CASE REPORT

Cyclical Cushing's: how best to catch the ups and downs

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SUMMARY

A 68-year-old man with a background of hypertension and type 2 diabetes presented with fluctuating symptoms of muscle aches and pains and tiredness. His initial work-up for the possibility of hypercortisolaemia showed a completely variable pattern, with 24-hour cortisol excretion and serum cortisol post 1 mg dexamethasone suppression test ranging from normal to significantly elevated. A series of salivary cortisol with symptom diary confirmed the cyclical nature of hypercortisolaemia, and his concomitant adrenocorticotrophic hormone (ACTH) levels were elevated. An inferior petrosal sinus sampling, performed during hypercortisolaemic phase of his cycle, suggested a central source of ACTH secretion. He had unsuccessful exploration of his pituitary and was eventually treated with bilateral adrenalectomy followed by lifelong steroid replacement. His symptoms improved immediately, and he came off his oral hypoglycaemic and antihypertensive agents within 6 months following his surgery.

BACKGROUND

Cyclical Cushing's syndrome (CCS) is a very rare disease and is characterised by the rhythmic fluctuations in cortisol production. This causes fluctuating symptoms with or without classical phenotypic features of cortisol excess. The cycles of cortisol excess can vary in their duration and severity. The precise mechanism of cyclical or intermittent hypersecretion of adrenocorticotrophic hormone (ACTH) or cortisol remains unclear.¹ It is extremely important to establish this diagnosis because if not recognised promptly, it can lead to errors in diagnosis and differential diagnosis and can lead to long-term complications.² The most common aetiology for the cyclical Cushing's is pituitary (ACTH) dependent. However, several other sources of cortisol excess have been reported, including primary adrenal disease, carcinoid tumours, and in ectopic ACTH production from the various tumours.^{3,4}

The diagnosis of cyclical Cushing's can be quite challenging and often requires a very close follow-up of the patient and request of the appropriate biochemical investigations at the appropriate time.⁵⁻⁷ This is time-consuming and can be frustrating for the patients and their families.

CASE PRESENTATION

A 68-year-old male pharmacist with a 3-year history of type 2 diabetes and hypertension was referred

to endocrine clinic for evaluation of a possible adrenal insufficiency due to his symptoms of episodic muscle aches and pains, extreme tiredness, increased sweating and generalised skin pigmentation. In the clinic, he also described symptoms of polydipsia, nocturia and difficulty in climbing the stairs, but there was no history of change in weight. His symptoms were intermittent and occurred at least twice a month, during which his myalgia would make it very difficult for him to walk. His blood sugars were fluctuant, with levels ranging between 3 and 20 mmol/L.

His medical history included hypertension and benign prostatic hypertrophy. His regular medications included glimepiride 2 mg once daily, aspirin 75 mg once daily, amlodipine 10 mg once daily and tamsulosin 400 µg once daily.

His biochemical work-up done prior to his referral showed a normal short synacthen test, normal pituitary profile including prolactin, thyroid function test, gonadotrophic profile (luteinizing hormone, follicle-stimulating hormone testosterone and free androgen index), liver function test, urea, electrolytes, B₁₂, folate, ferritin and chest X-ray.

On examination his blood pressure (BP) was 160/80 mm Hg, and he was diffusely pigmented with prominent pelvic girdle weakness, but there were no other phenotypic features of Cushing's.

In view of his proximal muscle weakness and increased pigmentation, he had initial screening tests for Cushing's, which showed a high 24-hour urinary free cortisol (UFC) level of 573 nmol/day (reference <270). He failed to suppress on a 1 mg overnight dexamethasone suppression test with initial postdexamethasone 09:00 cortisol level of 228 nmol/L (reference <50). His ACTH was elevated at 48 and 98 ng/L (reference range 5–40) at two different occasions.

