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The difficulties of pseudo-Cushing's syndrome (or "non-neoplastic hypercortisolism")

Les difficultés du pseudo syndrome de Cushing (ou hypercortisolisme fonctionnel)

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Abstract

Pseudo-Cushing's syndrome covers different pathological conditions responsible for mild-to-moderate ACTH-dependent hypercortisolism, related not to an ACTH-secreting tumor but rather to CRH and/or AVP hypothalamic secretion through activation of various neural pathways, in patients generally displaying excess central adiposity. It is better termed "non-neoplastic hypercortisolism" (NNH). The main conditions implicated in NNH comprise: neuropsychiatric disorder, alcohol abuse, insulin-resistant obesity, polycystic ovary syndrome, and end-stage kidney disease. Glucocorticoid resistance is one differential diagnosis, as are some cases of primary adrenal disease with incompletely suppressed ACTH. Differentiating between NNH and mild-to-moderate Cushing's disease can be a real challenge. Clinical analysis, based on thorough history taking and screening for catabolic signs is essential; useful explorations include midnight serum or salivary cortisol and Dex/CRH and ddAVP stimulation response. Pituitary MRI suffers from limitations regarding both sensitivity and specificity, while bilateral inferior petrosal sinus sampling cannot distinguish between pituitary ACTH secretion by a tumor or by normal cells stimulated by endogenous CRH. Definitive diagnosis of functional etiology requires demonstrating that treatment of the underlying condition restores normal secretion of ACTH and cortisol, but this is not always possible. Lingering diagnostic uncertainty has to be accepted in certain patients, who will have to be followed up for some time before diagnosis can be considered more or less definitive.
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Keywords: Pseudo-Cushing's syndrome; Non-neoplastic hypercortisolism; Dexamethasone/CRH test; ddAVP test; Alcohol abuse; Neuropsychiatric disorder

Résumé

Le terme « pseudo syndrome de Cushing » regroupe différentes situations pathologiques qui sont associées à un hypercortisolisme ACTH dépendant modéré, qui n'est pas en rapport avec une tumeur secrétant de l'ACTH, mais avec une stimulation de la sécrétion de CRH et/ou d'AVP par l'hypothalamus, en rapport avec l'activation de différents réseaux neuronaux, chez des patients qui ont généralement une adiposité centrale. Un meilleur nom est sans doute « hypercortisolisme fonctionnel » (HF). Les principales situations pathologiques responsables d'HF comprennent différents troubles neuropsychiatriques, l'alcoolisme, l'obésité associée à une résistance à l'insuline, le syndrome des ovaires polykystiques, et l'insuffisance rénale terminale. Le syndrome de résistance aux glucocorticoïdes est un diagnostic différentiel, comme le sont certaines pathologies surrénaliennes où l'ACTH n'est pas complètement freinée. La distinction entre un HF et une maladie de Cushing modérée peut représenter un véritable défi. Une analyse clinique soigneuse, comprenant une anamnèse précise et la recherche attentive de signes cataboliques est essentielle. Les explorations hormonales utiles comprennent la mesure du cortisol plasmatique ou salivaire à minuit, le test couplé Dex/CRH et le test au ddAVP. L'imagerie hypophysaire souffre de limitations à la fois en sensibilité et spécificité, alors que le cathétérisme des sinus pétreux n'est pas capable de différencier une sécrétion hypophysaire d'ACTH d'origine tumorale d'une sécrétion hypophysaire d'ACTH par des cellules normales stimulées par le CRH endogène. Il n'est parfois pas possible d'apporter la preuve ultime de l'origine fonctionnelle d'une hypersécrétion d'ACTH, et de démontrer que le traitement de la pathologie responsable d'HF restore une sécrétion normale d'ACTH et de cortisol. Il faut accepter que chez certains patients une incertitude diagnostique persiste, et que ces patients doivent être suivis avant qu'un diagnostic de quasi-certitude puisse être apporté.
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Mots clés : Pseudo syndrome de Cushing ; Hypercortisolisme fonctionnel ; Test Dex/CRH ; Test ddAVP ; Alcoolisme ; Troubles neuropsychiatriques

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1. Introduction: "non-neoplastic hypercortisolism" (NNH) rather than "pseudo-Cushing's syndrome"

Cushing's syndrome includes all clinical manifestations related to cortisol excess, or to chronic administration of drugs that activate the glucocorticoid receptor. Endogenous Cushing's syndrome may be related to primary cortisol hypersecretion by an adrenocortical tumor or hyperplasia, or to ACTH-dependent stimulation of adrenocortical secretion. ACTH hypersecretion is most often related to a pituitary corticotroph adenoma, which defines Cushing's disease (CD), or more rarely to an ACTH-secreting tumor not located in the pituitary, which defines ectopic (or paraneoplastic) Cushing's syndrome (ECS). All these causes of endogenous Cushing's syndrome are of neoplastic origin, with a tumor (or primary hyperplasia) originating from adrenocortical cells, pituitary corticotroph, or various ACTH-secreting endocrine tumor cells outside of the pituitary.

