CASE REPORT

Paradoxical response to dexamethasone and spontaneous hypocortisolism in Cushing's disease

Anurag R Lila, Vijaya Sarathi, Tushar R Bandgar, Nalini S Shah

Department of Endocrinology,
Seth GS Medical College,
Mumbai, Maharashtra, India

Correspondence to

Dr Vijaya Sarathi,
drvijayasarathi@gmail.com

SUMMARY

Paradoxical response to dexamethasone and spontaneous development of hypocortisolism are rare features of Cushing's disease. We report a 13-year-old boy with Cushing's disease owing to a pituitary macroadenoma. On initial evaluation, he had partial suppression of serum cortisol by dexamethasone. He developed transient hypocortisolism after first adenectomy, but the disease recurred after 1 year. Repeat evaluation showed recurrent hypercortisolism and paradoxical response to dexamethasone. He underwent second surgery and, postoperatively, hypercortisolism persisted even after 2 years of surgery. Repeat evaluations after 8 years of second surgery revealed persistent hypocortisolism despite residual tumour of same size and similar plasma adrenocorticotrophic hormone (ACTH) levels. We have also shown that the paradoxical increase in serum cortisol was preceded by a paradoxical increase in ACTH. The paradoxical response persisted despite hypocortisolism. This patient with Cushing's disease had two very rare features: paradoxical response to dexamethasone and spontaneous development of hypocortisolism.

BACKGROUND

Paradoxical response to dexamethasone is a classical feature of Cushing's syndrome owing to primary pigmented nodular adrenocortical disease.¹ However, this kind of abnormal response has also been rarely described in other types of Cushing syndrome including Cushing's disease (CD).¹⁻² Spontaneous development of hypocortisolism in CD is also a very rare entity. We report a case of CD characterised by both these rare features.

CASE PRESENTATION

A 13-year-old boy with weight gain, moon face, abdominal striae and growth failure was found to have adrenocorticotrophic hormone (ACTH) dependent endogenous hypercortisolism (table 1). CT scan showed a pituitary macroadenoma. He underwent transfrontal adenectomy in October 1999. Histopathology showed a pituitary adenoma with positive immunostaining for ACTH. Basal cortisol was 3 µg/dl on the fifth postoperative day and was started on hydrocortisone replacement. At 3 months after surgery, Cushingoid features had diminished with basal serum cortisol of 12.5 µg/dl and ACTH (250 µg)-stimulated serum cortisol level of 21.4 µg/dl. Hence, hydrocortisone replacement was stopped.

Evaluation after 1 year of surgery revealed reappearance of Cushingoid features with evidence of endogenous hypercortisolemia. MRI showed a pituitary macroadenoma encasing the right cavernous-carotid region. Repeat adenectomy was performed via a trans-sphenoidal approach in January 2001 and basal cortisol on the fifth postoperative day was 14.8 µg/dl. The patient was lost to follow-up for the next 1.5 years. On reinvestigation in October 2002, hypercortisolism and tumour persisted (table 1). Pituitary radiotherapy was recommended, but the family preferred conservative management. Adrenolytic medications were not started, as frequent follow-up was not feasible.

In May 2008, he returned with the complaints of obesity and poor secondary sexual characteristics. Basal cortisol was 3.23 µg/dl with basal ACTH of 94.1 pg/ml. Sleeping midnight serum cortisol was 4.49 µg/dl. Surprisingly, there was a paradoxical rise in serum cortisol to 49.7 µg/dl after a standard 2-day, 2 mg dexamethasone test. The review of previous responses to dexamethasone suggested paradoxical responses on all occasions except for the first (table 1).

He also had biochemical evidence of secondary hypothyroidism and hypogonadotropic hypogonadism and replaced accordingly. ACTH-stimulated cortisol was 10.2 µg/dl and he was started on hydrocortisone replacement.