In view of intermittent symptoms and the absence of significant phenotypic features of Cushing's, he underwent a series of 24-hour UFC assessments, which showed a huge variation with levels ranging from normal to as high as 19 000 nmol/day (reference <270) (table 1). Analysis of the urine sample with very high free cortisol levels (19 000 nmol/day) at a different biochemistry lab confirmed the high cortisol levels, ruling out any possibility of assay interference. High ACTH levels also suggested against exogenous use of steroids, as a working pharmacist he had daily access to medications. A low-dose dexamethasone suppression test did not show suppression, with a 09:00 cortisol at 48 hours of 1108 nmol/L (reference <50).

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Table 1 Urinary free cortisol levels

Date	Urine free cortisol, nmol/24 hours (ref <260)
15 January 2011	573
16 January 2011	320
14 March 2011	19767
21 March 2011	2052
23 March 2011	2971

In view of fluctuating hypercortisolaemia, it was decided to measure daily late-night salivary cortisol levels along with a symptoms diary to confirm the cyclical pattern of cortisol secretion and also to review if his symptoms were related to the cortisol spikes. His initial salivary cortisol results ([figure 1](#)) confirmed a cyclical pattern, with the cortisol troughs matching his symptoms, and further evaluations confirmed that his cycles lasted for 3–5 days and his symptoms corresponded to the cortisol nadir. Concomitant normal to high ACTH levels during the hypercortisolaemic phase confirmed the diagnosis of ACTH-dependent CCS.

To investigate the underlying cause for his ACTH secretion (ectopic vs pituitary), he underwent further investigations including a normal pituitary MRI ([figure 2](#)), and a subsequent CT chest/abdomen/pelvis and a nuclear medicine octreotide scan (single-photon emission computed tomography - SPECT CT) were also normal. His 5-hydroxyindoleacetic acid and chromogranin A levels were negative, suggesting against the possibility of underlying carcinoid syndrome. An inferior petrosal sinus sampling (IPSS) was planned. IPSS is an invasive procedure in which ACTH levels are sampled from the veins that drain the pituitary gland; these levels are then compared with the ACTH levels in the peripheral blood to differentiate between a pituitary and ectopic source of ACTH secretion. A central-to-peripheral ACTH maximal ratio ≥ 2 in basal conditions and ≥ 3 at any time point after corticotropin-releasing hormone (CRH) stimulation is strongly suggestive of pituitary secretion. The challenge was the cyclical nature of his Cushing's disease with hypercortisolaemia occurring every few days of the month. It was important to verify the hypercortisolaemic phase of his cycle at the time of the intervention so that ACTH levels could be assessed appropriately. Therefore a further series of daily late-night salivary cortisol collection was organised to confirm the appropriate stage of the cycle to make IPSS valuable on that particular day.

Figure 1 Salivary cortisol levels to establish the cyclicity. **Figure 2** Salivary cortisol levels to determine the timing of inferior petrosal sinus sampling.

This was also to be confirmed with an urgent early-morning cortisol levels at the day of procedure.

He could not undergo IPSS at the first two appointments as his salivary and early-morning cortisol levels were suggestive of the 'eucortisolaemic' or 'hypocortisolaemic' phase of the cycle. However, with the help of his symptom diary and daily salivary cortisol levels, it was possible to identify the 'peak of his hypercortisolaemic phase' at the third attempt ([figure 3](#)) and IPSS was done at that point ([table 2](#)). The IPSS values were below the cut-off to diagnose a pituitary source confidently, but it was thought that a pituitary source was more likely than an ectopic source based on the balance of probability, as there was some gradient and patients with ectopic ACTH are expected to have less or no response. Also, ACTH-driven cyclical Cushing's is reported to be mostly of pituitary origin. Based on these factors, a panel of experts decided that it was a reasonable approach to inspect the whole gland and resect any tumour seen during the pituitary exploration.

