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Cyclical Cushing's Syndrome – A Trap for the Unwary

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ABSTRACT

A woman with cyclical Cushing's syndrome due to periodic hormonogenesis from a corticotropin (ACTH) secreting pituitary adenoma is discussed. This patient presented with acute steroid-induced psychosis but she was found to have subtle cushingoid features that went undetected for two years. Laboratory evaluation for Cushing's syndrome showed incongruous results due to periodic ACTH production by the tumour. Cyclical Cushing's syndrome may be an under-recognised phenomenon and incorrect interpretation of investigative results may lead to wrong tumour localisation and inappropriate surgery. This case highlights the subtleties and complexities that one may encounter in the diagnostic evaluation of patients with Cushing's syndrome, and emphasises that the laboratory results must always be interpreted in the appropriate clinical context.

Keywords: Cushing's syndrome, corticotropin (ACTH), cyclical hypercortisolism, periodic hormonogenesis, diagnosis

CASE DISCUSSION

History: A 30-year-old woman was admitted to the psychiatric ward for paranoid ideations and auditory hallucinations. A thorough history predated her illness to some two years ago, with mild weight gain (3 kg), hypertension, spontaneous bruising, insomnia and emotional lability. She denied use of alcohol or tobacco. There was no history of ingestion of steroids or traditional medicinal preparations. Examination showed a young woman who was slightly cushingoid in appearance. Blood pressure was 150/110 mmHg in both arms. Height was 157 cm and weight, 57.5 kg. Skin fold thickness in the dorsum of right hand was 5 mm. She had mild facial rounding and plethora, some increased supraclavicular fullness and a small dorso-cervical fat pad. There were a few fading ecchymoses over her extremities. She had no purpuric striae and her muscle strength was normal. Visual fields were full. She had no hirsutism, pigmentary changes or acanthosis nigricans. There was no pedal oedema. Screening blood chemistry showed serum potassium, 2.9 mmol/L (N:3.5 – 5.3); bicarbonate, 33.2 mmol/L; fasting glucose, 5.6 mmol/L.

Question: How do you interpret the above clinical and laboratory findings? What are the appropriate tests to confirm the suspected diagnosis?

Answer: This patient is likely to have Cushing's syndrome giving rise to the acute presentation of organic psychosis. Although iatrogenic causes constitute the most common form of hypercortisolism, this has been appropriately excluded in our case. Biochemical screening showed hypokalaemic metabolic alkalosis, consistent with the mineralocorticoid effect of hypercortisolism. However, biochemical confirmation is necessary for subjects with clinical suspicion of endogenous hypercortisolism, the two useful tests being 24-hour urinary free cortisol (UFC) measurement and a low-dose dexamethasone suppression test (DST). In the latter test, dexamethasone can be administered as a 1 mg overnight screening test or a 2-day (0. 5 mg q 6 hourly) confirmatory test for endogenous hypercortisolism. However, patients with mild or cyclical disease may not consistently show positive result[1]. New diagnostic frontiers for the diagnosis of Cushing's syndrome include the measurement of midnight salivary cortisol, and contrasting it with an early morning salivary cortisol. The advantage lies in the fact that salivary cortisol reflects the free biologically active concentration of cortisol and is easy to collect as compared to plasma cortisol. Late night salivary cortisol levels are usually less than 5 nmol/L in normal subjects and diurnal rhythmicity is readily apparent. These measurements may be particularly helpful in some patients with mild or cyclical hypercortisolism (test currently not available locally).

Question: The patient's result were: UFC, 511 nmo/L 24 h (N:30 – 150); serum cortisol, post 1 mg overnight DST, 277 nmo/L. What is your comment?

Answer: This patient has biochemical evidence of hypercortisolism based on the elevated 24-hour UFC result and the lack of suppression of plasma cortisol after an overnight DST. The diagnostic criterion for Cushing's syndrome is based on a failure to suppress morning serum cortisol to less than 83 nmo/L ($< 3\ \mu g/L$) after an overnight 1 mg dexamethasone given at 2300 h. Although the two-day low-dose DST is considered to be the confirmatory test, it is not necessary here given the

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grossly elevated UFC (> 3x normal) in the context of a subject with a high index of clinical suspicion.

Question: What tests would you do next to help in the differential diagnosis of Cushing's syndrome?

