

Difficulty in the diagnosis of Cushing disease

Lynnette K Nieman

SUMMARY

Background A 48-year-old woman presented to our clinic 1 year after hypertension was discovered on a routine screening visit. During the previous year, she had noticed weight gain in the face and abdomen, easy bruising, oligomenorrhea and facial and periareolar hair growth. On presentation, she reported no weakness, fracture, back pain, depression, irritability, problem with cognition or memory, increased appetite, hot flashes or altered sleep. Previous medication history included 2.5 mg lisinopril daily and 25.0 mg hydrochlorothiazide daily for 12 months.

Investigations Measurement of urine glucocorticoid excretion, evening plasma and salivary cortisol levels, and basal and corticotropin-releasing-hormone-stimulated adrenocorticotrophic hormone and cortisol levels. An overnight 8 mg dexamethasone suppression test, pituitary MRI, inferior-petrosal-sinus sampling, cavernous sinus and jugular venous sampling were performed.

Diagnosis Cushing disease.

Management The patient underwent trans-sphenoidal resection, assessment of remission and subsequent treatment with hydrocortisone.

KEYWORDS adrenocorticotrophic hormone, cortisol, Cushing disease, Cushing syndrome, inferior-petrosal-sinus sampling

CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 48-year-old woman presented to our clinic 1 year after hypertension was discovered on a screening visit. In the interval, she noted weight gain in the face and abdomen, easy bruising, OLIGOMENORRHEA and facial and periareolar hair growth. She experienced no weakness, fracture, chronic pain, depression, irritability, impaired cognition or memory, increased appetite, hot flashes, or altered sleep. She denied alcohol use altogether. She had been taking 2.5 mg lisinopril daily and 25.0 mg hydrochlorothiazide daily since hypertension was diagnosed.

On physical examination, vital signs were normal, weight was 57.7 kg and height was 152.1 cm. Mild plethora and facial rounding, minimal dorsocervical and moderate supraclavicular fat, truncal obesity, facial and periareolar hirsutism, fundoscopic hypertensive changes and a systolic ejection murmur were present. Despite intact isolated muscle strength, she had difficulty rising from a squat. The skin was thin with many bruises, but no striae were present.

The initial laboratory results confirmed hypercortisolism, with an elevated 24-h urinary excretion of free cortisol (UFC; 538 nmol/day; standard range 70–300 nmol/day) and 17-hydroxycorticosteroids (30 µmol/day; standard range 6–20 µmol/day). She also had increased midnight plasma cortisol (375 nM; standard value <210 nM for awake patients) and salivary cortisol levels (29 nM; standard value <15 nM). Plasma adrenocorticotrophic hormone (ACTH) values were not suppressed (91 pM measured at 11:00 h; standard range 0–13 pM, Table 1). Evaluation for the cause of Cushing syndrome showed that the patient responded to corticotropin-releasing hormone (CRH), with increases in plasma cortisol and ACTH (336% and 90%, respectively, over baseline levels). An overnight

LK Nieman is a Senior Investigator in the Reproductive Biology and Medicine Branch of the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA.

Correspondence

Building 10, CRC, 1 East, Room 1-3140, 10 Center Drive, MSC 1109, Bethesda, MD 20892-1109, USA
niemanl@nih.gov

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Table 1 The results of the patient's initial laboratory examinations.

Test (units)	Duration or time	Results	Normal range
24-h urinary free cortisol test (nmol/day) (µg/day)	24 h	538 195	70–300 24–108
Urine 17-hydroxysteroids (µmol/day) (mg/day)	24 h	30 11.1	6–20 2–6
Urine creatinine (mmol/day) (mg/day)	24 h	7.3 0.83	7.1–15.9 0.8–1.8
Plasma ACTH (pg/ml) (pmol/l)	11:00 h	91 20	0–59 0–13
Plasma ACTH (pg/ml) (pmol/l)	16:00 h	21 5	0–59 0–13
Plasma cortisol (nM) (µg/dl)	16:00 h	303 11	140–550 5–20
Plasma cortisol (nM) (µg/dl)	00:00 h	375 13.6	<210 <7.5
Salivary cortisol (nM) (µg/dl)	00:00 h	29 1.05	<15 <0.55

ACTH, adrenocorticotrophic hormone.