Following pituitary multidisciplinary team discussion, he proceeded to have pituitary exploration, which proved to be unsuccessful with postoperative cortisol levels of 1790 and was complicated by a pneumocranium and meningitis. His postoperative pituitary function is shown in [table 3](#).

In view of significant ongoing symptoms, he was started on metyrapone and hydrocortisone on the block-and-replace regimen with significant improvement in his symptoms except his girdle weakness and increasing pigmentation of his skin. His glycaemic control also improved significantly. After discussion with the patient, he was referred for bilateral adrenalectomy with a plan to start lifelong steroid replacement after his surgery. He underwent an uneventful laparoscopic bilateral adrenalectomy, and the histology of adrenal glands was consistent with bilateral adrenal hyperplasia.

Figure 3 Salivary cortisol levels to determine the timing of inferior petrosal sinus sampling.

INVESTIGATIONS

Outcome and follow-up

Following his bilateral adrenalectomy, the patient required a combination of hydrocortisone and fludrocortisone replacement. His symptoms improved significantly and he started to develop hypoglycaemic episodes on his oral hypoglycaemic agents, which were eventually stopped. His haemoglobin A1c improved from 70 mmol/mol to 44 mmol/mol 2 months after his bilateral adrenalectomy and remained optimal after stopping his oral hypoglycaemic agents. He also managed to come off his antihypertensive medication within 6 months following his surgery. The patient has not developed any signs or symptoms of Nelson's syndrome in the 3-year follow-up period following his bilateral adrenalectomy.

DISCUSSION

Once the diagnosis of Cushing's has been made, the next step is to confirm the cyclical nature of hypercortisolaemia.² Commonly performed screening tests in UK include 24-hour UFC, first voided early-morning urines measured for cortisol-to-creatinine ratios, or overnight dexamethasone suppression test. All these tests can be quite laborious and require a lot of undertaking on the part of patients and the treating physician and have higher risks of errors.

Late-night salivary cortisol is very easy to perform and a lot easier for patients. The measurement of cortisol in saliva is a simple, reproducible and reliable test to evaluate the normal and disordered control of the hypothalamic–pituitary–adrenal axis.^{7–9} There are a variety of simple methods to obtain saliva samples without stress, making this a robust test applicable to many different experimental and clinical situations.¹⁰ Despite its convenience and accuracy, this has not been widely used in the diagnosis of cyclical Cushing's. Hermus *et al*¹¹ initially

Table 3 Postoperative pituitary profile

	Day 1	2 weeks	6 weeks	3 months
Free T4 (10–22 pmol/L)		18	13	19
TSH (0.3–5.6 mU/L)		2.7	0.78	2.7
IGF-1 (94–255 µg/L)		187		
09:00 cortisol (200–700 nmol/L)	1790	603	1186	
Testosterone (7–26 nmol/L)		3.8	2.8	5.3
Free Androgen Index (>24)		8.1	12.7	24.1
ACTH (0–40 ng/L)	98			

ACTH, adrenocorticotrophic hormone; IGF-1, Insulin Like Growth Factor 1; TSH, Thyroid Stimulating Hormone

reported using daily measurement of salivary cortisol, collected at home, as a convenient and reliable method for detecting intermittent hypercortisolism in patients with Cushing's syndrome. Mosnier-Pudar *et al*¹² also found that measurement of salivary cortisol was a valuable tool in difficult clinical situations such as intermittent hypercortisolism in the outpatient settings.

Recent data suggest the usefulness of measuring hair cortisol in the diagnosis of cyclical Cushing's.¹³ However, the demonstration of hypercortisolaemic phase in cyclical Cushing's would require spot tests like salivary cortisol. Our case demonstrated that salivary cortisol assessment is very useful to establish the cyclical patterns of cortisol rise, which is also helpful in determining the appropriate timing of IPSS. This is because IPSS can only be reliable when performed in the hypercortisolaemic phase of the cycle; hence, a very close cooperation with the laboratory is essential. The timing is quite crucial as cortisol is under direct control of ACTH, and a flat or hypocortisolaemic phase would be associated with low or absent ACTH. This would, therefore, invalidate IPSS, which investigates differences in ACTH levels, both central to peripheral, and potentially could lateralise left to right pituitary lobes. Our case highlights the usefulness of performing late-evening salivary cortisol, and an early-morning serum cortisol level prior to IPSS can avoid the failure of procedure.

