CASE REPORT

An unusual case of Cushing's syndrome due to bihormonal ACTH–prolactin secreting pituitary macroadenoma with rapid response to cabergoline

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SUMMARY

A 23-year-old man presenting with florid Cushing's syndrome was found to have high plasma ACTH and very high serum prolactin. Pituitary MRI showed a large invasive macroadenoma. Low-dose cabergoline promptly suppressed both ACTH and prolactin levels within 2 weeks, with unexpected clinical and biochemical hypocortisolism requiring hydrocortisone replacement. Secondary hypogonadism was reversed. Clinical and biochemical remission of his Cushing's syndrome together with significant shrinkage of his macroadenoma has been maintained for 1 year on cabergoline 0.5 mg twice weekly. Reduction in pituitary tumour volume and brisk fall in serum prolactin in response to low-dose cabergoline is regularly observed in patients with macroprolactinomas, but the concurrent fall in the plasma ACTH level and hypocortisolism was a pleasant surprise. We assume that he most likely has a single bihormonal adenoma that is enriched with dopamine-2 receptors.

BACKGROUND

Plurihormonal pituitary adenomas have been clearly described in medical literature as functional tumours that secrete two or more pituitary hormones. Most of these plurihormonal adenomas are associated with acromegaly. Although concomitant hyperprolactinaemia is present in approximately 20%–30% of Cushing's disease (CD), this is usually mild. Bihormonal secretion of ACTH and prolactin is very rare. We present a case of Cushing's syndrome due to a pituitary macroadenoma with dual secretion of ACTH and prolactin, responsive to low-dose cabergoline treatment.

CASE PRESENTATION

A 23-year-old Indian man was investigated for suspected Cushing's syndrome. He presented with a 6-month history of rapid weight gain, lethargy and recurrent mild headaches. Clinical examination revealed florid Cushing's syndrome with typical facies, central obesity, dark striae, pigmented finger nails and acanthosis nigricans on his posterior neck and axilla. His blood pressure was elevated at 150/110 mm Hg. He had no visual impairment, gynaecomastia or galactorrhoea. He was not known to have any other pre-existing co-morbidity and was not on any regular medication, other than a combination of ACE inhibitor/thiazide diuretic, recently commenced for treatment of hypertension.

INVESTIGATIONS

Hormonal testing revealed hypercortisolaemia, hyperprolactinaemia (40 724 mIU/L, reference range: 70–300 mIU/L) and hypogonadotropic hypogonadism. He had markedly elevated 24-hour urinary free cortisol (6309 nmol/L, reference range: 100–400 nmol/L), non-suppressible plasma cortisol after 1 mg dexamethasone (cortisol=906 nmol/L, reference range: <50 nmol/L) but suppressible with 8 mg dexamethasone (35 nmol/L, reference range: <50 nmol/L) and elevated ACTH level (40 pmol/L, reference range: 2–11 pmol/L) consistent with pituitary-based CD. Laboratory investigation results are as summarised in [table 1](#).

MRI confirmed a 3.7×1.9×2.1 cm pituitary macroadenoma filling the pituitary fossa with extension into the sphenoid sinus and both cavernous sinuses ([figure 1](#)). Some suprasellar extension was present on the right side causing optic nerve displacement without chiasmal compression. Formal visual field testing was normal.

DIFFERENTIAL DIAGNOSIS

The diagnosis of a bihormonal pituitary macroadenoma secreting both ACTH and prolactin was made.

TREATMENT

He was commenced on cabergoline 0.5 mg twice weekly.

OUTCOME AND FOLLOW-UP

Within 2 weeks of starting treatment, he began to experience persistent headache, nausea and anorexia. Initially, this was thought to be a side effect of the dopamine agonist and the cabergoline dose was halved. However, this dose reduction had no impact on his symptoms. His serum prolactin concentration fell to 3521 mIU/L, plasma cortisol to 102 nmol/L and serum testosterone rose to normal at 12.2 nmol/L.

Cortisol deficiency was then diagnosed (102 nmol/L, reference range=180–500 nmol/L) and he was commenced on a replacement dose of hydrocortisone with immediate clinical response. The cabergoline dose was later increased to 0.5 mg twice weekly. After 2 weeks, his blood pressure normalised and his antihypertensive treatment was stopped. He lost 5 kg of weight and his abdominal circumference decreased by 11 cm. He remained well

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Table 1 Baseline laboratory investigations and response to treatment

Results	Basal	Week 2	Week 16	Week 32*	1 year	Reference range
09:00 plasma cortisol	874	102	99		425	180–500 nmol/L
24-hour urinary free cortisol	6309					100–400 nmol/L
1 mg dexamethasone suppression test	906				27	<50 nmol/L
8 mg dexamethasone test	35					<50 nmol/L
ACTH	40	8	<10		8	2–11 pmol/L
Testosterone	3.6	12.2			10.2	8–29 nmol/L
FSH	2.5				1.8	2–12 IU/L
LH	3.0				3.9	2–9 IU/L
Prolactin	40 724	3521	974	1206*	814	70–300 mIU/L
IGF-1	−0.1					Up to 2 SD
Growth hormone	1.4					0–24 µg/L
Blood pressure	150/110	135/90	114/50		100/70	mm Hg
Pituitary dimensions/vol	3.7×1.9×2.1 cm=vol 14.7 mL		2.4×1.6×1.4 cm=vol 5.4 mL	1.9×1.1×0.9 cm=Vol 3.6 mL*		
Metrapone test					11-deoxycortisol=328	>200 nmol/L