INVESTIGATIONS

In January 2009, his initial evaluation revealed similar findings as that in May 2008 (table 1). Then, he was subjected for a detailed hormonal evaluation. After collection of blood for basal cortisol, basal ACTH, midnight cortisol and midnight ACTH, a 2 mg dexamethasone test was started. Blood samples for cortisol and ACTH were collected from day 1, at 08:00, 16:00, and 23:00 h and then daily until cortisol concentrations returned to near baseline, after the paradoxical rise. Serum cortisol increased from a basal concentration of 4.9 to 48 µg/dl and plasma ACTH from 75 to 359 pg/ml. It took 5 days after stoppage of the drug for ACTH and cortisol to return to baseline (figure 1). An MRI scan showed a pituitary macroadenoma.

TREATMENT

The patient is continued on hydrocortisone, testosterone and thyroxine replacement.

To cite: Lila AR, Sarathi V, Bandgar TR, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-008035

Table 1 Hormonal profile of pituitary adrenal function tests from September 1999 to January 2009.

	September 1999	October 2000	December 2000	October 2002	May 2008	January 2009
B cortisol ($\mu\text{g/dl}$)	55.39	20.16	17.9	13.8	3.23	4.16
B ACTH (pg/ml)	60.1			68.1	94.1	95
Midnight cortisol ($\mu\text{g/dl}$)			16.5	15.9	4.49	3.99
Midnight ACTH (pg/ml)			84.9	75	50.2	81.6
Standard 2-day, 2 mg test ($\mu\text{g/dl}$)	20.58	44.67	45.7	59.2	49.7	48
Overnight 8 mg test ($\mu\text{g/dl}$)	14.58					
Size of pituitary adenoma (mm)	19 X17X17		18X12 X10		15X14 X14	
	First surgery (October 1999)		Second surgery (January 2001)			

ACTH, adrenocorticotrophic hormone

OUTCOME AND FOLLOW-UP

At present, on telephonic follow-up, the patient is clinically asymptomatic on hormonal replacement and does not have any symptoms suggestive of visual field defects or raised intracranial tension. He was advised to watch for recurrence of Cushingoid features, symptoms of hypocortisolism and appearance of visual field defects or signs of raised intracranial tension and report immediately if any such serious features appear.

DISCUSSION

We report a paradoxical response to dexamethasone in a patient with CD due to a pituitary macroadenoma. In this patient, we also demonstrated the persistence of the paradoxical response to dexamethasone few days after stopping the drug.

Variable hormonogenesis is one of the explanations for a paradoxical response to dexamethasone in CD patients.³ Because of highly variable duration and regularity of cycles, it may be difficult to distinguish periodic hormonogenesis from other mechanisms of paradoxical response.⁴ However, owing to the consistent paradoxical response on several occasions, periodic hormonogenesis is less likely in our patient.

In our case, after starting dexamethasone, the rise in ACTH preceded the rise in cortisol, which suggests that the paradoxical response was likely mediated via the pituitary gland. ACTH rise has also been demonstrated in previous reports of paradoxical response to dexamethasone in patients with CD.⁵ In cultured pheochromocytoma cell lines with ectopic ACTH secretion,

dexamethasone-stimulated the production of ACTH-related peptides.⁶ In vivo metyrapone reduced the concentrations of ACTH precursors by 10-fold, suggesting positive feedback by glucocorticoids on ACTH precursor production.⁶ A similar mechanism may occur in corticotrope adenoma cells leading to feed-forward glucocorticoid stimulation of proopiomelanocortin (POMC), which may cause secretion of ACTH precursors. However, we could not avail POMC values which would have better substantiated this hypothesis.

In our case, dexamethasone partially suppressed the corticotroph adenoma on first evaluation (preoperative). After the first operation, tumour changed its character to respond paradoxically to dexamethasone. During the transition period from partial suppression to paradoxical response, there was a period of hypocortisolism (basal cortisol $3.0 \mu\text{g/dl}$). It may be possible that sudden hypocortisolism could have altered the tumour behaviour, resulting in feed-forward regulation of ACTH precursors by glucocorticoids. In a previous study, glucocorticoid infusion caused a transient paradoxical rise in ACTH in patients with postadrenalectomy CD, but not in Addison's disease.⁷ Paradoxical rise of ACTH in postadrenalectomy CD who were hypocortisolemic may support this hypothesis.

