CASE REPORT

Ocular hypertension secondary to high endogenous steroid load in Cushing's disease

Sofia Noor Habib,¹ Zhiheng Lin,² Narman Puvanachandra¹

¹Ophthalmology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

²Ophthalmology, James Paget University Hospitals NHS Foundation Trust, Great Yarmouth, UK

Correspondence to

Zhiheng Lin,
zlin@doctors.org.uk

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SUMMARY

This case report describes a 35-year-old Caucasian man who was referred to the glaucoma clinic with high intraocular pressure (IOP) after routine optometrist assessment. He was diagnosed with ocular hypertension (OHT) and the management plan was for monitoring without treatment. Three months later, he presented to the endocrine clinic with symptoms of Cushing's disease and was diagnosed with an adrenocorticotrophic hormone secreting pituitary microadenoma. His symptoms preceded his presentation at both departments by 5 years. He underwent definitive surgical treatment of his adenoma via transsphenoidal resection. At 1-year follow-up in glaucoma clinic, it was noted that his IOP had normalised. Due to his high endogenous cortisol level at diagnosis, long disease duration, the pattern of IOP rise and subsequent normalisation after treatment, it is suggestive that his OHT is secondary to his Cushing's disease. There are infrequent reports of this association in published literature.

BACKGROUND

Ocular hypertension (OHT) describes high pressure in the eye without any evidence of glaucoma. Glaucoma describes a progressive optic neuropathy with corresponding visual field defects that may exist with or without high pressure in the eye. OHT can sometimes be a precursor to glaucoma.

Cushing's disease describes pathological hypercortisolism caused by an adrenocorticotrophic hormone (ACTH) secreting pituitary tumour. The clinical manifestations of the disease are caused by endogenous steroid excess. It has been established since 1950 that exogenous ACTH/steroid load can cause OHT/glaucoma; however, cases of Cushing's disease associated with OHT/glaucoma are infrequently published in medical literature.^{1,2}

Described is a case of a 35-year-old male structural engineer who presented with OHT as a manifestation of high endogenous cortisol load caused by an ACTH secreting pituitary adenoma. He complained of a 5-year history of weight gain and change in facial appearance. He had been diagnosed as hypertensive and was treated unsuccessfully with two antihypertensives. If this extended history had been recognised at his first ophthalmology appointment, then it is possible that they could have been linked with his raised intraocular pressure (IOP).

Figure 1 Right then left optic disc photos. The images show symmetrical optic discs with a healthy neuroretinal rim demonstrated by a cup-to-disc ratio of 0.2 in both eyes.

CASE PRESENTATION

A visually asymptomatic 35-year-old Caucasian man presented to glaucoma clinic after his optometrist referred him for high IOP at a routine community assessment. He had no previous ocular history. Systemically, he was noted to be hypertensive on lisinopril and amlodipine, and also overweight. The only risk factors elicited for glaucomatous disease included male gender, smoking status and hypertension.^{3–5}

On examination, the visual acuities in both eyes were normal. IOPs were above the normal threshold at 24 mm Hg in the right eye and 26 mm Hg in the left eye. He had thin central corneal thickness associated with an increased risk of developing glaucoma and contributing to a measurement underestimation of his true IOPs.³ His anterior chamber angles were open in both eyes. His optic discs were assessed as being within normal limits and baseline photographs of these were taken (cf figure 1). His visual fields were normal.

The above findings were consistent with the diagnosis of OHT, and based on National Institute for

Table 1 Cortisol day profile

Time	Cortisol level (nmol/L)
00:00	311
09:00	561
11:00	537
13:00	627
15:00	923
17:00	554
0:00	432

Results show a reduction in diurnal variation where the highest cortisol level would be in the early morning with a subsequent decrease at night.

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Figure 2 T2-weighted MRI pituitary with dynamic contrast sequencing. The image shows a 5 mm poorly enhancing region within the right lobe of the pituitary gland (white arrow) suggestive of a microadenoma.

Health and Care Excellence guidelines, the patient was brought back for annual follow-up to watch for the potential development of glaucoma.⁶

Three months later, the patient had an appointment in the endocrine clinic having been referred by his general practitioner for presumed Cushing's disease. He gave a 5-year history, with particular deterioration in the preceding 10 months of lethargy, weakness, 5-stone weight-gain, 'stretch-marks', easy bruising, labile blood pressure, changes in facial appearance and shortness of breath on exertion. He did not have any psychiatric symptoms. He had no history of exogenous glucocorticoid use and consumes 35 units of alcohol per week. On examination, he was found to have a body mass index of 32.6 kg/m² with marked central obesity, abdominal striae, a buffalo hump, supraclavicular fat pad and flushed facies.

INVESTIGATIONS

Initial investigations included routine bloods, low dose dexamethasone suppression test (LDDST) and 24 hours urine free cortisol. Routine bloods indicated 'prediabetes', additionally total cholesterol and low-density cholesterol were high. LDDST demonstrated a failure of cortisol to be suppressed at a level of 656 nmol/L (reference range, RR: <50 nmol/L). 24 hours urine free cortisol showed a high level of urinary cortisol at 1162, 3680 and 1706 nmol/24 hours (RR: 50.0–300.0 nmol/24 hours). After evidence of pathological hypercortisolism was established, further investigations were requested to determine the underlying cause.