*Investigation carried out at an overseas centre in India using different magnetic resonance scanner and laboratory assay.

on cabergoline 1 mg per week and a replacement dose of hydrocortisone of 15 mg per day. A follow-up MRI was performed after 4 months and demonstrated reduction in size of the macroadenoma to 2.4×1.6×1.4 cm. Assuming a spherical neoplasm for the calculation of volume, this indicates an approximate 2/3 volume reduction from 14.8 to 5.4 mL. There was no evidence of pituitary infarction or apoplexy.

Follow-up investigations at 32 weeks performed in an overseas centre (India) showed further reduction in the size of adenoma on MRI (figure 2) and persisting biochemical response to cabergoline. On return to New Zealand 1 year post initial diagnosis, he remained in remission from the CD along with persistent control of hyperprolactinaemia on cabergoline therapy (table 1). Off hydrocortisone supplements, he now has a normal baseline serum cortisol, normal cortisol suppression after 1 mg overnight

dexamethasone and normal overnight metyrapone test, as summarised in table 1, indicative of a normal HPA axis.

Figure 3A,B and figure 4A,B depict his physical changes pretreatment and post treatment.

DISCUSSION

Pituitary adenomas secreting both ACTH and prolactin are very rare. Table 2 summarises the findings in six other published cases of bihormonal ACTH–prolactin secreting adenomas.^{1–6}

Pituitary tumours are the most common intracranial neoplasm with a prevalence of 200/100 000 and an incidence of 2/100 000.⁷ An analysis of immunohistochemical examination of 3403 pituitary adenomas in a large German Registry⁷ revealed that 66.5% of these tumours were monohormonal, 6.5% were bihormonal

Figure 1 T1 and T2 coronal dynamic enhanced post gadolinium contrast MRI brain demonstrating large pituitary macroadenoma with extension into the sphenoid sinus and cavernous sinuses with suprasellar extension on the right causing optic nerve displacement.

Figure 2 T1 and T2 coronal dynamic enhanced post gadolinium contrast MRI brain demonstrating reduction in overall tumour bulk following 32 weeks of cabergoline treatment. Reduced enhancement suggesting loss of vascularity following treatment. Enhancing tissue in the sella is the normal pituitary gland.

(GH and PRL), 1.3% expressed more than two hormones and 25.6% did not express any hormones.⁷

There have been few reports of multiple distinct pituitary adenomas synchronously secreting different hormones. In a surgical series of 117 patients, three were found to have co-existing double pituitary adenomas.⁸ The presence of two or more distinct lesions on MRI may aid in differentiating double adenomas from a plurihormonal adenoma; however, definitive diagnosis is not possible without pathological examination.⁸

Surgical intervention is presently not indicated for control of either his mass lesion or CD. We think it most likely that he

has a single large bihormonal secreting macroadenoma, which is enriched with dopamine-2 (D2) receptors. This opinion is based on the initial MRI appearance of an atypical invasive macroadenoma, his unusual sensitivity to cabergoline and the rate and degree of reduction of serum levels of both ACTH and prolactin.

Cabergoline, a D2 receptor agonist, is the established first-line therapy for *prolactinomas*.⁹ A macroprolactinoma typically responds quickly to cabergoline and such adenomas show intense immunohistochemical staining for DA2 receptors when compared with other pituitary adenomas.^{9,10} There appears to be a widening role for cabergoline therapy in pituitary non-prolactinomas.

The first-line therapy for CD is surgical resection of the adenoma, which is typically a small microadenoma of median size 3 mm. Medical therapy is usually sought only when surgery is deemed unsuitable. D2 receptors have a variable and heterogeneous expression in nearly 90% of all types of pituitary tumours and are expressed in the corticotroph cells of the anterior pituitary, as well as the melanotroph cells in the intermediate lobe of the pituitary gland.¹¹

Although approximately 80% of ACTH secreting pituitary tumours express D2 receptors,¹² a prospective study of 6-week treatment with cabergoline found this to be of limited value.¹³ Conversely, a review of cabergoline treatment of 88 patients with CD in five studies reported control of CD in 31% of patients, but escape occurred in one third during the 12–24 months follow-up period.¹¹

In our patient, we were able to demonstrate significant biochemical and clinical response of both ACTH and prolactin that persists after 12 months of therapy to date, together with

Figure 3 (A) Facial appearance at presentation and (B) at 1 year post treatment.

