Case Report

CUSHING DISEASE MASQUERADING AS GLAUCOMA

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ABSTRACT

Objective: Glaucoma is a well-recognized side effect of corticosteroids. However, steroid-induced glaucoma typically refers to that caused by exogenous corticosteroid administration. Glaucoma secondary to endogenous overproduction of corticosteroids has only been reported in a few case reports. We aim to bring attention to glaucoma as a rare but important manifestation of endogenous hypercortisolism.

Methods: Patient history, physical exam, laboratory results, and imaging studies were reviewed.

Results: We report a case of glaucoma as the initial presentation of Cushing disease (CD). The patient was diagnosed with glaucoma 16 months prior to his endocrinology evaluation. At our initial encounter, the patient had a cushingoid appearance. Levels of 24-hour urinary cortisol and late-night salivary cortisol were elevated. Serum cortisol was not suppressed by 1 mg of dexamethasone overnight, but it was suppressed by 8 mg of dexamethasone. Adrenocorticotropic hormone was also elevated. All other pituitary hormone axes were unremarkable (thyroid-stimulating hormone, free thyroxine, follicle-stimulating hormone, luteinizing hormone, growth hormone, prolactin, and insulin-like growth factor). Pituitary magnetic resonance imaging suggested a small adenoma (2 to 3 mm); therefore, the patient underwent inferior petrosal sinus sampling. The results were consistent with CD. Transsphenoidal resection was performed and final pathology confirmed an adrenocorticotropic hormone-positive adenoma. Hypercortisolism and intraocular pressures improved after the surgery.

Conclusion: Glaucoma can lead to irreversible blindness if left untreated or uncontrolled. However, endogenous hypercortisolism-induced glaucoma can be reversed with treatment of the underlying CD. Thus, heightened awareness of extraocular manifestations of secondary causes of glaucoma such as endogenous hypercortisolism is necessary in order to promote prompt evaluation and treatment. **(AACE Clinical Case Rep. 2019;5:e290-e293)**

Abbreviations:
ACTH = adrenocorticotropic hormone; **CD** = Cushing disease; **GR** = glucocorticoid receptor; **IOH** = intraocular hypertension

INTRODUCTION

Cushing disease (CD) may present as a wide spectrum of symptoms and signs including easy bruising, facial plethora, proximal muscle weakness, and striae (1). Osteoporosis, hyperglycemia, and venous thromboembolism are commonly associated complications and increase the risks of mortality and morbidity. However, ophthalmic complications such as glaucoma are not well recognized even though untreated glaucoma can lead to irreversible blindness (2). Therefore, prompt diagnosis of potentially treatable causes of glaucoma such as CD is crucial. We describe a case of glaucoma secondary to CD.

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CASE REPORT

A 37-year-old man with a recent diagnosis of glaucoma was referred for high adrenocorticotropic hormone (ACTH) and random serum cortisol levels from the ophthalmology department. He was seen for 16 months prior to the endocrinology referral by ophthalmology for bilateral blurry vision and elevated intraocular pressures of 48 mm Hg in the right eye and 68 mm Hg in the left eye (normal range is 10 to 20 mm Hg). He was diagnosed with open angle glaucoma and was initially treated with topical solutions of brimonidine 0.2%, acetazolamide, and timolol 0.5% with dorzolamide 2%. However, intraocular pressures remained elevated at 25 mm Hg (right) and 38 mm Hg (left) 6 months after topical treatment, so he underwent a glaucoma drainage device placement in the left eye.

Upon initial his encounter with the endocrinology department, the patient reported weight gain (30 pounds) with increased abdominal girth, round facies, and neck width over the past 6 months. His worsening cushingoid appearance prompted a request for endocrinological evaluation by the ophthalmology department. The patient had purple striae on his abdomen but denied easy bruising or muscle weakness. There was no increase in body or facial hair. He reported occasional headaches and noted his blood pressure was intermittently high. He also denied recent glucocorticoid use.

