www.nature.com/clinicalpractice/endmet

Cushing's syndrome in women with polycystic ovaries and hyperandrogenism

P Gerry Fegan, Derek D Sandeman, Nils Krone, Deborah Bosman, Peter J Wood, Paul M Stewart and Neil A Hanley*

SUMMARY

Background A 41-year-old woman presented to an endocrinology–gynecology clinic having been diagnosed 7 years earlier with polycystic ovarian syndrome on account of hirsutism, subfertility, greasy skin, acne and multiple ovarian cysts. Ovulation induction had led to a successful pregnancy. Subfertility recurred, however, and persisted alongside a new diagnosis of hypertension and progressive weight gain. Upon examination, the patient was hypertensive with facial plethora, rounded facies and violaceous abdominal striae.

Investigations Low-dose dexamethasone test, bedtime salivary and 24-h urinary free cortisol estimations, CT scan of the abdomen, and serum hormone and gonadotropin analyses.

Diagnosis Cushing's syndrome due to a right adrenocortical adenoma.

Management The patient underwent laparoscopic right adrenalectomy, which led to resolution of all symptoms, signs and biochemical abnormalities.

KEYWORDS cortisol, Cushing's syndrome, polycystic ovarian syndrome

CME

PG Fegan is a Wessex Region Specialist Registrar in Diabetes and Endocrinology. DD Sandeman is a Consultant Endocrinologist and PJ Wood is a Consultant Biochemist at Southampton University Hospitals NHS Trust, Southampton, UK. N Krone is a Wellcome Trust Clinician Scientist Fellow and PM Stewart is Professor of Medicine, at the University of Birmingham, Birmingham, UK. D Bosman is a Consultant Endocrinologist at The Royal West Sussex Trust, Chichester, UK. NA Hanley is Professor of Endocrinology, at the University of Southampton, UK.

Correspondence
*School of Medicine, University of Southampton, Duthie Building / Mailpoint 808, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
n.a.hanley@soton.ac.uk

Received 23 February 2007 **Accepted** 4 September 2007
www.nature.com/clinicalpractice
doi:10.1038/ncpendmet0665

Vanderbilt Continuing Medical Education online
This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 41-year-old woman presented at an endocrinology–gynecology clinic. Seven years previously she had tbeen investigated at another hospital for primary infertility of 5 years standing, associated with secondary amenorrhea for the preceding 6 months, oily skin, acne and facial hirsutism. At the time, laparoscopy and dye infusion had demonstrated multiple, small ovarian cysts with patent oviducts. A diagnosis of polycystic ovarian syndrome (PCOS) was made. Attempts at ovulation induction were then undertaken with 50 mg clomifene citrate on days 2–6 of the menstrual cycle, following which she conceived aged 35 years and carried a successful pregnancy to term, giving birth to a healthy baby girl.

Subfertility was again problematic and led to the patient's referral for *in vitro* fertilization, one cycle of which was unsuccessful. At this time, the patient's BMI was 26 kg/m^2 and investigations revealed serum total testosterone levels of 2.6 nmol/l (75 ng/dl; normal range 0.5–2.6 nmol/l [14–75 ng/dl]) and serum estradiol levels of 47 pmol/l (13 pg/ml; normal range 100–500 pmol/l [27–136 pg/ml] early follicular phase; 300–1,250 pmol/l [82–341 pg/ml] luteal phase). The patient's serum androstenedione, dehydroepiandrosterone sulfate and gonadotropin levels were normal. She was commenced on metformin off-licence (titrated up to a dose of 500 mg three times daily).[1] Oligomenorrhea, however, persisted and weight gain increased. Hirsutism and acne remained troublesome. The patient's attempts to conceive were abandoned. Dianette® (cyproterone acetate 2 mg plus ethinylestradiol 35 μg; Schering Health, Burgess Hill, UK) was prescribed, but was later withdrawn by the primary care physician because the patient was hypertensive.

