Pseudo-Cushing’s States

Updated: August 22, 2012

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Pseudo-Cushing’s states (PCS) are defined as those conditions associated with increased cortisol production with all or some of the clinical features of Cushing’s syndrome (CS), combined with biochemical evidence of hypercortisolism (1). Although resolution of the primary condition leads to disappearance of the Cushing-like features and hypercortisolism the underlying mechanisms remain unclear. Most evidence suggests central stimulation of a corticotropin-releasing hormone (CRH), either at the hypothalamic or supra-hypothalamic level (2).

Conditions Associated with Pseudo-Cushing’s States

PCS are a heterogeneous group of disorders, either physiological or non-physiological, that lead to increased cortisol production and stigmata of hypercortisolism. The physiological conditions include surgery associated stress, severe illness, emotional stress, intense aerobic exercise and caloric restriction.Stress-related cortisol secretion is associated with lack of diurnal cortisol rhythm, failure to adequately suppress cortisol levels after dexamethasone administration, abdominal obesity, hypertension, hyperlipidemia and insulin-resistance (3). Non physiological conditions often associated with PCS are amongst others chronic alcoholism and alcohol withdrawal syndrome, major depression, poorly controlled diabetes mellitus, polycystic ovary syndrome (PCOS) and obesity (4-7).

Chronic alcoholism is a rare cause of pseudo-Cushing’s syndrome (8). In the literature less than 50 cases of alcoholic patients that manifested clinical or biochemical features of CS, which eventually proved to be the result of alcoholic addiction, have been reported so far. Ninety percent of the patients had a moon face, 69% hypertension, 81% muscle weakness or tiredeness, 12.5% striae and 75% truncal obesity (9). In the majority of cases hormonal abnormalities cannot be attributed solely to the coexistant liver dysfunction. Most of these patients have increased secretion of CRH or impaired hypothalamic or pituitary responsiveness to cortisol (10). There is also evidence that genetic influences may determine the predisposition of alcoholics to develop PCS (11). Typically, the hormonal abnormalities disappear rapidly after at least a month abstinence from alcohol. Alcoholic patients diagnosed with CS should have repeat clinical and biochemical work-up after cessation of alcohol before subsequent

investigation and/or intervention can be performed.

The vast majority of patients with major depressive disorders exhibit some degree of cortisol hypersecretion (2). Even in severely depressed patients with substantially increased cortisol production clinically evident CS is rarely encountered. However, some patients may be difficult to be distinguished from those with Cushing's disease (CD). The primary defect is hypothesised to be above the hypothalamic level leading to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis that is reversible after remission of depression (12). Patients with renal failure often exhibit cortisol hypersecretion that is not associated with typical end organ effects of hypercortisolism (13). Furthermore, patients with primary glucocorticoid receptor resistance may manifest some symptoms and/or signs of CS due to high levels of adrenocorticotrophin (ACTH) and cortisol but rarely exhibit the whole spectrum of cutaneous or muscular signs of CS (14). Finally, another often difficult to diagnose PCS state is factitious glucocorticoid intake (15). Patients present with rapid onset of symptoms, low ACTH levels, whereas cortisol levels can be high or low depending on the glucocorticoid taken (high with hydrocortisone, low with synthetic glucocorticoids) and the adrenal glands may be atrophic (15).

Some commonly but less specific signs encountered in patients with CS (hypertension, disorders of carbohydrate and lipid metabolism and abdominal obesity) are found in patients with abdominal obesity and the metabolic syndrome. Some of this patients may have subtle abnormalities of the HPA axis (cortisol hypersecretion and abnormal cortisol dynamics) and thus could represent a PCS. However, such patients lack the specific signs of endogenous hypercotisolism (thinning of the skin, bruising and proximal myopathy). Occasionally, when uncertainty remains further investigation may be required to distinguish them from patients with CS.