On examination, the patient was normotensive with a body mass index of 26.5 kg/m^2. He had a plethoric moon face, supraclavicular fat pads, central obesity, violaceous striae over the abdomen, and dark hyperpigmentation over his knuckles and knees. Laboratory findings confirmed hypercortisolism with midnight salivary cortisol at 0.88 μg/dL (normal range is 0.01 to 0.09 μg/dL), and 24-hour urinary cortisol of 416.3 μg/24 hours (normal range is <60 μg/24 hours). His cortisol was not suppressed (17 μg/dL) after overnight test with 1 mg dexamethasone, but was suppressed (to a low of 4.0 μg/dL) after test with 8 mg dexamethasone. ACTH was 134.2 pg/mL (normal range is 7.2 to 63.3 pg/mL) at presentation. There was no hypokalemia (4.1 mmol/L) or hyperglycemia.

All other pituitary hormone axes were unremarkable including thyroid-stimulating hormone, free thyroxine, follicle-stimulating hormone, luteinizing hormone, growth hormone, prolactin, and insulin-like growth factor. Magnetic resonance imaging of the pituitary revealed a hypoenhancing lesion measuring 2 to 3 mm within the left pituitary gland suggestive of a microadenoma. Given the small size of the tumor, inferior petrosal sinus sampling was performed. Serum ACTH levels were obtained after administration of 70 μg of corticotropin-releasing hormone (1 μg/kg) from the left inferior petrosal sinus, right inferior petrosal sinus, and peripheral vein at 0, 2, 5, 10, and 15 minutes (Table 1).

Inferior petrosal sinus sampling findings were consistent with CD with suspicion for focus in the left pituitary. The patient subsequently underwent transsphenoidal microadenectomy. The neurosurgeons identified an area in the left pituitary gland which appeared soft and white, suggestive of an adenoma. This area was excised and pathology of the lesion confirmed a pituitary adenoma. Immunohistochemical staining was diffusely positive for ACTH and positive for the protein MIB1 in <2% of cells. Postoperative morning cortisol was <1.0 μg/dL and ACTH was 6.7 pg/mL.

The patient's lipid profile was not documented prior to surgery, but 1 year, 8 months after surgery triglycerides were 98 mg/dL (normal range is <150 mg/dL), total cholesterol was 266 mg/dL (normal range is <200 mg/dL), high-density lipoprotein was 46 mg/dL (normal range is >40 mg/dL), and low-density lipoprotein was 203 mg/dL (normal range is <130 mg/dL). Dual energy X-ray absorptiometry was also performed at this time and showed lumbar spine T-score of -2.4, left femur T-score of -1.7, and left femoral neck T-score of -2.7, which is consistent with osteoporosis. The patient did not have any symptoms suspicious of venous thromboembolism before or after surgery.

The patient is currently being treated with hydrocortisone for adrenal insufficiency and weekly alendronate for osteoporosis. Postoperative intraocular pressures normalized to 17 mm Hg (right) and 14 mm Hg (left) and he no longer requires topical medications. He continues to follow up with ophthalmology for monitoring.

DISCUSSION

We present a rare case of CD manifesting as glaucoma. This is a phenomenon only documented sporadically in case reports and a few clinical studies. Steroid-induced glaucoma is a type of open-angle glaucoma which is more commonly reported in exogenous steroid administration (particularly topical) compared to endogenous hypercortisolism. Becker (3) documented that approximately 30% of the general population has an increase in intraocular pressures after a short duration of topical 0.1% betamethasone use (4 times daily for 6 weeks).

The timing in which the rise in intraocular pressure begins depends on factors such as individual risk factors, the type of drug, frequency, and dosage. Although most studies report the onset of intraocular pressure elevation after approximately 3 to 6 weeks of topical steroid use (4), one study demonstrated a rise as early as 1 to 2 weeks after 0.1% dexamethasone eye drops used 3 times per day (5). In exogenous corticosteroid-induced glaucoma, intraocular pressure elevation can be reversible although it depends on the duration of steroid use (6).