Upon examination, the patient's plethoric round facies, purple abdominal striae and

© 2007 Nature Publishing Group

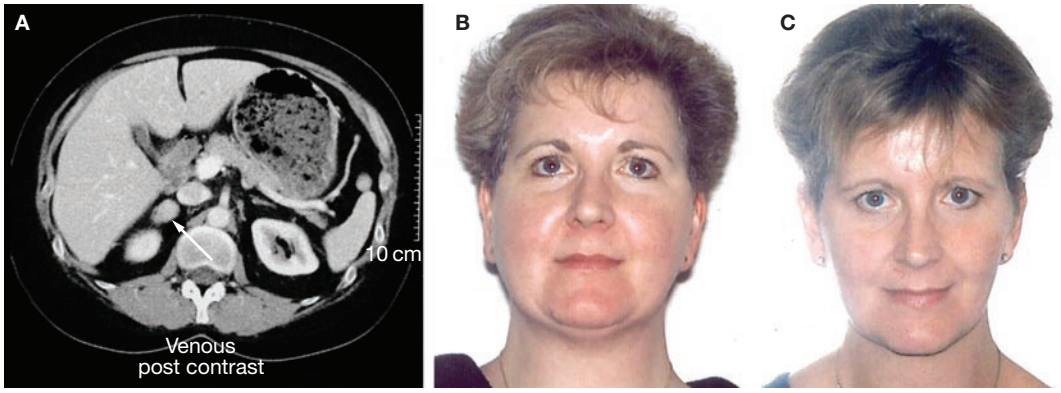

Figure 1 Abdominal CT scan and patient's appearance. (**A**) Abdominal CT from the patient showing a right adrenocortical adenoma (arrow). The same patient is shown (**B**) 1 month before and (**C**) 6 months after laparoscopic right adrenalectomy. Permission obtained from Blackwell Publishing © Holt RIG and Hanley NA (2006) *Essential Endocrinology & Diabetes*, edn 5.

supraclavicular fat pads raised concern that she had Cushing's syndrome. There was no bruising or proximal myopathy. Her blood pressure in the clinic on ramipril 2.5 mg and bendroflumethiazide 2.5 mg was 175/105 mmHg. On metformin, random blood glucose was 5.0 mmol/l (90 mg/dl; reference range for fasting blood glucose 3.6–5.5 mmol/l [65–99 mg/dl]) and serum electrolyte levels were normal.

Screening tests were performed for Cushing's syndrome. Three 24-h collections for urinary free cortisol demonstrated 784, 1,187, and 608 nmol per specimen (normal <260 nmol per specimen), 1 mg of dexamethasone failed to suppress overnight cortisol (537 nmol/l; normal <50 nmol/l) and a bedtime salivary cortisol test confirmed loss of diurnal variation (22.6, 14.8 and 22.1 nmol/l; reference range from 2200 h to 2400 h <5 nmol/l). Serum adrenocorticotropic hormone was undetectable. CT of the abdomen showed a 2.5-cm-diameter mass in the right adrenal gland with features of high lipid content (Figure 1A). The patient was diagnosed with Cushing's syndrome secondary to an adrenal adenoma. She underwent laparoscopic right adrenalectomy without complication. Pathological analysis of the removed adrenal gland revealed a lipid-rich tumor consistent with a functional adrenocortical adenoma. Within 10 months, all symptoms had resolved (Figure 1B,C).

DISCUSSION OF DIAGNOSIS

Diagnosis of polycystic ovarian syndrome

PCOS is a multifactorial complex genetic disorder with dysregulated steroidogenesis.[1] The initial diagnosis of PCOS in this patient was made owing to the presence of its hallmark clinical features of hyperandrogenism, anovulation and polycystic ovaries: the three diagnostic criteria included in the Rotterdam Consensus Statement on PCOS.[2,3] At presentation to the clinic 7 years later, however, the case bore cardinal features of Cushing's syndrome, which were inconsistent with PCOS; namely, plethoric round facies, supraclavicular fat pads and violaceous striae.[4] The hypercortisolism had probably existed during the preceding 7 years and was certainly present immediately before the correct diagnosis was made when the patient was under active PCOS treatment. It is interesting that during this period the patient carried a pregnancy to term, when, potentially, the cortisol excess was temporarily attenuated by placental type 2 11β-hydroxysteroid dehydrogenase.[5]

All definitions of PCOS make reference to infrequent or absent ovulation and clinical or biochemical features of hyperandrogenism.[1–3] The Rotterdam Consensus Statement adds polycystic ovaries as a third criterion, with a diagnosis of PCOS requiring two out of three factors.[2,3] In addition, serum estradiol should be detectable in cases of PCOS[6] and, unlike in this case, in our experience serum estradiol is usually more than 150 pmol/l (40.9 pg/ml).

Most importantly, all definitions of PCOS require the exclusion of other causes of hyperandrogenism; failure to do so increases the potential for misdiagnosis.[1,7] Although the present case illustrates this risk on its own, we know of three other cases in which an original diagnosis

© 2007 Nature Publishing Group

Table 1 Three additional women with very similar clinical features eventually diagnosed with Cushing's syndrome.