Differential diagnosis has to be made very carefully in cyclical disease. Important differentials of CCS include depression, alcohol abuse, aberrant receptor-mediated CCS, factitious CCS and glucocorticoid resistance. Although usually described as a rare phenomenon, a large population study by Alexandraki *et al*¹⁴ revealed that cyclical Cushing's was not an uncommon phenomenon in people with Cushing's, with a prevalence of about 15%.

Treatment depends on the source of cortisol production, and the first plan of action for patients with ACTH-dependent CCS is pituitary surgery. Patients with cyclical Cushing's disease appear to have a higher recurrence rate following a neurosurgical intervention as compared with non-cyclical Cushing's disease. It is also very challenging to establish a true remission of the condition after transphenoidal pituitary surgery in these patients as they may simply 'cycle out' after pituitary surgery and have low-morning cortisol levels postoperatively. Such findings can be mistaken for remission of hypercortisolism.

Bilateral adrenalectomy is used for patients where pituitary surgery has been unsuccessful or the source of ACTH/cortisol production is peripheral. Long-term block-and-replace treatment with metyrapone and hydrocortisone can be used for patients who are not suitable candidates for surgery. After bilateral adrenalectomy, people require a combination of glucocorticoids and mineralocorticoid replacement with regular electrolytes and

Table 2 Simultaneous bilateral inferior petrosal sinus sampling

	ACTH, ng/L		
	Peripheral	Left IPS	Right IPS
Pre-CRH	43	48	47
3 min post-CRH	46	74	62
5 min post-CRH	45	100	78
10 min post-CRH	50	73	68

ACTH, adrenocorticotrophic hormone; IPS, inferior petrosal sinus.

Learning points

- ▶ Cyclical Cushing syndrome (CS) is a rare but well-defined and probably under-reported entity, which poses a greater than usual diagnostic challenge.
- ▶ Clinicians should be aware that hypercortisolism could manifest in a periodic fashion. Cyclical CS can be due to both adrenocorticotrophic hormone-dependent and independent causes, and differentials should be carefully ruled out.
- ▶ Cyclical CS should also be considered in patients with intermittent/periodic symptoms, signs and findings (such as intermittent/periodic muscle weakness, oedema, hypertension, hypokalaemia, easy bruisability), especially when a patient presents with typical clinical findings of CS but has normal or varying screening tests for Cushing's.
- ▶ Repeated late-night salivary cortisol levels should be measured to establish the cyclical nature of excess cortisol production.
- ▶ Inferior petrosal sinus sampling should be performed during the hypercortisolaemic phase of the cycle. A late-night salivary or early-morning serum cortisol measured on the planned day of testing before it proceeds can be very useful under such circumstances.
- ▶ It is important to point out that most patients do not require this type of testing, and endocrinologists with experience in managing this disorder should make the decision about the appropriateness of further investigations.

close BP monitoring to avoid problems with orthostatic changes and also potassium abnormalities.

Patients with ectopic ACTH production from a tumour should be considered for surgical removal of the source wherever possible.

In every case where the possibility of Cushing's syndrome is being investigated, a sensible clinical decision should be made as to how far to take the investigation. The decision should be based on the clinical index of suspicion while considering the overall benefits to the patients.

Contributors MAH: Wrote the manuscript and performed the literature search. TH: Contributed in writing up the manuscript and important contribution in the

management of this case. TR: Contributed in writing up the manuscript and is treating physician of the case.

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