Routine screening for Cushing’s syndrome is not required in patients presenting with hirsutism

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Abstract
Context: Prevalence of Cushing’s syndrome (CS) in patients presenting with hirsutism is not well known.
Objective: Screening of CS in patients with hirsutism.
Setting: Referral hospital.
Patients and other participants: This study was carried out on 105 patients who were admitted to the Endocrinology Department with the complaint of hirsutism.
Intervention: All the patients were evaluated with low-dose dexamethasone suppression test (LDDST) for CS.
Main outcome measure: Response to LDDST in patients presenting with hirsutism.
Results: All the patients had suppressed cortisol levels following low-dose dexamethasone administration excluding CS. The etiology of hirsutism was polycystic ovary syndrome in 79%, idiopathic hirsutism in 13%, idiopathic hyperandrogenemia in 6%, and nonclassical congenital hyperplasia in 2% of the patients.
Conclusion: Routine screening for CS in patients with a referral diagnosis of hirsutism is not required. For the time being, diagnostic tests for CS in hirsute patients should be limited to patients who have accompanying clinical stigmata of hypercortisolism.

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Introduction
Hirsutism is the presence of excessive terminal hair in androgen-sensitive skin areas of women. Functional causes such as polycystic ovary syndrome (PCOS), idiopathic hirsutism (IH), and idiopathic hyperandrogenemia (IHA) account for most hirsutism cases. Nonclassical congenital adrenal hyperplasia (NCAH), hyperprolactinemia, androgen-secreting tumors, acromegaly, and Cushing’s syndrome (CS) are other rare causes of hirsutism (1, 2).

The diagnosis of CS is noteworthy as it leads to significant morbidities and increased mortality. Hypercortisolism-associated morbidities, particularly increased cardiovascular risk, may persist in a substantial number of CS patients despite normalization of hypercortisolism (3, 4). Increased mortality and morbidities like hypertension, hyperglycemia, increased fat mass, hypercoagulability, decreased bone mineral density and quality, psychopathologies, and cognitive impairment significantly improve after successful treatment of CS, but even after long-term remission, these morbidities and mortality may not be completely reversible (5). Therefore, early diagnosis and treatment is important before the presentation of overt cardiovascular, metabolic, and psychiatric disorders.

CS has previously been screened in different diseases such as diabetes mellitus, obesity, and hypertension with variable outcomes (6, 7, 8, 9, 10). Most of the patients diagnosed as CS in these studies were subclinical cases that would be missed unless they were tested.

It is essential to rule out other causes of hirsutism such as CS for the diagnosis of functional causes of hirsutism (11, 12). The exclusion of CS is usually based on clinical findings. Although clinical findings may be helpful in the diagnosis of CS in patients with hirsutism, the frequency of CS in patients presenting with hirsutism, who lack physical stigmata suggestive of hypercortisolism, is not well known.

In this study, we primarily aimed to screen CS in patients admitting with the complaint of hirsutism for the first time.
Materials and methods

Subjects

One hundred and five women, who were admitted to the Endocrinology Clinic with hirsutism and accepted to participate in the study, were consecutively enrolled in the study between February 2011 and June 2012. Exclusion criteria were i) being treated for hirsutism in the last 6 months and ii) having any diseases or using any medications that would affect the hypothalamo-pituitary-adrenal axis.

Patients were evaluated by a detailed medical history, including the onset and characteristics of hirsutism, presence of symptoms regarding etiology, menstrual cycle, and fertility. Hirsutism was assessed with modified Ferriman–Gallwey score (FGS) (13). A score ≥8 was accepted as hirsutism.

Materials and protocols

All patients were evaluated in follicular phase of their menstrual cycle. If the patient had oligomenorrhea or amenorrhea, evaluation was carried out during withdrawal bleeding induced by medroxyprogesterone acetate. Serum samples for measurement of LH, FSH, estradiol (E2), prolactin (PRL), total testosterone, androstenedione, 17-hydroxyprogesterone (17-OHP), sex hormone binding globulin (SHBG), DHEAS, androstenedione, 17-hydroxyprogesterone (17-OHP), 11-deoxycortisol (11-S), cortisol, free thyroxine (FT4) and TSH, and IGF1 levels were obtained in the morning after an overnight fast at baseline.

The ACTH stimulation test was performed in patients by administration of a single i.v. bolus of 250 μg synthetic ACTH (Synacthen 0.25 mg/ml; Novartis Healthcare) at 0800 h. Venous blood was drawn through an indwelling catheter at 0, 30, and 60 min after ACTH administration for the determination of 17-OHP and 11-S. On the luteal phase of the cycle (menstrual days 22–24), progesterone was measured.