After 10 months of second surgery, he had documented persistent hypercortisolism. Subsequently, he developed hypocortisolism with slightly elevated ACTH, large residual tumour, loss of circadian rhythm and paradoxical response to dexamethasone. Spontaneous hypocortisolism after such a long period of surgery may be because of dedifferentiation of the tumour-producing bioinactive ACTH. Abnormal POMC processing, leading to high-molecular-weight ACTH, has been described with invasive corticotroph adenomas without clinical signs of Cushing's syndrome.⁸ Patients with corticotroph macroadenomas also have reduced processing of POMC to ACTH, a characteristic that is usually associated with the ectopic ACTH syndrome.⁹

The pituitary corticotroph macroadenoma of our patient behaved like a chameleon, changing its colours. The tumour changed its character in its response to dexamethasone from partial suppression to paradoxical response. It also changed its character from hypercortisolism to hypocortisolism spontaneously with same-sized tumour and same level of plasma ACTH.

A case of CD due to pituitary macroadenoma has been reported to have paradoxical response to dexamethasone after adenomectomy, and hypocortisolism occurred over the subsequent years.¹⁰ To the best of our knowledge, our patient is the second case to be characterised by both these rare features.

Figure 1 Concentration of cortisol and adrenocorticotrophic hormone before, during and after standard 2-day, 2 mg dexamethasone test.

Learning points

- ▶ Paradoxical response to dexamethasone may be seen in Cushing's disease, especially in those with pituitary macroadenoma.
- ▶ Paradoxical increase in serum cortisol was preceded by increase in plasma adrenocorticotrophic hormone (ACTH) suggesting it to be a pituitary (corticotroph) adenoma response.
- ▶ Spontaneous hypocortisolism can occur in Cushing's disease even with a same-sized tumour and the same level of plasma ACTH.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Stratakis CA, Sarlis N, Kirschner LS. Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease. *Ann Intern Med* 1999;131:585–9.
- 2 Alexandraki KI, Kaltsas GA, Isidori AM, *et al*. The prevalence and characteristic features of cyclicity and variability in Cushing's disease. *Eur J Endocrinol* 2009;160:1011–18.
- 3 Brown RD, Van Loon GR, Orth DN. Cushing's disease with periodic hormonogenesis: one explanation for paradoxical response to dexamethasone. *J Clin Endocrinol Metab* 1973;36:445.
- 4 Shapiro MS, Shenkman L. Variable hormonogenesis in Cushing's syndrome. *QJM* 1991;79:351–63.
- 5 Checchi S, Brilli L, Guarino E, *et al*. Cyclic Cushing's disease with paradoxical response to dexamethasone. *J Endocrinol Invest* 2005;28:741–5.
- 6 Liu J, Heikkilä P, Voutilainen R. Pheochromocytoma expressing adrenocorticotropin and corticotropin-releasing hormone; regulation by glucocorticoids and nerve growth factor. *Eur J Endocrinol* 1994;131:221–8.
- 7 Fehm HL, Voight KH, Lang RE. Paradoxical ACTH response to glucocorticoids in Cushing's disease. *N Engl J Med* 1977;297:904–7.
- 8 Reincke M, Allolio B, Saeger W. A pituitary adenoma secreting high molecular weight adrenocorticotropin without evidence of Cushing's disease. *J Clin Endocrinol Metab* 1987;65:1296–300.
- 9 Gibson S, Ray DW, Crosby SR. Impaired processing of proopiomelanocorticotropin in corticotroph macroadenomas. *J Clin Endocrinol Metab* 1996;81:497–502.
- 10 Peacock I, Jeffcoate WJ. Corticotrophic macroadenoma of the pituitary associated with hypoadrenalism. *Clin Endocrinol* 1997;46:765–8.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow