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A woman presenting with hypercortisolism

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Cushing's syndrome is the result of extended exposure to excessive glucocorticoids from endogenous or exogenous sources (1). The most common cause of endogenous Cushing's syndrome is a pituitary adenoma (Cushing disease). Less common causes are adrenocortical tumors and extrapituitary adrenocorticotropin-producing neoplasias. Cushing's syndrome is challenging to diagnose (2). During the last decades a condition named 'Pseudo-Cushing' has been described (3). In this medical condition patients display signs, symptoms, and abnormal hormone levels as seen in Cushing's syndrome. The glucocorticoid excess may be caused by alcohol abuse, anorexia nervosa, visceral obesity, and depression. These conditions with secondary glucocorticoid excess can make the diagnosis of Cushing's syndrome particularly difficult (4). This case report describes the diagnostic challenges we met to discriminate between Cushing's syndrome and 'Pseudo-Cushing'.

Case

At the emergency department a 43-year-old female with a history of depression, alcohol and cannabis abuse was admitted. She was found at home sitting naked on the floor, mentally confused, neglected and inactive. Physical examination showed cushingoid signs with accumulation of fat in the face (moon facies), central obesity, marked abdominal striae, extensive acne, hirsutism and dorsocervical fat pads (buffalo hump). Laboratory investigations demonstrated elevated levels of glucose, bilirubin, alanin-aminotransferase (ALAT), gamma glutamyl transpeptidase (gamma GT), and CRP (Table 1). Levels for aspartate aminotransferase (ASAT) and alkaline phosphatase (AF) were normal (Table 1). A tox-screen showed an ethanol level of 0.02 g/L (= promille).

Cushing's disease was suspected besides intoxication, de novo hyperglycemia and psychosis. Additional investigations were carried out. An elevated urinary free cortisol level (265 nmol/24h and 549 nmol/24h; reference value 55-250 nmol/24h) was measured on two separate occasions. The morning adrenocorticotrophin (ACTH) concentration was also elevated (43.9 ng/L; reference value 9-52 ng/L). A short dexamethason suppression test (1mg of dexamethason overnight) showed inadequate suppression of a morning plasma cortisol (0.58 umol/L; reference value <0.05 umol/L). Magnetic resonance imaging (MRI) of the pituitary revealed no abnormalities. In view of the raised urinary free cortisol and the non-suppressible cortisol concentrations after dexamethasone, together with high-normal ACTH concentrations, pituitary-dependent Cushing's syndrome was considered. However, as the MRI of the pituitary was normal, a high-dose dexamethasone test was performed together with midnight and morning cortisol sampling, in order to confirm this suspected diagnosis. The results of these additional investigations are summarized in table 2. Following high-dose dexamethasone (5 mg) the cortisol concentration was appropriately suppressed at 0.02 umol/L. There was a normal diurnal variation of cortisol as shown by the morning and midnight cortisol concentrations. As these results were not in line with the previous findings another measurement of urinary free cortisol was performed and was within the normal range (219 nmol/24h; reference value 55-250 nmol/24h). Taking all these results into consideration the diagnosis of Pseudo-Cushing was finally made.

Table 1. Laboratory results of the patient

	Patient's values	Reference values	
Glucose	21.8	4.0-5.6	mmol/L
Bilirubin	19.6	<17	umol/L
CRP	47	<10	mg/L
ALAT (U/L)	46	<40	U/L
Gamma GT (U/L)	420	<45	U/L
ASAT (U/L)	35	<35	U/L
AF (U/L)	132	<140	U/L
Ethanol (g/L)	0.02	<0.1	g/L

Conclusion

This case clearly demonstrates the difficulties to establish the diagnosis of Cushing's syndrome and

Table 2. Results of timed cortisol and ACTH concentrations together with cortisol concentrations after low-dose (1 mg) and high-dose (5 mg) dexamethasone testing

	Patient's values	Reference values	
Urinary free cortisol	549	55-250	nmol/24 h
9 a.m. ACTH	43.9	9-52	ng/L
Cortisol after 1 mg dexamethasone	0.58	< 0.05	umol/L
Cortisol after 5 mg dexamethasone	0.02	< 0.05	umol/L
8 a.m. cortisol	0.61	0.14-0.64	umol/L
Midnight cortisol	0.08	< 0.2	umol/L

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illustrates the nuances of a so-called pseudo-Cushing state, which aggravates the differential diagnostic dilemmas of elevated cortisol concentrations. The discrimination between Cushing's syndrome and these frequently occurring pseudo-Cushing states is difficult because many symptoms of Cushing's syndrome, such as overweight, depressed mood, hypertension and irregular menses, are also prevalent in pseudo-Cushing's syndrome, and therefore, biochemical tests often provide equivocal results resulting in a low specificity.

The most frequent occurring abnormalities are insufficient suppression after low-dose dexamethasone or increased 24-hour urinary free cortisol. An urinary free cortisol concentration more than 4 times above the upper reference limit confirms the diagnosis of Cushing's syndrome. However, values up to 2-4 times increased may also be found in case of stress and in patients with pseudo-Cushing. Each test has its limitations. Twenty-four-hour urinary collections are inconvenient and often incomplete. The 1mg overnight dexamethasone suppression test has a significant false positive rate, especially in chronically ill or obese patients and in patients with major depression or other psychiatric disorders. An additional problem is the variable metabolic clearance of dexamethasone, which is especially problematic in patients receiving medications that induce the cytochrome P450-related enzymes or in patients with renal or hepatic failure.

Physiological cortisol secretion is characterized by a circadian rhythm. Serum cortisol concentration reaches its zenith in the morning (06:00-08:00h) and its nadir in the night during the first half of normal sleep. A study of Papanicolauo et al. showed that Pseudo-Cushing individuals retain a normal circadian rhythm for cortisol, in contrast to patients with Cushing's syndrome (5). This is in agreement with our findings. The authors believe that midnight cortisol sampling may be an extremely useful adjunct in patients who pose a diagnostic dilemma.

Yanovski et al. demonstrated that the low-dose dexamethasone test followed by corticotrophin-releasing factor (CRF) stimulation could be used to discriminate between patients with pituitary-derived Cushing's disease and pseudo-Cushing's (6). Another tool available to the clinician is the desmopressin (DDAVP) test (7). Albeit of little use in patients with adrenal Cushing's syndrome or ectopic ACTH syndrome, the test has been proposed to be valuable in patients with mild hypercortisolism and normal ACTH levels in whom the differential diagnosis has narrowed to Cushing's disease or Pseudo-Cushing (8). Its ability to discriminate between Cushing's disease and Pseudo-Cushing is related to the fact that DDAVP usually elicits a marked elevation of plasma ACTH and serum cortisol in most patients with Cushing's disease - likely due to up-regulation of pituitary vasopressin receptors (V3) – but generally not in Pseudo-Cushing or in healthy subjects (9).

The overlapping clinical features of the two conditions and the similar values frequently determined in tests such as urinary free cortisol and serum cortisol after dexamethasone suppression in the respective patients make it difficult to distinguish subjects with Pseudo-Cushing from Cushing's syndrome patients.

In conclusion, this case demonstrates the complexities of accurately diagnosing Cushing's syndrome.

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