Features	Patients			
	The Case (A)	Case B	Case C	Case D
Age at diagnosis of Cushing's syndrome; gap since first investigated	41 years; 7 years	24 years; 3 months	35 years; 1 year	25 years; 12 years
Diagnosis	Right adrenal adenoma	Corticotroph adenoma	Corticotroph adenoma	Corticotroph adenoma
Pelvic ultrasound or laparoscopy result	Polycystic ovaries	Polycystic ovaries	Polycystic ovaries	Polycystic ovaries
Clinical features initially attributed to PCOS	Hirsutism, subfertility, greasy skin and acne	Hirsutism, secondary amenorrhea, weight gain	Subfertility, weight gain	Obesity, weight gain, primary amenorrhea
Serum total testosterone	2.6 nmol/l (75 ng/dl)	4.6 nmol/l (133 ng/dl)	3.2 nmol/l (92 ng/dl)	4.5 nmol/l (130 ng/dl)
Screening test confirming Cushing's syndrome	Overnight LDDST Three 24-h UFC collections Bedtime salivary cortisol measurement	Overnight LDDST Three 24-h UFC collections	Overnight LDDST Three 24-h UFC collections Bedtime salivary cortisol measurement	Overnight LDDST Three 24-h UFC collections 0900 h and 2400 h cortisol measurement
Clinical features that distinguished Cushing's syndrome from PCOS (see Table 2)	Facial plethora, rounded facies, violaceous abdominal striae	Facial plethora	None	Short stature[a], depression
Biochemical investigation against a diagnosis of PCOS	Low estradiol (47 pmol/l [13 pg/ml])	None	None	Low LH (1.1 IU/l) and low estradiol
Hypertension	Yes	No	Yes	No
Diabetes or impaired glucose tolerance	No	No	Yes	No
Hypertension	Yes	No	Yes	No
Diabetes or impaired glucose tolerance	No	No	Yes	No
Final curative treatment	Laparoscopic right adrenalectomy	Transsphenoidal surgery	Transsphenoidal surgery	Transsphenoidal surgery

[a]Short stature with obesity is a particularly useful feature pointing towards Cushing's syndrome in childhood or adolescence. Abbreviations: LDDST, low dose dexamethasone suppression test; LH, luteinizing hormone; PCOS, polycystic ovarian syndrome; UFC, urinary free cortisol.

of PCOS became revised to that of Cushing's syndrome (Table 1). Upon curative treatment, all symptoms, originally attributed to PCOS, resolved. The diagnosis, treatment and management of Cushing's syndrome have been the subject of recent discussion in this journal.[4] Here, we address the importance of correctly distinguishing Cushing's syndrome from PCOS to minimize the risk of misdiagnosis.

How common might this scenario be and is it important?

PCOS is one of the commonest endocrine conditions and affects up to 10% of women of reproductive age.[8] Accordingly, PCOS is a frequent presentation to primary care. By contrast, classical Cushing's syndrome is considered rare, yet unlike PCOS it is curable.[4,9] Screening 340 referrals for hirsutism found only 1 case of Cushing's syndrome.[10] Where clinical features overlap to a greater extent, however, rates of detection of Cushing's syndrome are much higher. Screening individuals with type 2 diabetes, which is associated with PCOS, detects cortisol excess in 2–5% of patients.[9]

These findings imply that beneath the classical, rare presentation of Cushing's syndrome with specific but insensitive features (e.g. purple striae)[4] there exists an undercurrent of more prevalent subtle cortisol excess,[9] which reinforces the importance of careful history taking, examination and (potentially repeated) investigations in order to exclude Cushing's syndrome. A recent survey, however, found that only 17% of endocrinologists and 6% of gynecologists screened 'PCOS referrals' for Cushing's syndrome,[11] and Table 1 illustrates cases in which the diagnosis of Cushing's syndrome was

© 2007 Nature Publishing Group

Table 2 Causes of hyperandrogenism, other than polycystic ovarian syndrome, which merit consideration, especially if irregularity of the menstrual cycle does not date back to menarche.

