Board (IRB) determined that this report is not research involving human subjects and IRB review and approval is not required.

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Authorship

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2019.100573.

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