GLOSSARY

OLIGOMENORRHEA

Infrequent or light menstruation

DEXAMETHASONE SUPPRESSION TEST

Measurement of cortisol levels after administration of dexamethasone to assess response of the adrenal glands to adrenocorticotrophic hormone

8 mg DEXAMETHASONE SUPPRESSION TEST (DST) showed an 87% suppression of plasma cortisol (from 1,170 nM [42.3 µg/dl] to 86 nM [3.1 µg/dl]); the expected suppression is more than 69% for a diagnosis of Cushing disease (i.e. Cushing syndrome caused by a corticotrope tumor). MRI of the pituitary gland (T1 Spin-echo with gadolinium) was normal. Inferior-petrosal-sinus sampling (IPSS) revealed plexiform petrosal sinuses, with drainage to the right jugular and left vertebral veins (Figure 1). Despite catheterization of the right cavernous sinus and retrograde flow into the left petrosal sinus catheter, there was no central-to-peripheral ACTH gradient, suggesting a nonpituitary source of ACTH. CT and MRI of the chest and abdomen were unrevealing. Repeat venous sampling showed no step-up in the cavernous sinus or vertebral samples, but a right jugular-to-peripheral ACTH gradient of 6.2 to 14.9 was present after administration of CRH, implying a pituitary source of ACTH.

A left paramedian 6 mm tumor was resected at trans-sphenoidal exploration and histologically

confirmed. Plasma cortisol levels were in the range 66–110 nM (2.4–4.1 µg/dl) on post-operative days 3–5. Subsequent daily levels were in the range 160–220 nM (5.9–8.1 µg/dl), but UFC was undetectable. The patient experienced emesis, dizziness and somnolence on post-operative day 15, with plasma cortisol levels of 135 nM (4.9 µg/dl). She was considered to be hypoadrenal, and 20 mg daily hydrocortisone was started. At consultation 6 months after surgery, plasma cortisol levels had increased to 469 nM (17 µg/dl) after a 250 µg ACTH test, and the hydrocortisone dose was tapered and then stopped. Postoperatively, weight decreased to her baseline of 51 kg and hypertension resolved but she experienced joint aches.

DISCUSSION OF DIAGNOSIS

Cushing syndrome is recognized in two to five people per million in the general population annually. This reversible disorder occurs in up to 3.0% of people with poorly controlled type 2 diabetes and 0.5% of hirsute women, in whom screening should be considered.¹ Many people in the general population display some of the signs and symptoms of Cushing syndrome (Table 2), and exactly who should be screened is debated. One approach targets individuals with multiple features, with progression over time, or with unmistakable clinical signs (e.g. wide purple striae, proximal myopathy or unusual fat deposition). We screened the patient described because she developed features of Cushing syndrome in a short time frame.

There is no consensus on the best screening test. The classic tests, UFC and 1 mg DST, are prone to false results. In one report, up to 8% of patients with Cushing disease had completely suppressed cortisol levels during the 1 mg DST; a significant false-positive rate also reduces the clinical utility of the test.^{2,3} UFC can be up to four times normal in the so-called pseudo-Cushing states, including psychiatric disorders, chronic pain and obligate exercise.^{3,4} A clear diagnosis cannot be established from a mildly elevated UFC unless the clinical presentation is unequivocal, and other tests might be needed.⁴

The development of late-evening plasma and salivary cortisol measurement as more accurate screening tests exploits the loss of the diurnal cortisol rhythm in Cushing syndrome.^{1,3,5} Although collection of saliva is more convenient, assay variability and lack of validated criteria for interpretation reduce the