There are, however, patients with ACTH-dependent cortisol hypersecretion unrelated to any neoplasia, but rather to "functional" chronic hypersecretion of ACTH by normal pituitary corticotroph cells. One hypothesis is that different pathophysiological conditions activate the paraventricular nuclei of the hypothalamus through neural pathways [1] resulting in hypersecretion of hypothalamic CRH (and maybe also AVP), and thus ACTH-dependent hypercortisolism. Besides activation of neural pathways, local overproduction of cortisol by excess visceral adipose tissue, without suppression of ACTH secretion, probably plays a role in patients with metabolic syndrome. Whatever its origin, this functional ACTH-dependent hypercortisolism is thought to resolve if the underlying condition can be effectively treated, which is unfortunately not always the case.

These underlying conditions include (Table 1): alcohol abuse, depression and other neuropsychiatric disorder, obesity, type 2 diabetes, insulin resistance, polycystic ovary syndrome, chronic kidney disease, anorexia, chronic intense exercise, and multiple sclerosis. Glucocorticoid resistance is sometimes included in the list, as it is responsible for ACTH-dependent hypercortisolism, although its pathophysiology is different, and some cases of primary adrenal disease with unsuppressed ACTH can also represent differential diagnoses.

This "functional" ACTH-dependent hypercortisolism is generally called pseudo-Cushing's syndrome (PCS) – which is rather confusing, as PCS patient have real, rather than "pseudo", ACTH-dependent cortisol hypersecretion.

It can be argued that the term "pseudo" is justified by the fact that patients with PCS do not have a real Cushing's syndrome, as they are supposed to be free of the more specific tissue catabolic signs and generally present only metabolic syndrome signs (obesity, hypertension, insulin resistance). It can, however, be very difficult clinically to distinguish a patient with metabolic syndrome related to mild CD with few catabolic signs from a patient with metabolic syndrome related to PCS. To further complicate clinical analysis, other features of "true" Cushing's syndrome, such as secondary hypogonadism in both sexes or excess androgen in female patients, may be present in patients with different conditions responsible for PCS.

Finally the term "pseudo" suggests that, although there may be real cortisol hypersecretion, it has no significant clinical relevance. There are, however, some data suggesting that the metabolic syndrome signs found in patients with PCS might be related, at least partially, to moderate hypersecretion of cortisol.

Pseudo-Cushing's syndrome raises many difficulties regarding both pathophysiology and diagnosis, and excellent reviews have been published on the topic [2], including some recent ones [3,4]. The most recent review [4] proposed abandoning the term "pseudo-Cushing's syndrome" and replacing it either by "non-neoplastic hypercortisolism" or by "physiologic hypercortisolism". In the present article, we will use the term "non-neoplastic hypercortisolism" (NNH) rather than PCS, and will focus on the diagnostic difficulties of distinguishing NNH from the other causes of ACTH-dependent hypercortisolism.

2. Clinical conditions responsible for non-neoplastic hypercortisolism

Table 1 summarizes the most frequent pathological conditions linked to non-neoplastic ACTH-dependent hypercortisolism and the clinical presentation of patients harboring these conditions.

2.1. Depression and other neuropsychiatric disorders

Many different psychiatric disorders are associated with activation of HPA, including melancholic depression, panic disorder, obsessive-compulsive disorder and schizophrenia [5]. Patients with these conditions frequently have elevated levels of urine cortisol and midnight cortisol and abnormally low dose suppression test results. Psychiatric disorders are most likely the cause of NNH in which elevation of free urinary cortisol can be the highest, up to 4 times the upper limit of normal in at least one series [6].

2.1.1. Diagnostic difficulties linked to the used of Dex-CRH test to diagnose both NNH and neuropsychiatric disorders, including some that may be responsible for NNH

Regarding diagnosis of neuropsychiatric disorders that may be responsible for NNH, some confusion arises from the fact that psychiatrists use a combined dexamethasone/CRH (Dex/CRH) test to define severe depression or other psychiatric disorders that are classically associated with NNH, whereas endocrinologists also use a Dex/CRH test to diagnose NNH, but with a different protocol.

For endocrinologists [6], 1 μg/kg ovine CRH (in recent studies ovine CRH was replaced by human CRH) is injected at 8 am after 2 days' dexamethasone suppression by 0.5 mg dex every 6 hours, with the last dose of dexamethasone given at 6 am 2 hours before CRH injection. For psychiatrists [7], 100 μg human CRH is injected at 3 pm after a single administration of 1.5 mg dexamethasone the previous day at 11 pm, 16 hours before CRH injection. In the first of these two studies, using the endocrinologists' protocol, all 19 patients with PCS had cortisol levels < 38 nmol/L 15 minutes after 1 mg/kg ovine CRH

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