Differential Diagnosis between Pseudo-Cushing's States and Cushing's syndrome

The discrimination between CS and PCS is difficult because many symptoms of CS, such as excessive body weight, depressed mood, hypertension and irregular menses, are also prevalent in PCS. Furthermore, the substantial overlap of biochemical tests commonly used for the diagnosis of CS and the presence of subtle if any clinical features makes the differentiation of true, particularly mild CS from PCS challenging for the physician. Although persistent elevation of 24-h urinary free cortisol (UFC) levels in the presence of cutaneous or muscle signs of CS that are seldomly present in PCS suggest the diagnosis of CS, patients with less obvious signs present a diagnostic dilemma.

Biochemical tests commonly used for the diagnosis of CS

Morning serum total and free cortisol levels among patients with CS, PCS and normal subjects overlap making this test unsuitable for the diagnosis CS and/or PCS (16). Similarly, the absence of diurnal serum cortisol rhythm fails to discriminate patients with PCS from patients with CS(17). Twenty-four hour urinary free cortisol levels (UFC) can be mildly elevated in patients

with PCS but can also be normal in approximately 10-20% of patients with CS (7,18). Both the 1mg overnight and the formal 2-day low-dose dexamethasone suppression tests (LDDST) although being highly sensitive have a low specificity as inadequate cortisol suppression has been documented in patients with obesity, severe illness, alcoholism, depression and other psychiatric disorders (19-20). In a recent study that included patients with CS and PCS the specificity of the above tests in correctly identifying patients with CS was 18% for abnormal cortisol rhythm, 44% for UFC, 58% for the 1mg DST and 74% for the LDDST, respectively (17).

Midnight serum or salivary cortisol

The loss of normal cortisol circadian rhythm with absence of a late-night cortisol nadir is consistent with the abnormal cortisol dynamics seen in patients with CS. Midnight serum cortisol (MSC) levels have been used to distinguish patients with CS from those with PCS. In a study that included 240 patients with CS and 23 patients with PCS, a MSC value greater than 7.5 μ g/dl correctly identified 96% patients with CS, while a value less then this cut-off was found in all patients with PSD (96% sensitivity and 100% specificity) (19). In a more recent study including a smaller number of patients that used a 9.3 μg/dl MSC value as a cut-off, the test achieved 100% sensitivity and specificity in distinguishing patients with CS from PCS (21). The midnight cortisol measurement requires inpatient admission for a period of 48h or longer to avoid false positive responses due to the stress of hospitalization. The blood sample must be drawn within 5–10 min after waking the patient, or through an indwelling line, to avoid false positive results. Recently, measurement of salivary cortisol (SC) has also been used as it is in equilibrium with serum free cortisol and independent of saliva production (22). In a study that included 151 subjects a cut-off SC value of 3.6 nmol/L (0,13 μg/dl) at 11 P.M., achieved a sensitivity and specificity of 92% and 96%, respectively (23). In a subsequent study of 122 patients with CS and 21 patients with PCS, a 93% sensitivity and 100% specificity was obtained using a 15.2 nmol/L (0,55 μg/dl) SC value as a cut-off (24). Several factors that can affect SC measurement should be considered when evaluating the results. Patients are advised to restrain from smoking or licorice consumption on the day of the test, as both contain the 11 β -hydroxysteroid dehydrogenase type 2 inhibitor, glycyrrhizic acid, and may lead to false elevated results (25).

Dexamethasone-CRH Test

A recommended test to distinguish between mild CD and PCS is the dexamethasone-CRH test. This test combines two tests, the LDDST and the CRH test. Two hours after the last dexamethasone dose of the LDDST, 1μg/kg of ovine CRH is administered intravenously and serum cortisol is measured 15 minutes after CRH administration. In theory, dexamethasone suppresses serum cortisol levels in individuals without CS as well as in a small number of those with CD, but following CRH administartion patients with CD respond with an increase in ACTH and cortisol secretion. In a study that included 39 patients with mild CD with UFC values that overlapped with those of 19 patients with PCS, a serum cortisol measured 15 minutes after CRH greater than 1.4 μ g/dl correctly identified all patients with CD, while all patients with PCS had values less than 1.4 μ g/dl (100% sensitivity and specificity) (20). In the same study, the CRH test without dexamethasone pre-treatment exhibited a 100% specificity and 64% sensitivity respectively. However, subsequent studies did not confirm these findings and