Not many clinical studies have been performed on endogenous hypercortisolism-induced intraocular hyper-

Table 1
Inferior Petrosal Sinus Sampling Results

	Adrenocorticotropic hormone (pg/mL)			Ratios*		
Time (min)	Left IPS	Right IPS	Peripheral	Left IPS/ Peripheral	Right IPS/ Peripheral	Left IPS/ Right IPS
0	>2000	766	116	17.2	6.6	2.6
2	>2000	>2000	140	14.3	14.3	1.0
5	>2000	888	162	12.4	5.5	2.3
10	>2000	1270	34	59.3	3.8	15.7
15	>2000	>2000	52	38.5	38.5	1.0

Abbreviation: IPS = inferior petrosal sinus.
*For ACTH levels >2000 pg/mL, 2000 was used to calculate ratios.

tension (IOH). Jonas (7) investigated 62 patients with CD and found that only 2 patients (3.2%) had intraocular pressures >21 mm Hg prior to surgery (7). In another study investigating 70 patients with adrenal CD (55 hyperplasia, 12 adenoma, 3 carcinoma), 31 patients (41.3%) had intraocular pressures >21 mm Hg (8). In both studies, resolution of the IOH was seen after surgery for the underlying hypercortisolism with the exception of 1 case (7,8). Although IOH due to topical steroid administration is well known, the effect of excess endogenous cortisol on intraocular pressure has not been well studied and existing data provide conflicting results.

Certain risk factors are associated with exogenous steroid-induced IOH. Underlying ophthalmologic conditions such as primary open-angle glaucoma, family history of glaucoma, old age, age <6 years, and history of connective tissue disease play a role in IOH (4). Genetic susceptibility is also an important predisposing factor (4). Studies by Becker (3) and Armaly (5) suggested 3 different levels of genetically predetermined responses to topical steroid administration: high responders (presumed to have primary open-angle glaucoma), intermediate responders, and low responders. In Becker's (3) study, 100% of the participants in the high responder group developed increased intraocular pressures >20 mm Hg compared to only 30% in the low responder group (3).

Recent studies suggest a possible molecular mechanism behind this difference in glucocorticoid response. In general, glucocorticoids alter trabecular meshwork morphology and reduce aqueous humor outflow and thereby elevate intraocular pressures (9). For example, in vitro research has suggested that the differences in the trabecular meshwork expression of glucocorticoid receptor (GR) isoforms α and β are responsible for the regulation of glucocorticoid responsiveness. GRα activates gene transcription whereas GRβ acts as a negative regulator of GRα resulting in decreased gene transcription (9). Lower levels of GRβ are expressed in the glaucomatous trabecular meshwork of cells making them more sensitive to glucocorticoids (9). In addition, the protein FKBP51, a part of the immunophilin family of proteins, detains GRs in the cytoplasm and ultimately reduces the transcriptional activity of glucocorticoids (10). Thus, increased expression of FKBP51 may promote glucocorticoid resistance (10).

It is unknown whether the previously mentioned risk factors for exogenous steroid-induced IOH apply to endogenous hypercortisolism-induced IOH. However, predisposition to IOH from topical steroid administration may increase one's risk of developing IOH when exposed to excess endogenous cortisol. In 1974, Haas and Nootens (11) reported a case of glaucoma caused by CD secondary to an adrenal adenoma. They demonstrated the patient's predisposition to glaucoma by administering topical 0.1% dexamethasone to the patient (after removal of the adrenal adenoma and normalization of intraocular pressures) and confirming redevelopment of IOH (11). Because not all patients with endogenous hypercortisolism develop IOH, the authors concluded that the development of glaucoma secondary to endogenous CD is related to inherent steroid sensitivity.

There may be a genetic predisposition to developing IOH from exogenous and endogenous steroids alike. From previous studies, we can hypothesize that those who develop exogenous steroid-induced IOH also have the potential to develop endogenous hypercortisolism-induced IOH. Therefore, a personal history of steroid-induced IOH or glaucoma and family history of glaucoma are 2 factors that clinicians should be cognizant of when evaluating patients with CD.

Although glaucoma is a rare complication of CD, it is critical to recognize it as a potential manifestation of endogenous hypercortisolism as untreated glaucoma can have grave consequences including irreversible blindness. Knowing the risk factors for steroid-induced glaucoma may lead to prompt, sight-saving interventions in patients with CD.

CONCLUSION

Sight-threatening glaucoma as a complication of CD is not well appreciated in current practice. Our case highlights the importance of recognizing and investigating secondary causes of glaucoma such as endogenous hypercortisolism. This may expedite diagnosis and treatment, thereby preventing irreversible blindness.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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