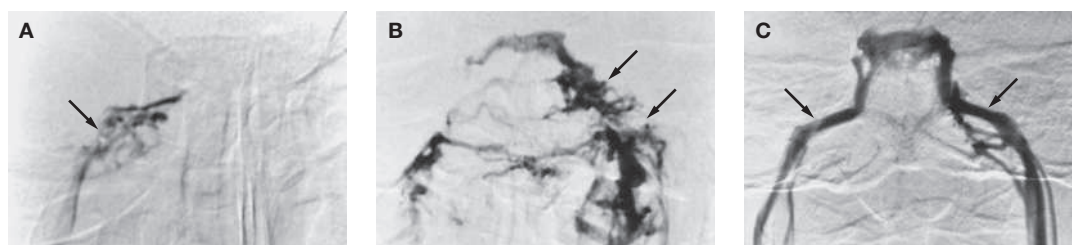


Figure 1 Abnormal venogram obtained during inferior petrosal-sinus sampling in the patient compared with a normal petrosal-sinus venogram. **(A)** The right petrosal sinus is plexiform, with drainage to the left jugular vein (junction at arrow). **(B)** The left petrosal sinus is more obviously abnormal (arrows), and drains to the vertebral veins. **(C)** A normal venogram obtained during petrosal-sinus sampling with catheters in the correct location (arrows).

utility of this test. The patient described had indeterminate UFC test results, but salivary and midnight cortisol were elevated, confirming the diagnosis of Cushing syndrome. When other tests are equivocal, the dexamethasone–CRH test might be helpful.⁴

DIFFERENTIAL DIAGNOSIS

As shown in Box 1, the differential diagnoses of endogenous Cushing syndrome can be classified as ACTH dependent (caused by excessive ACTH) or ACTH independent (caused by autonomous adrenal cortisol production). As tumor resection is the optimum treatment, the specific cause of Cushing syndrome must be determined and then the tumor located. Excessive cortisol inhibits ACTH secretion to less than 1.1–2.2 pM (<5–10 pg/ml) in primary adrenal disorders.⁶ In the patient described, normal-to-increased ACTH levels indicated an ACTH-dependent etiology. Biochemical and functional tests, rather than imaging, must be used to distinguish pituitary (Cushing disease) from ectopic tumoral production of ACTH, because pituitary MRI is normal in up to 50% of patients.⁷ Generally, corticotrope tumors show responsiveness to glucocorticoid feedback and CRH stimulation, which characterizes normal corticotropes, whereas most ectopic ACTH-secreting tumors do not.⁸ The overlap in responses to 8 mg dexamethasone is, however, substantial and this test alone cannot reliably distinguish between a corticotrope adenoma and ectopic ACTH secretion.⁹ The CRH stimulation test has better sensitivity and specificity (~90%) than the DST.^{3,10}

Given the potential for false-positive results with the CRH and 8 mg DST tests, many advocate the use of IPSS, which has diagnostic

Table 2 Signs and symptoms of Cushing syndrome.

Signs and symptoms	% patients ^a
Decreased libido (men/women)	100
Obesity or weight gain	97
Plethora	94
Round face	88
Menstrual changes	84
Hirsutism	81
Hypertension	74
Ecchymoses	62
Lethargy, depression	62
Striae (especially if >1 cm, purple)	56
Weakness (especially proximal)	56
ECG changes or atherosclerosis	55
Dorsal fat pad	54
Edema	50
Abnormal glucose tolerance	50
Osteopenia or fracture	50
Headache	47
Backache	43
Recurrent infections	25
Abdominal pain	21
Acne	21
Female balding	13

^aThe percentage of 70 patients with Cushing syndrome who experienced each of the signs and symptoms listed. Modified with permission from reference 15 © (1982) Elsevier Limited. ECG, electrocardiogram.

accuracy of around 95%.^{7,11} This procedure involves catheterization of the petrosal sinuses and a peripheral vein with simultaneous

Box 1 Causes of endogenous Cushing syndrome.**ACTH-independent (autonomous adrenal activation)^a**