The diagnosis of PCOS was made according to ESHRE/ASRM (Rotterdam) criteria (14). Women with cycle lengths of >35 days were classified as oligomenorrheic. The ultrasound (USG) diagnosis of polycystic ovaries was made by the presence of ten or more cysts 2–10 mm in diameter arranged around a dense stroma or scattered throughout an increased amount of stroma (15). Ovarian USG was performed by the same investigator (YS). IH was diagnosed in patients with hirsutism if they had normal ovulatory functions, normal ovarian morphology on USG, and normal androgen levels. Patients with elevated serum androgen levels in the presence of normal ovulatory functions and normal ovarian morphology were included in IHA group. All the patients with IH or IHA have been shown to be ovulatory by the measurement of day 22–24 serum progesterone level (>8 nmol/l). Hyperandrogenemia was defined as increased serum testosterone, androstenedione, and/or DHEAS levels. An ACTH-stimulated 17-OHP concentration >30 nmol/l (10 ng/ml) was considered as the criterion for NCAH due to 21-hydroxylase deficiency (16, 17, 18). The diagnosis of 11-β hydroxylase deficiency was made if the adrenal 11-S response to ACTH stimulation exceeded threefold the 95th percentile of controls (16). The 95th percentile for the 11-S response measured in our healthy subjects was defined as 36.6 nmol/l (12.2 ng/ml) previously (19). Patients filling the biochemical criteria of NCAH were tested for the presence of genetic mutation.

CS was excluded by low-dose dexamethasone suppression test (LDDST). Forty-eight-hour dexamethasone (2 mg/day) suppression test was used and a cortisol value of ≤1.8 μg/dl was considered as normal. Androgen-producing tumors were diagnosed/excluded by the history of rapid-onset hirsutism, highly elevated testosterone and DHEAS levels, and the radiological investigation of the adrenal glands and the ovaries.

Assays

Testosterone (DIAsource ImmunoAssays, Louvain-la-Neuve, Belgium), DHEAS (Immunotech, Marseille, France), androstenedione (DSL-3800, Diagnostic System Laboratories, Inc., Texas, U Costa Mesa, CA, USA), 17-OHP (DSL-3SA, TX, USA), 11-S (DIAsource ImmunoAssays), and cortisol (DSL-2100, TX, USA) were measured by RIA method. Serum SHBG and IGF1 levels were measured by IRMA (SHBG: Zentech, Angleur, Belgium, and non-extraction IGF1 DSL-2800, TX, USA). FSH, LH, progesterone, and E2 (ACS:180, Bayer) were measured with a chemiluminescence enzyme immunoassay system. The free androgen index (FAI) was calculated using the following formula: testosterone (nmol/l)/SHBG nmol/l) × 100. FT4, TSH, and PRL were measured by automated random-access immunoassay analyser (Advia Centaur, Siemens, Erlangen, Germany).

Statistical analyses

All statistical analyses were performed by the Statistical Package for Social Sciences (SPSS) for Windows version 15. The continuous data were presented as mean ± S.D.
Results

The etiology of hirsutism in the patients was IH in 13%, IHA in 6%, NCAH in 2%, and PCOS in 79% of the patients. Acromegaly was excluded in the patients as all of them had normal IGF1 levels according to age and sex (data not shown).

Five of 105 patients were suspected to have NCAH according to ACTH stimulation test results. Basal 17-OHP levels were above 2 ng/ml in all patients suspicious for NCAH. Peak 17-OHP responses following ACTH administration were found to be 14.4, 13.5, 13.3, and 43.3 ng/ml and the latter two were found to have CYP21 (CYP21A2) mutations (patient 1: P453S heterozygote on exon 10 and patient 2: Q318X heterozygote on exon 8). Patients with confirmed diagnosis of NCAH after genetic analysis had the highest baseline 17-OHP levels (7.8 and 43.3 ng/ml for patients 1 and 2 respectively). One of the patients was suspected to have NCAH due to 11β-hydroxylase deficiency as baseline and peak 11-S response to ACTH stimulation was 5.4 and 14.7 ng/ml respectively, but it could not be confirmed with genetic analysis. These three patients without CYP21 and CYP11 mutations were diagnosed as PCOS.

All the patients had suppressed cortisol levels following low-dose dexamethasone administration excluding CS. None of the patients had acromegaly, prolactinoma, adrenal, or ovarian androgen-secreting tumors.

Clinical features and basal hormone levels of patients are summarized in Tables 1 and 2. Cortisol levels following LDDST in the patients are presented in Fig. 1. Cortisol levels after LDDST were 0.35 ± 0.27, 0.46 ± 0.38, 0.48 ± 0.42, and 0.15 ± 0.01 μg/dl respectively in IH, IHA, PCOS, and NCAH groups.