Figure 4 Abdominal appearance with striae (A) at presentation and (B) 1 year post treatment.

marked tumour shrinkage. What was most unusual was the rapid remission of CD to the extent of developing hypocortisolism in the absence of pituitary infarction/apoplexy, which has not previously been described. The biochemical remission of CD is comparable to another case report of an isolated ACTH secreting pituitary adenoma¹⁴ where a 47-year-old woman with CD underwent surgical resection of a 3 cm ACTH secreting adenoma. Histopathology confirmed high levels of D2 receptor expression. The remnant adenoma was then treated with

cabergoline with successful biochemical remission in 90 days and tumour shrinkage at 6 months.¹⁴

Normalisation of testosterone deficiencies have been described in most patients treated with cabergoline for macroprolactinomas or microprolactinomas after 6 months.¹⁵ Prolactin is thought to effect sexual steroid secretion by suppressing LH pulse frequency and by regulating levels of testosterone precursors for conversion under the influence of LH.^{16 17}

Table 2 Summary of previous case reports published in comparison to present case

Case #	Comments	Anatomy (cm)	Biochemistry: Prolactin (mIU/L), cortisol (nmol/L) and ACTH (pmol/L)	Management	Response to DA	Ref
1.	59 y/o male. Presented with Cushing's disease. Histology=70% immunoreactive PRL cells and 5% ACTH cells.	Macroadenoma (NA)	PRL=20246 Cortisol=872 ACTH=14	Surgery	NA	1
2.	13 y/o male. Presented with Cushing's disease and visual field defect.	Macroadenoma (NA)	PRL=636 000 Cortisol=574 ACTH=n/a	Bromocriptine	Yes — PRL, ACTH and tumour size	2
3.	36 y/o male. Presented with Cushing's syndrome and hypogonadism. Immunostaining positive for PRL and ACTH.	Macroadenoma (2.2 cm)	PRL=94 679 Cortisol=803 ACTH=47	Surgery with cure of CD. Post-op hyperprolactinaemia treated with bromocriptine	Only PRL	3
4.	42 y/o female. Presented with hyperprolactinoma. Initially treated ? Cabergoline. Developed CD 1 year later despite DA, requiring surgery. Immunostaining for both ACTH + PRL	Macroadenoma (NA)	PRL=269 664 Cortisol=966 ACTH=50	Cabergoline then surgery.	Only PRL	4
5.	31 y/o male. Presented with Cushing's disease	Macroadenoma (1.5 cm)	PRL=17 850 Cortisol=1313 ACTH=25	Cabergoline	Yes — PRL and ACTH	5
6.	38 y/o female presented with Cushing's syndrome and hypogonadism.	Macroadenoma (3 cm)	PRL=41 424 Cortisol=466 ACTH=18	Cabergoline	Only PRL. Persistent Cushing's with no change to tumour size over 6 months.	6
7.	Present case. Assumed bihormonal with sustained response to cabergoline over 1 year.	Macroadenoma (3.7 cm)	PRL=40 724 Cortisol=874 ACTH=40	Cabergoline	YES — PRL, ACTH and tumour size.	This report.

y/o, year old.

The rapid improvement in serum testosterone levels with cabergoline suppression of serum prolactin in our patient is interesting. Dr Rosa and colleagues found that serum testosterone rose 15 days after starting cabergoline treatment in patients with prolactinomas, and a similar improvement was seen within 1 month of commencing cabergoline in prolactinoma patients by Bhansali *et al.*^{18 19} This rapid improvement, similar to the finding in our patient, raises the possibility that the testes in hyperprolactinaemic individuals may contain synthesised testosterone which is not being secreted, and lowering prolactin levels allows hormone secretion to proceed promptly.

The responsiveness of pituitary adenomas to cabergoline ultimately depends on the intensity and number of D2 receptors in the adenoma. Our patient with a presumed co-secreting ACTH-PRL macroadenoma has shown a remarkable response to cabergoline. We hope that this response is sustained in the long term.

Patient's perspective

'Upon reflection, I am happy because I feel that my rare condition was diagnosed promptly. Initially I thought that my physical symptoms were simply due to rapidly gaining weight with the change in diet after travelling overseas. Overall, I am very glad that my symptoms have resolved promptly with simple oral medication. I feel relieved that I do not require pituitary surgery at present and am not anxious about my future health. I understand the need for long-term follow up and that surgery may still be required in the future if symptoms and biochemical abnormalities return.'

Learning points

- ▶ While dual prolactin/cortisol secreting pituitary macroadenomas presenting as Cushing's disease are very rare, the regular measurement of prolactin in patients with Cushing's disease is needed to prevent such diagnoses from being missed, which respond very well to cabergoline therapy.
- ▶ Development of nausea, headaches and anorexia after cabergoline treatment in cases of Cushing's disease due to dual prolactin/cortisol secreting pituitary macroadenomas may be a manifestation of hypocortisolism requiring transient hydrocortisone supplementation.
- ▶ More rapid normalisation of serum testosterone may be seen in dual prolactin/cortisol secreting pituitary macroadenomas treated with cabergoline than single hormone pituitary macroadenomas secreting either prolactin or cortisol.

Contributors SK has produced the report and literature review. RM and MSC were involved in the patients' clinical care and contributed to the writing. IH provided guidance and contributed to the writing.

Competing interests None declared.

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