'Non-PCOS' causes of hyperandrogenism	Distinguishing clinical features	Screening tests to consider
Cushing's syndrome	Facial plethora, rounded facies, violaceous striae, thin skin, bruising and proximal muscle weakness In younger patients: growth arrest, primary amenorrhea	See Table 3
Late onset congenital adrenal hyperplasia	Positive family history	Serum 17α-hydroxyprogesterone
Drugs (e.g. anabolic steroids, androgenic progesterones)	Onset timed with drug-taking	Gas chromatography or liquid chromatography plus mass spectrometry
Androgen-secreting adrenocortical or ovarian tumor	Progressive virilization	DHEAS (adrenocortical tumor) Serum total testosterone: androgen-secreting tumors are unlikely if levels are below 4 nmol/l (115 ng/dl) and become increasingly probable with higher values; PCOS is rarely associated with values higher than 7 nmol/l[a] (202 ng/dl)
Acromegaly	Bony and soft tissue overgrowth	Oral glucose tolerance test Serum IGF-I

[a]For detailed review, see Kaltsas GA *et al*.[7] Abbreviations: DHEAS, dehydroepiandrosterone sulfate; IGF-I, insulin-like growth factor I; PCOS, polycystic ovarian syndrome.

initially missed. In Case B only written advice on PCOS management was issued by the initial referral center. Case D presented with primary amenorrhea, the false diagnosis of PCOS being made on the basis of ultrasonography findings and hyperandrogenism.

The ability to distinguish between PCOS and Cushing's syndrome is important because Cushing's syndrome, which is more frequent in women than men, increases age-adjusted and sex-adjusted mortality fivefold; yet—as shown by the case described here—once identified can be cured.[9] By contrast, PCOS is a heterogeneous disorder that can be managed but not eliminated.[1]

TREATMENT AND MANAGEMENT

How might polycystic ovarian syndrome and Cushing's syndrome be distinguished?

The menstrual cycle of individuals with PCOS is likely to have always tended towards irregularity (the amenorrhea in this case developed after years of a regular cycle).[1] The onset of PCOS is uncommon after the age of 30 years. Both PCOS and Cushing's syndrome are associated with obesity, an increased risk of hypertension and impaired glucose tolerance or secondary diabetes.[4,7,9] Clinical and/or biochemical hyperandrogenism with menstrual infrequency is found commonly in women with Cushing's syndrome. In fact, there are data to suggest that menstrual irregularity is linked to the level of glucocorticoid excess rather than to androgen levels.[7] Ovarian cysts are certainly not discriminatory; they are present in almost half of women with Cushing's syndrome.[12] It is also noteworthy that cysts, in isolation, do not predict the development of PCOS;[13] furthermore, whereas imaging the ovaries can help to exclude a tumor, our experience would suggest that identifying cysts either laparoscopically or by ultrasound scanning can inappropriately curtail the search for alternative causes of clinical and/or biochemical hyperandrogenism.

Virilization in PCOS, characterized by a deepened voice or clitoromegaly, is highly unusual and more in keeping with an androgen-secreting tumor (none of the cases illustrated in Table 2 experienced virilization).[7] Other clinical features lend support to the diagnosis of Cushing's syndrome, but these can be absent, especially in the early phases of cortisol excess.[9] Biochemically, relative luteinizing hormone excess has been reported in patients with PCOS,[14] whereas low gonadotropin levels might increase the suspicion of Cushing's syndrome (as in Case D in Table 1, who presented with primary amenorrhea).[12] None of these features is absolute, the overlap between syndromes is large and, thus, screening tests are needed to exclude Cushing's syndrome (Table 3).

© 2007 Nature Publishing Group

Table 3 Screening tests for Cushing's syndrome.

Perturbation to normal physiology	Screening test for Cushing's syndrome[a]	Potential use during 'work-up'
At least partial autonomy of cortisol production (either direct from the adrenal cortex or secondary to adrenocorticotropic hormone secretion)	Failure to suppress cortisol levels below 50 nmol/l after low dose dexamethasone (0.5 mg every 6 h for eight doses ending at 0300 h, or 1 mg at 2300 h with serum cortisol measured the following day at 0800 h to 0900 h)	A useful out-patient first-line investigation
Loss of diurnal rhythm of cortisol production	High midnight or bedtime cortisol (serum or salivary)	Salivary assays are practical, because multiple samples can be posted to the laboratory over the course of a few days. Useful if backed up by a robust normal range
Excess cortisol production leading to increased free cortisol excretion	Increased 24-h urinary free cortisol	Useful investigation, but patients can find it inconvenient or difficult; commonly performed three times

[a]Physicians should retain a high index of suspicion and be willing to repeat screening tests. Salivary cortisol measurements are particularly useful to investigate cyclical Cushing's syndrome.