Discussion

In the routine evaluation of hirsutism, endocrinological disorders such as CS, acromegaly, hyperprolactinemia, and thyroid dysfunction need to be excluded. PRL is recommended to be measured particularly in patients with oligo/amenorrhea. Assessment of CS, acromegaly, and thyroid dysfunction is suggested if other features of these conditions are present (12).

There are striking similarities between CS and one of the most common causes of hirsutism, namely PCOS. Both may be associated with hirsutism, menstrual irregularities, polycystic ovaries, obesity, and insulin resistance (20). Proximal muscle weakness and delicate skin are some clues in favor of CS. However, CS is associated with increased cardiovascular mortality (21). The standardized mortality ratio (SMR) was found to be 1.85–1.9 in patients with CS. SMR was shown to be increased to 3.73 in patients with persistent Cushing’s disease after transsphenoidal surgery (22).
Furthermore, persistently increased mortality had been reported even after long-term biochemical remission (23, 24). In a recent study, cardiovascular risk was found to be persistent despite dramatic improvements in body composition abnormalities (25). The lack of complete reversibility of associated morbidities and mortality may reinforce the need for revision of CS remission criteria, but at least as important is to limit the duration of exposure to hypercortisolism. Therefore, early diagnosis of CS is of great importance before the presentation of overt cardiovascular or metabolic disorders.

In this study, we screened 105 patients, who were admitted to the Endocrinology Department with the main complaint of hirsutism, for CS irrespective of their suggestive findings of hypercortisolism. None of the patients was diagnosed as CS by LDDST. In a study by Glintborg et al., whose aim was to compare the metabolic features of patients with hirsutism, only one CS was defined in patients with hirsutism who had clinical findings suggestive of CS. However, the suspicious findings were not mentioned in that study. They used either 24-h urinary free cortisol or overnight dexamethasone suppression test for exclusion and confirmed diagnosis of CS with LDDST (26). Therefore, although there may be overlapping clinical features, CS seems to be rare among patients with hirsutism. As we did not detect any CS in hirsute patients, it is not possible to comment on the suggestive clinical findings.

The prevalence of CS among diabetic patients was reported to range from 0 to 9.4% depending on the associated features (7, 8, 9, 27, 28, 29). Clinical features such as being overweight, having poor metabolic control, and hospitalization for DM were found to be associated with increased prevalence of CS in diabetics (8, 27, 28). Not only patient selection criteria but also differences in test methodology, cut-off values, and cortisol assay used are thought to be responsible for the large range of variation in performed studies (30).

Overnight dexamethasone suppression test has been reported to have a false positivity rate of 20–30% in previous studies when performed for screening of CS in diabetic individuals (7, 9, 10, 28). The specificity of overnight DST, midnight salivary cortisol, and urinary free cortisol were found to be 90, 96, and 84–92% respectively for the diagnosis of CS (6). No false positivities were detected in this study presumably due to two reasons: first, skipping over the overnight DST and directly performing LDDST and secondly, different disorders screened.

Screening studies for obese populations usually revealed a low prevalence of CS except for one study that found a prevalence of 9% (6, 31, 32, 33). Moreover, false-positivity rate was found to be 25%, which resulted in unnecessary further investigations (6). In contrast, CS was found to be present in 4.8% of patients with osteoporosis and the prevalence increased up to 10.8% when an accompanying vertebral fracture was found (34). Despite the relatively high prevalence of CS in screening studies, screening of occult CS was suggested to have more cons, like relatively low performance of diagnostic tests, unknown outcomes, and beneficial impact of treatment and acceptability by patients or health care systems (35). The authors also addressed the unknown prevalence of occult CS in hirsute patients in their review (35). Regardless of the study population, screening for CS will diagnose unrecognized cases in cost of increased unnecessary diagnostic test procedures. So cost-effectiveness analysis will be valuable besides performing studies with larger numbers of subjects and using more specific standardized tests.

Nevertheless, LDDST seems to be rather specific at least for hirsute patients, as we did not detect any false positivity.

The etiologies of hirsutism in this study were PCOS (79%), IH (13%), IHA (6%), and NCAH (2%), which was similar to the previous literature (26, 35, 36, 37, 38). Patients were checked for the presence of ovulation, and hirsute patients with anovulatory regular cycles were included in the PCOS group. We did not detect any androgen-secreting tumor, which can be explained by its rarity as a cause of hirsutism.

In conclusion, routine screening for CS in patients with a referral diagnosis of hirsutism is not required. For the time being, diagnostic tests for CS in hirsute patients cannot be recommended if the patient does not have accompanying clinical stigmata of hypercortisolism.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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