Answer: After confirming endogenous hypercortisolism, measurement of plasma corticotropin (ACTH) level helps to differentiate between ACTH-dependent vs ACTH-independent Cushing's syndrome. The former arises from either ACTH secreting pituitary adenoma or ectopic ACTH production from neuroendocrine neoplasms such as carcinoid tumour. Conversely, ACTH-independent Cushing's syndrome almost always originates from a cortisol secreting adrenal tumour (adrenal adenoma or carcinoma). Due to the technical difficulties involved with ACTH assay, the traditional high-dose DST remains of some use to distinguish ACTH-secreting pituitary tumour (which shows suppression of serum cortisol by > 50%) from ectopic ACTH syndrome and cortisol-secreting adrenal tumour[2]. However, there is significant overlap in the high-dose DST results, giving a diagnostic accuracy of < 80%. It is therefore important to adopt a "common sense" approach, taking the complete clinical picture into consideration. This is illustrated by using a simple logistic regression model that includes the age and sex of the patient, the presence or absence of hypokalaemia and the duration of the hypercortisolism: this provides a > 90% diagnostic accuracy in the differentiation of Cushing's syndrome subtypes, as compared to < 80% derived from laboratory tests. Taking the complete clinical picture into consideration, the most probable diagnosis in this young, non-smoking woman with an insidious presentation, is pituitary Cushing's disease.

Question: Subsequent investigation results were as follows (all specimen were taken at 0800 h): plasma ACTH, 9.8 ng/L (N:10 – 40); serum cortisol pre-8 mg overnight DST, 771 nmol/L; serum cortisol post 8 mg overnight DST, 66 nmol/L. What is unusual about these results and how would you proceed further?

Answer: This patient has a suppressible high-dose DST result, which points towards the diagnosis of pituitary dependent Cushing's disease. As noted above, this test is not fully discriminatory and patients with large and poorly differentiated corticotroph tumour may show a lack of suppression, whereas those with ectopic ACTH syndrome (particularly carcinoid tumour) may exhibit positive suppression. Although a positive suppression result is generally incompatible with an adrenal aetiology, exceptions do occur in patients with mild or cyclical Cushing's syndrome. The low plasma ACTH level noted in this case tends to indicate an ACTH-independent aetiology, at variant with the high-dose DST result. As ACTH is a labile peptide with short plasma half-life, its measurement can be unreliable and repeat determinations may be necessary before one can arrive at a definitive diagnosis.

History: Repeat 0800 h plasma ACTH level became undetectable whereas the concurrent serum cortisol measurement was 214 nmol/L. CT scan of the adrenals were then performed with 3 mm fine cuts and showed both adrenal glands to be normal in size and configuration (Fig 1).

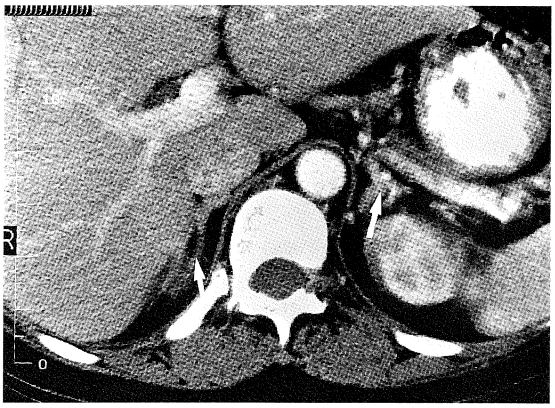


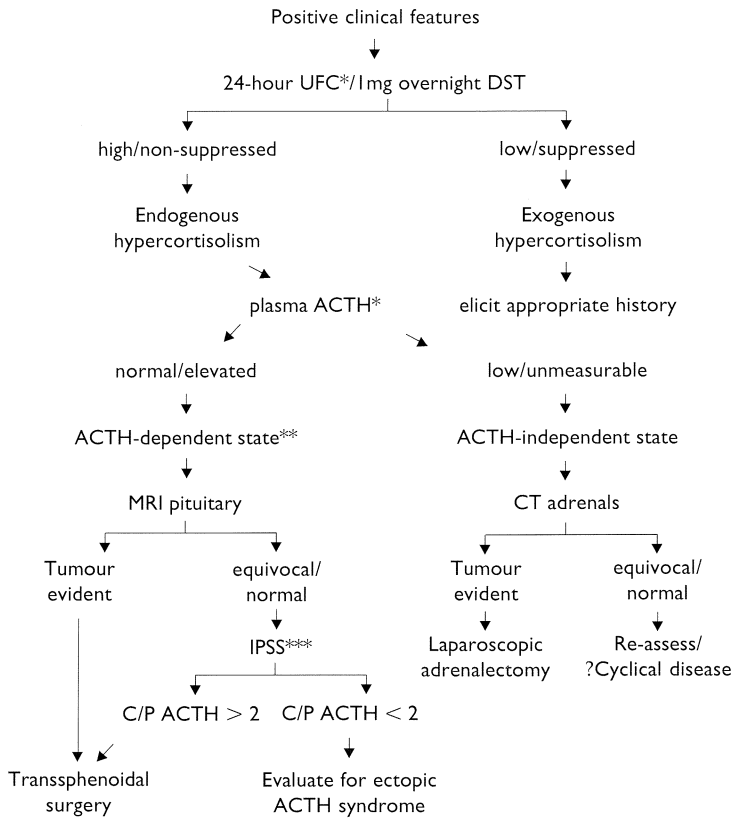
Fig 1 – CT scan of the adrenals (3 mm section) showing both adrenal glands to be of normal size and configuration (arrows).