Adrenal adenoma^b
 Adrenal carcinoma^b
 Primary pigmented nodular adrenal disease (rare)
 McCune–Albright syndrome (rare)
 Massive macronodular adrenal disease (rare)
 GIP/food-induced (rare)

ACTH-dependent (adrenal activation by excessive ACTH)^c

Corticotrope adenoma (Cushing disease)^d
 Ectopic ACTH secretion^e
 Ectopic CRH secretion (rare)

^aAccounts for 20% of Cushing syndrome. ^bAccounts for 40–50% of ACTH-independent Cushing syndrome. ^cAccounts for 80% of Cushing syndrome. ^dAccounts for around 80% of ACTH-dependent Cushing syndrome. ^eAccounts for around 20% of ACTH-dependent Cushing syndrome.
 ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; GIP, gastric inhibitory polypeptide.

measurement of ACTH before and after CRH administration and calculation of a central-to-peripheral ACTH gradient at each time point. Only experienced interventional radiologists familiar with the potential complications should perform this costly procedure. Patients should have sustained hypercortisolism sufficient to suppress normal corticotrope ACTH secretion to minimize the chance of false-positive results in those with ectopic ACTH secretion. The case we report illustrates abnormal venous drainage leading to a false-negative result for Cushing disease and underscores the importance of obtaining venography to evaluate the reliability of the results. When venous anatomy is abnormal, the venogram can be used to identify the actual drainage. Catheterization of affected veins might or might not be useful, as illustrated by the fact that the jugular venous step-up in this patient was clear-cut, but vertebral sampling was uninformative. Finally, the right-sided gradient in the presence of a left-sided tumor illustrates the lack of utility of venous sampling for tumor localization.

The present case also illustrates the importance of using multiple tests and evaluating all results together. Here, the DST and CRH tests suggested the presence of Cushing disease. Although one positive result might occur in patients with ectopic ACTH secretion, two positive results are extremely unlikely.

TREATMENT AND MANAGEMENT

Optimum treatment of Cushing syndrome involves resection of autonomous adrenal tissue or ACTH-producing tumor. When this is not possible (e.g. with metastatic or occult ectopic ACTH-producing tumor, or metastatic adrenal cancer), bilateral adrenalectomy or steroidogenesis inhibitors might control hypercortisolism, and radiation could reduce ACTH secretion from a corticotrope adenoma.¹² The neurosurgeon should be experienced with Cushing disease as these tumors are often small, difficult to recognize and not localized by MRI. Remission rates, however, rarely exceed 90%.¹³

The criteria for remission of Cushing disease are controversial. We deemed the patient to be in remission because of low cortisol levels, UFC and hypoadrenal symptoms; undetectable cortisol values are required in some centers' criteria.¹⁴ Patients with conflicting results or unusual temporal responses should be followed-up closely. If clinical features do not resolve, biochemical assessment is repeated.

The risk of recurrence of Cushing syndrome requires follow-up in all patients, and increases with high postoperative cortisol values, such as in the case described. Anecdotally, patients frequently seem to sense when Cushing syndrome has recurred. Biochemical assessment can confirm hypercortisolism even with few clinical features. Corticotrope tumors regrow at the initial site; reoperation might be successful if there was no previous dural invasion and a target is visible on MRI. Adrenalectomy, radiation therapy or both are the next therapeutic options. If surgery is deemed unlikely to succeed, adrenalectomy might be more desirable in patients who need immediate reduction of hypercortisolism, or who wish to avoid radiation-induced hypopituitarism.

CONCLUSION

This case illustrates the potential difficulty in making the diagnosis of Cushing syndrome in patients with mild hypercortisolism. The markedly positive responses to dexamethasone and CRH caused us to question the 'flat' ACTH values during IPSS, and illustrate the importance of aggregate test results. If abnormal venogram results occur, other sampling strategies should be considered; we made our diagnosis by jugular venous sampling. Successful resection of a corticotrope adenoma was followed by an atypical postoperative course, with a delay in symptoms of hypoadrenalism.

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Competing interests

The author declared she has no competing interests.