Screening for Cushing's syndrome

Loss of diurnal variation, assessed by midnight serum cortisol levels, is an early perturbation to normal glucocorticoid homeostasis.[9] Out-of-hours venesection can, however, be impractical in the community. Instead, bedtime salivary assays, which enable samples to be posted to the laboratory, are increasingly available. These assays are useful if backed up by robust normal ranges. Patients can find 24-h urine collections inconvenient and difficult, which results in incomplete specimens that give misleading results. Mildly increased cortisol excretion can occur in PCOS,[15,16] possibly related to recognized changes in the hypothalamic–pituitary–adrenal axis.[17] An alternative approach is the use of a low-dose dexamethasone test. Although it can be debated whether to use the overnight test or the formal eight-dose test over 48 h to screen for Cushing's syndrome, either investigation is relatively straightforward (Table 3), especially if issued with written guidance.[9] In light of this case and others, our current practice is to screen all new referrals with 'PCOS-like' symptoms for glucocorticoid excess.

CONCLUSIONS

The Rotterdam Consensus Statement establishes criteria for the diagnosis of PCOS only when other etiologies have been excluded. The importance of this caveat is illustrated by the presented case and three additional reported cases, in each of which Cushing's syndrome was missed. Recent data obtained by screening individuals with type 2 diabetes suggest that cortisol excess, widely considered a rare endocrinopathy in the form of classical Cushing's syndrome, is in fact more common than supposed. As economic pressures drive health care to be delivered within fewer consultation sessions outside of specialist centers, it is pertinent to emphasize that not all cases of hyperandrogenism or ovarian cysts are related to PCOS and that curable causes, such as Cushing's syndrome, must be excluded by careful history taking, examination and (potentially repeated) investigation.

References

1 Setji TL and Brown AJ (2007) Polycystic ovary syndrome: diagnosis and treatment. *Am J Med* **120:** 128–132
2 The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* **19:** 41–47
3 The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* **81:** 19–25
4 Nieman LK (2006) Difficulty in the diagnosis of Cushing disease. *Nat Clin Pract Endocrinol Metab* **2:** 53–57
5 Hammer F and Stewart PM (2006) Cortisol metabolism in hypertension. *Best Pract Res Clin Endocrinol Metab* **20:** 337–353
6 Broekmans FJ and Fauser BC (2006) Diagnostic criteria for polycystic ovarian syndrome. *Endocrine* **30:** 3–11
7 Kaltsas GA *et al.* (2004) Secondary forms of polycystic ovary syndrome. *Trends Endocrinol Metab* **15:** 204–210
8 Knochenhauer ES *et al.* (1998) Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* **83:** 3078–3082

© 2007 **Nature Publishing Group**

9 Newell-Price J *et al.* (2006) Cushing's syndrome. *Lancet* **367:** 1605–1617
10 Glintborg D *et al.* (2004) Prevalence of endocrine diseases and abnormal glucose tolerance tests in 340 Caucasian premenopausal women with hirsutism as the referral diagnosis. *Fertil Steril* **82:** 1570–1579
11 Cussons AJ *et al.* (2005) Polycystic ovarian syndrome: marked differences between endocrinologists and gynaecologists in diagnosis and management. *Clin Endocrinol (Oxf)* **62:** 289–295
12 Kaltsas GA *et al.* (2000) How common are polycystic ovaries and the polycystic ovarian syndrome in women with Cushing's syndrome? *Clin Endocrinol (Oxf)* **53:** 493–500
13 Murphy M *et al.* (2006) Polycystic ovarian morphology in normal women does not predict the development of polycystic ovary syndrome. *J Clin Endocrinol Metab* **91:** 3878–3884
14 Balen AH *et al.* (1995) Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. *Hum Reprod* **10:** 2107–2111
15 Invitti C *et al.* (1991) Increased urinary free cortisol and decreased serum corticosteroid-binding globulin in polycystic ovary syndrome. *Acta Endocrinol (Copenh)* **125:** 28–32
16 Putignano P *et al.* (2003) Screening for Cushing's syndrome in obese women with and without polycystic ovary syndrome. *J Endocrinol Invest* **26:** 539–544
17 Invitti C *et al.* (1998) Altered morning and nighttime pulsatile corticotropin and cortisol release in polycystic ovary syndrome. *Metabolism* **47:** 143–148

Acknowledgments
N Krone is a Wellcome Trust Clinician Scientist.
NA Hanley received support as a UK Department of Health Clinician Scientist.
Written consent for publication of Figure 1 was obtained from the patient.

Competing interests
The authors declared no competing interests.

© 2007 **Nature Publishing Group**