Plasma ACTH was elevated at 82 ng/L (RR: <50.0 ng/L). The cortisol day profile showed loss of diurnal variation (cf table 1). MRI pituitary with dynamic contrast sequencing revealed a

5 mm poorly enhancing region within the right lobe of the pituitary gland suggestive of a microadenoma (cf figure 2). The optic pathways were normal. Unfortunately, petrosal venous sampling was significantly delayed, but it demonstrated an asymmetrical central-to-peripheral ratio of 4:1 helping to localise the increased ACTH secretion to the right pituitary lobe (cf table 2). CT chest, abdomen and pelvis excluded any source of ectopic ACTH secretion in the chest. It showed bilateral small adrenal nodules presumed to be adenomas in keeping with a history of Cushing's disease.

DEXA scan was requested due to the secondary risk of osteoporosis, bone density was acceptable with a T-score of −1 for lumbar spine and 1.4 for total left hip (RR: > −1).

DIFFERENTIAL DIAGNOSIS

A patient presenting to the hospital ophthalmology service with raised IOPs at optometry screening may have a false-positive reading, secondary high IOP for example, iatrogenic or due to another disease process, OHT or glaucoma.

A patient presenting to the endocrine service with signs of hypercortisolism may be taking exogenous steroids, have a non-ACTH dependent syndrome with causes including adrenal adenoma or ACTH-dependent disease with causes including pituitary or ectopic adenomas. Depression or alcohol abuse may lead to high cortisol levels and may also have non-specific manifestations of hypercortisolism such as weight gain, which can present a diagnostic dilemma.

TREATMENT

The hospital ophthalmology service gave this man a diagnosis of OHT and the management plan was for annual monitoring without treatment.

The endocrine team diagnosed an ACTH secreting pituitary adenoma or Cushing's disease and started him on metyrapone for symptomatic relief.⁷ Metyrapone is a competitive inhibitor of 11β-hydroxylation in the adrenal cortex which acts to reduce cortisol levels.⁸

Following discussion at a multidisciplinary team meeting between medical and surgical teams, it was agreed that definitive surgical treatment via transphenoidal resection of his pituitary adenoma was the best option.

OUTCOME AND FOLLOW-UP

After hypophysectomy, this man achieved chemical remission and was started on steroid replacement. Histology showed a pituitary adenoma with diffuse ACTH expression, and no atypical change. He was transferred from the neurosurgical team back to the endocrine team. He no longer requires antihypertensives and is achieving a stable weight-loss. Despite a successful surgical and chemical outcome, he remains troubled by symptoms of low-mood (which developed just prior to his surgery), lethargy and proximal myopathy. Additionally, although initial

Table 2 Petrosal venous sampling

Time (min)	Adrenocorticotrophic hormone (ACTH) left (ng/L)	ACTH right (ng/L)	ACTH peripheral (ng/L)	Central: peripheral ratio	Side-to-side ratio
0	63.5	64.9	62.8	1.03	1.02
5	130	354	85.3	4.1	2.71
10	181	179	140	1.2	0.9

Results show an asymmetrical central-to-peripheral ratio of 4:1 (grey) indicating increased ACTH secretion in the right pituitary lobe.

Table 3 Ocular manifestations of hypercortisolism

Endogenous	Both endogenous and exogenous
Vertical visual field defects, typically bitemporal	Ocular hypertension
Extraocular movement palsies following pituitary apoplexy	Central serous chorioretinopathy
	Cataracts

DEXA scan results were within normal limits, he developed osteoporosis and a resultant vertebral crush fracture.

At this man's 1-year follow-up with the hospital ophthalmology service, his IOP normalised to 17 mm Hg in the right eye and 16 mm Hg in the left eye. This was after his subsequent diagnosis and treatment of his Cushing's disease. With hindsight, an association was realised between his previous OHT and Cushing's disease. Further history on this occasion revealed the preceding 5 years of Cushing's disease symptoms and on examination signs of this such as moon facies and a buffalo hump were still evident. Repeat automated static perimetry was performed and again no visual field defect was apparent.

It is the opinion of his clinical team that the severity of his symptoms including his OHT was due to the long duration and high intensity of endogenous cortisol load caused by his ACTH secreting pituitary adenoma.

DISCUSSION

Ocular manifestations of hypercortisolism depend on whether the source is exogenous or endogenous (cf table 3). The link between OHT/glaucoma and exogenous steroid load has been extensively documented in published literature.⁹ However, there are few published cases linking OHT/glaucoma and endogenous steroid load secondary to an ACTH secreting pituitary adenoma.^{10–14} In these patients, there may be no bitemporal or mixed vertical field defect particularly in microadenomas (<10 mm) or macroadenomas (>10 mm) less than 2.2 cm.^{15 16} Therefore, in these patients, there may be no indication on ophthalmic examination for investigation of endocrine/intracranial disease: this highlights the need for an extended history in young patients who present atypically.

Interestingly, in three similar cases in the literature, definitive surgical treatment of the tumour resulted in a normalisation of the IOP.^{10 11} One of the patients in the three cases went on to develop a sudden relapse in high IOP which proved to be an indicator of re-emergence of their pituitary tumour. Although this is only a small group of patients, their case pattern seems to suggest that the aetiology of their high IOP is associated to their Cushing's disease process, probably due to the excessive endogenous cortisol secretion. The cases also highlight that ongoing ophthalmic follow-up in the community or by the hospital

eye service may be useful in assessing early relapse of pituitary adenomas.

Learning points

- An extended history at the first assessment may have pointed to the association of his ocular hypertension with Cushing's disease and led to an earlier diagnosis.
- It is important to consider other factors causing ocular hypertension in young patients who present atypically.

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