Question: How do you interpret the findings? How would imaging study help at this point?

Answer: At cursory level, the repeat measurements seem to further support an ACTH-independent aetiology. However, one could not rule out laboratory errors or cyclical disease. While it is correct that imaging study for tumour localisation should be performed after complete endocrinological evaluation (Fig 2), adrenal imaging was done at this stage with an aim to expedite diagnosis and appropriate treatment. If she has a cortisol secreting adrenal tumour, it would be readily apparent as a solitary adrenal lesion with contralateral adrenal gland atrophy. Imaging study in this instance has helped to exclude such a possibility. Conversely, her adrenals would either appear enlarged with or without concurrent nodules, or simply appear normal (as noted here) in the context of ACTH-dependent hypercortisolism.

Question: Based on all the results available, what are the possible differential causes of Cushing's syndrome in this patient?

Answer: The possible differential causes of Cushing's syndrome in this patient are:
a) tumoral production of an abnormal or a variant ACTH peptide that was not totally measured by our ACTH assay. However, this does not account for the cyclicity in both ACTH and cortisol concentrations. b) periodic tumoral production of ACTH causing cyclical Cushing's syndrome. The low ACTH level obtained initially can be explained by sampling during the downswing phase of tumoral ACTH secretion. Subsequent sampling during the quiescent phase accounts for an undetectable ACTH level, as the normal corticotrophs have not recovered from negative feedback inhibition.



Footnotes
UFC: urinary free cortisol; DST: dexamethasone suppression test; ACTH: corticotrophin; IPSS: inferior petrosal sinus sampling; C/P: central to peripheral gradient; *serial measurements often required; **A routine chest X-ray should be done to exclude obvious bronchial carcinoid tumour; ***C/P ACTH cut-off value of 3 meant for IPSS performed with corticotrophin releasing hormone (CRH) stimulation.

Fig 2

c) ACTH-independent Cushing's syndrome arising from ectopic cortisol production. This extremely rare phenomenon has been reported in ovarian lipoid cell tumour. However, most of these individuals also manifest virilising features from concomitant androgen production.

Question: Sampling of 0800 h serum cortisol levels on consecutive days (labelled as day 1 – 5) was done to establish her cortisol secretory profile. Plasma ACTH concentration was measured on days 1 and 3. Please comment on the results and what further study would you pursue?

Day (consecutive)	1	2	3	4	5
Serum cortisol (nmol/L)	277	700	778	337	82
Plasma ACTH (pmol/L)	63	-	3.4	-	-
(- not measured)					

Answer: The daily cortisol measurements support the diagnosis of cyclical Cushing's syndrome from periodic ACTH production. On day 1, sampling was performed during the upswing phase of tumoral ACTH release, thus accompanied by elevated cortisol levels on days 2 and 3. ACTH production began to turn off on day 3, which was mirrored by declining cortisol levels on days 4 and 5. Therefore, the next logical step is to do a MRI of the pituitary to exclude a pituitary tumour. Although MRI is superior to CT scan in the evaluation of pituitary lesion, up to 30% – 50% of patients with Cushing's disease may have inconclusive imaging result as the majority of patients with Cushing's disease (90%) have pituitary microadenoma which is smaller than 10 mm in size. Conversely, 5% – 10% of normal individuals may show incidental finding of non-significant pituitary microadenoma on sensitive MRI study[3]. A routine chest X-ray is useful to exclude obvious bronchial carcinoid tumour.

History: Pituitary MRI study was done and this revealed a right-sided relatively non-enhancing pituitary adenoma, measuring 12 x 8 x 10 mm and just abutting the optic chiasm with displacement of the stalk to the left. The cavernous sinus appeared not involved (Fig 3). Chest X-ray was normal.

