European Journal of Obstetrics & Gynecology and Reproductive Biology 175 (2014) 145–148

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Polycystic ovarian syndrome and Cushing's syndrome: a persistent diagnostic quandary

Jessica Brzana [a], Christine G. Yedinak [b,c], Nadia Hameed [a], Adeline Plesiu [a], Shirley McCartney [b,c], Maria Fleseriu [a,b,c,*]

[a] Department of Medicine, Division of Endocrinology, Portland, OR, USA
[b] Department of Neurological Surgery, Portland, OR, USA
[c] Northwest Pituitary Center, Oregon Health & Science University, Portland, OR, USA

ARTICLE INFO

Article history:
Received 26 June 2013
Received in revised form 2 December 2013
Accepted 31 December 2013

Keywords:
Cushing's syndrome
Cushing's disease
Polycystic ovary syndrome
Diagnosis
Hypercortisolism
Screening

ABSTRACT

Objective: To retrospectively review institutional records of female patients of reproductive age with Cushing's disease (CD) and determine if and how many had been previously diagnosed as having solely polycystic ovarian syndrome (PCOS). To determine whether clinical patterns might be useful in identifying appropriate candidates for hypercortisolism screening in women suspected of PCOS.
Study design: The study included 50 patients with pathologically proven CD at Oregon Health & Science University, Northwest Pituitary Center between 2006 and 2011. Physical, clinical, and biochemical features for hypercortisolism were compared.
Results: Of 50 patients with pathologically proven CD, 26 were women of reproductive age. Of these, half had previously been diagnosed with and treated initially solely for PCOS. Hirsutism and menstrual abnormalities were more common in the group with an initial PCOS diagnosis than in the group with an initial CD diagnosis.
Conclusions: Prolonged exposure to hypercortisolism has been linked with increased mortality and morbidity. Tests for hypercortisolism in all the PCOS cases we report led to an appropriate CD diagnosis. Future research should focus on when and which (if not all) women with suspected PCOS should be tested for hypercortisolism.

1. Introduction

Cushing's syndrome (CS) is a rare condition of chronic hypercortisolism most often caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (i.e., Cushing's disease (CD)). Early identification and treatment of CD are essential [1] as CD is associated with increased mortality rates of 1.8- to 4.8-fold that of the general population [2–4]. CD is also associated with chronic debilitating complications and reduced quality of life [5]. Regrettably, however, CD diagnosis is often delayed, with a mean time-to-diagnosis interval of 6 years from initial symptom onset [6].

Delayed diagnosis may stem in part from the fact that many CS/CD signs and symptoms, including centripetal obesity, depression, fatigue, menstrual abnormalities, acne, and peripheral edema, are common to other hormonal disorders [7]. Other CD signs such as hirsutism, facial plethora, abdominal striae, proximal myopathy and a dorsocervical fat pad may aid differential diagnosis [7], but distinguishing CD based on clinical features alone remains problematic.

In contrast to CS, polycystic ovarian syndrome (PCOS) occurs commonly among women of reproductive age [8]. PCOS is a complex endocrine disorder with an etiology not completely understood, and represents a significant cause of female infertility [9]. PCOS definitions vary [10–12], but the condition is generally diagnosed based on the presence of at least two of three key features: hyperandrogenism, anovulation, and polycystic ovaries [11]. Generally, PCOS is diagnosed when other specific causes of hyperandrogenism have been excluded [13–15]. While CD is less common than PCOS [9,16,17], particularly among women of reproductive age, the serious outcomes associated with CD indicate that a CD diagnosis should be considered [2,3]. This also offers the opportunity to identify the underlying (and treatable) cause in the small proportion of women with CD. It is possible that women may have both a pituitary adenoma and PCOS, but differential diagnosis is required. Typically, clinicians test for CS only in specific circumstances that include the multiple and progressive features predictive of CS [7].

* Corresponding author at: Medicine and Neurological Surgery, Oregon Health & Science University, Mail Code: BTE 28, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA. Tel.: +1 503 494 4314; fax: +1 503 346 6810.
E-mail addresses: fleseriu@ohsu.edu, mccartns@ohsu.edu (M. Fleseriu).

0301-2115/$ – see front matter © 2014 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejogrb.2013.12.038

In this retrospective review we noted a high prevalence of women with pathology-proven CD, who had previously been diagnosed with, and treated for, PCOS alone. In patients such as these, consideration of the possible presence of CD could have allowed timely treatment of hypercortisolemia and a reduction in associated morbidity. We sought to determine if specific physical, clinical, or biochemical features could be useful in identifying candidates for hypercortisolism screening in women suspected of having PCOS.