revealed a lower diagnostic accuracy of the Dexamethasone-CRH Test (sensitivity 100% and specificity 50-62,5%) (17,21). By increasing the threshold to 4 μ g/dl sensitivity was maintained at 100% and specificity was improved to 86% (21).The reasons for the differences in the responses to the combined test are not clear. In part, they may be attributed to conditions that alter the metabolic clearance of dexamethasone or differences in the performance of cortisol assays used. Furthermore, medications commonly prescribed in hypercortisolemic patients undergoing dexamethasone-CRH testing such as antidepressants, statins, calcium channel blockers, proton pump inhibitors may contribute to the variable diagnostic accuracy of this test (26).

Since CRH test alone does not reliably distinguish CD from normality or PCS a novel approach of the test by taking into account both ACTH and cortisol increments after CRH infusion has been proposed. Simultaneous presence of either basal serum cortisol >12 mg/dl and peak plasma ACTH>54 pg/ml or peak serum cortisol >21 mg/dl and peak plasma ACTH >45 pg/ml had 91.3% and 94.8% sensitivity and 98.2% and 91.2% specificity respectively in detecting CD. Further studies are needed to validate these findings (27).

Desmopressin Test

The vasopressin analogue desmopressin (1-deamino-8D-arginine vasopressin, DDAVP) that stimulates ACTH release in patients with CD but not in the majority of normal, obese, and depressed subjects, has also been used to distinguish patients with PCS from those with CD. In a study that included 20 patients with CD and 30 patients with PCS, a peak absolute ACTH increase of 6 pmol/L (27.2 pg/mL) within 30 minutes after DDAVP infusion exhibited a sensitivity of 90% and a specificity of 96.7% respectively (17). In a similar study including 29 patients with CD and 23 patients with PCS using the same peak ACTH cut-off the sensitivity and specificity was 81,5% and 90% respectively (28). In a recent study simultaneous positivity for basal serum cortisol greater than 331 nmol/liter and absolute ACTH increment after DDAVP greater than 4 pmol/liter yielded a sensitivity of 90.3% and a specificity of 91.5% for the diagnosis of CD (29). A comparative study between this novel approach of interpreting DDAVP and the CRH test as described above showed identical and excellent diagnostic performance (sensitivity 96,6% and specificity100% for both tests) with a significantly higher number of concordant diagnoses (58 cases of 60) (30).

In conclusion, the differential diagnosis between CS and PCS still represents a considerable challenge as no test warrants 100% diagnostic accuracy (table 1). Further studies with a larger number of patients with mild CS and pseudo-Cushing's state evaluating the diagnostic accuracy of each of tests alone or their combination are necessary.

Table.1 : Tests used to distinguish Cushing's syndrome from Pseudo-Cushing's states and their respective sensitivity and specificity.

Test used	Diagnostic Cut-off	Sensitivity (%)	Specificity (%)	reference

Midnight serum cortisol	7.5 µg/dl	96	100	19
	9.3 µg/dl	100	100	21
Midnight salivary cortisol	3.6 nmol/L	92	96	23
	15.2 nmol/L	93	100	24
CRH Test	basal serum cortisol >12 mg/dl and peak plasma ACTH>54 pg/ml	91.3	98.2	27
CRH Test	peak serum cortisol >21 mg/dl and peak plasma ACTH >45 pg/ml	94.8	91.2	27
Dexamethasone-CRH Test (serum cortisol 15 minutes after CRH administration)	1.4 µg/dl	100	100	20
	1.4 µg/dl	100	50	17
	1.4 µg/dl	100	62.5	21
	4 µ g/dl	100	86	21
Desmopressin Test (peak absolute ACTH increase within 30 minutes after DDAVP)	6 pmol/L	90	96.7	17
	6 pmol/L	81.5	90	26
Desmopressin Test	basal serum cortisol > 331 nmol/lt and absolute ACTH increment >4 pmol/lt	90.3	91.5	29

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