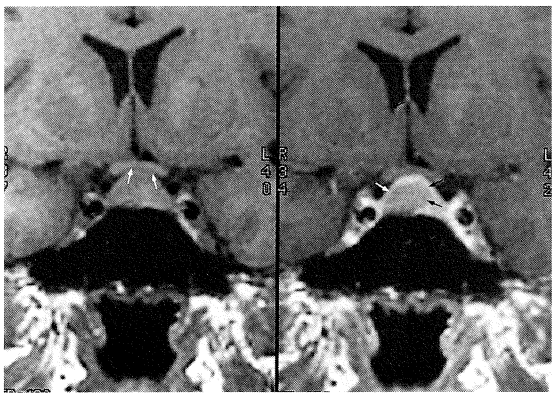


Fig 3 – MRI of the pituitary fossa before (left panel) and after (right panel) administration of gadolinium contrast. The pituitary tumour shows suprasellar extension and abuts against the optic chiasma (arrows; left panel). On the post contrast film, the lesion (arrows) can be readily demarcated from normal pituitary tissue on the left by reduced uptake of contrast.

Question: What is inferior petrosal sinus sampling (IPSS) for ACTH? Comment on its value in this patient.

Answer: IPSS is regarded as the gold standard for localisation of ACTH source and it involves measuring ACTH level in proximity of the pituitary gland via catheters that are advanced into both inferior petrosal sinuses. In patients with ACTH-dependent hypercortisolism, the ratio of ACTH obtained from inferior petrosal sinus (called central ACTH) to that from a peripheral vein (called peripheral ACTH) provides differentiation of pituitary Cushing's disease (central: peripheral ACTH ratio > 2) from ectopic ACTH producing tumour (central: peripheral ACTH ratio < 2). However, as IPSS is invasive in nature, its indication should be judiciously applied. In our case, IPSS is not necessary as she has a pituitary macroadenoma that warrants transsphenoidal surgery. Furthermore, incorrect localisation result may arise from periodic hormonogenesis with cyclical tumoral ACTH secretion. Nevertheless, this can be overcome with corticotropin releasing hormone (CRH) stimulation in conjunction with IPSS[4].

Question: What should the treatment and prognosis for this patient be?

Answer: The definitive treatment involves surgical resection of the pituitary tumour, which can be readily accomplished via transsphenoidal surgery. Histological confirmation of the pituitary adenoma cell type by immunocytochemical staining is essential. This patient has a good chance of surgical cure as the tumour does not show extrasellar or cavernous sinus invasion on imaging. As the chances of cure are highest at the initial operation, she should be operated by a neurosurgeon well-experienced in transsphenoidal pituitary surgery.

DISCUSSION

Cyclical Cushing's syndrome is an unusual phenomenon first observed in a patient with ectopic ACTH production from a bronchial adenoma, and later being described in patients with pituitary or adrenal tumours as well[5]. Affected subjects have temporary biochemical remission of hypercortisolism due to periodic hormonogenesis by the tumour, as illustrated by our case. In cyclical Cushing's syndrome, the clinical features usually persist despite periodic hormonogenesis, thus posing a challenge in its diagnosis, as in our case. In an extensive study by Atkinson et al[6], they found cycles of excess cortisol secretion varying in duration between 12 h and 85 days. The criteria they suggested for diagnosis of cyclicity consisted of three peaks and two troughs of cortisol production with similar intervals between the peaks. Although there are insufficient measurements obtained in this patient to characterise three peaks and two troughs of cortisol production, such a criterion for diagnosis should not be absolute. Other findings in our patient which are consistent with periodic hypercortisolism include the history of fluctuating mood changes, subtle cushingoid features, and the lack of overt adrenal hyperplasia on CT scan.

The key point to emphasise in this case is that one should not abide by absolute rules pertaining to the diagnostic work-up or the interpretation of results in a patient with suspected Cushing's syndrome. Indeed, every patient with hypercortisolism poses a unique challenge as one tries to avoid treacheries not infrequently encountered even by the experienced. It is imperative that the laboratory or imaging results must not be interpreted in isolation. An incorrect diagnosis often leads to inappropriate surgery and failure to ameliorate or cure the disease, resulting in aggravated patient distress from the attendant perioperative morbidity as well as persistent hypercortisolism which can be fatal.

In conclusion, the subtleties and complexities that one may encounter in the diagnostic evaluation of Cushing's syndrome cannot be overemphasised. When faced with a diagnostic conundrum as in this case, a good mix of 'common sense' approach, patience in waiting out with repeat laboratory evaluation, and clinical experience may be ultimately ewarding.

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