2. Materials and methods

We conducted a retrospective chart review from a prospectively maintained database of all patients who had a proven CD pathology at Oregon Health & Science University (OHSU) Northwest Pituitary Center between 2006 and 2011. Patients were stratified based on initial diagnosis: PCOS (Group 1) or CS (Group 2). Screening for CS was achieved with recommended first line tests: two salivary cortisol, two 24-h urinary free cortisol (UFC), and/or an overnight dexamethasone test [7]. Urinary free cortisol determination has been widely used as an initial screening tool for CS because it provides measurement of cortisol over a 24-h period; however, sensitivity has been estimated at 45–71% to achieve 100% specificity. Results are assay dependent. Elevations of greater than 2–3 times the upper limit of normal (ULN) are recommended for an unequivocal hypercortisolism diagnosis [7,18,19]. In the normal population, cortisol levels are lowest late at night, thus late-night salivary cortisol measurements take advantage of the alterations in circadian rhythm of cortisol secretion to identify patients with CS. Salivary cortisol levels >4.2 nmol/L are 90–95% sensitive and specific for CS. The overnight low-dose dexamethasone suppression test (LDDST) requires administration of 1 mg of dexamethasone at 11 pm with subsequent measurement of cortisol at 8 am. A cutoff value of less than 1.8 μg/dL (50 nmol/L) excludes CS with an overall sensitivity of 90–95% [7,19]. Mild CS is often difficult to distinguish from normal cortisol secretion or pseudo-Cushing states. Our patients with abnormal 24 h UFC, midnight salivary cortisol or LDDST underwent further testing, including dexamethasone suppression-corticotropin-releasing hormone (CRH) stimulation test as a final arbiter to exclude pseudo-Cushing's [7].

Patients with positive screening and confirmatory testing underwent inferior petrosal sinus sampling (IPSS), which helps localize ACTH excess to the pituitary. Bilateral IPSS and simultaneous peripheral ACTH measurements were made at baseline, 2–3 min, 5 min, and 10 min after intravenous administration of CRH at 1 μg/kg. An inferior petrosal sinus-to-peripheral ACTH ratio of greater than 2 is consistent with CD. This study should not be used to establish a CS diagnosis, but is useful in determining tumor lateralization.

Positive pathology was defined as the presence of ACTH staining, basophilic hyperplasia and Crooke's hyaline changes in the tumor on histological analysis.

Both groups were evaluated for differences in clinical features (Table 1), biochemical findings, and estimated duration of CD symptoms. Biochemical data were analyzed as available.

2.1. Statistics

Inter-group differences in biochemical results and physical features were evaluated using ANOVA. Correlations between biochemical screening tests for CS were calculated using Spearman's rank correlation coefficient. Data are presented as ±standard deviation (SD). The OHSU Institutional Review Board approved the study.

Table 1
Clinical features analyzed.

Age
Weight gain (self-reported)
Body mass index
Abnormal menses
Hirsutism
Acne
Alopecia
Central adiposity
Facial rounding
Facial plethora
Proximal muscle weakness
Fatigue
Sleep disturbance
Depression
Easy bruising
Violaceous striae
Dorsocervical fat pad
Supraclavicular fat pad

3. Results

3.1. Patient selection

Fifty patients from the surgery cohort, during the period studied, had pathology-confirmed ACTH-secreting corticotroph tumor. Thirty-eight were female and 26/38 (68.4%) were of reproductive age (≤50 years). Of the 26, 13 were initially diagnosed with PCOS alone (Group 1), while the other 13 were initially diagnosed with CS (Group 2) (Fig. 1).

3.2. General patient demographics

Overall, mean patient age at presentation was 37 ± 8.3 years, mean body mass index (BMI) was 35.6 ± 7.3 kg/m^2 and 85% presented with a BMI of >30 kg/m^2. Estimated mean disease duration before diagnosis was 38.4 ± 32.8 months. Overall, six patients (23.1%) had macroadenomas, 18 (69.2%) had microadenomas, and two (7.7%) had no available imaging data. Common clinical features at presentation included weight gain (96% of patients), history of abnormal menses (87%, mean duration 29.8 ± 39.5 months), hirsutism (85%), acne (69%), and alopecia (46%). Mean duration of follow-up was 17.6 ± 15 months. Tests for hypercortisolism had a high inter-test correlation, with the highest correlation found between UFC and dexamethasone suppression test (DST; $rs = 0.883$, $P < 0.001$).

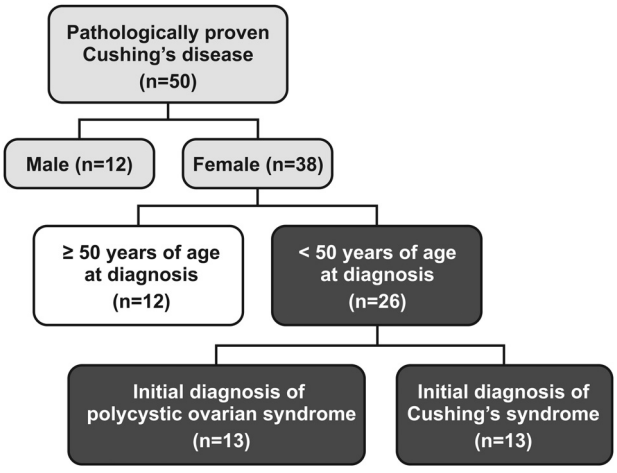

Fig. 1. Retrospective patient selection criteria of all patients who had a proven Cushing's disease pathology (years 2006–2011).