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Original article

Performance of the 4-mg intravenous dexamethasone suppression test in differentiating Cushing disease from pseudo-Cushing syndrome

Évaluation de la performance du test de freination à la dexaméthasone 4 mg IV pour différencier une maladie de Cushing d'un pseudo-Cushing

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Abstract

Context. – Discriminating Cushing disease (CD) from pseudo-Cushing syndrome (PCS) is a challenging task that may be overcome with the 4-mg intravenous (IV) dexamethasone suppression test (DST). *Objective.* – Assess the performance of the 4-mg IV DST in the differential diagnosis between CD and PCS in well-characterized patients. *Design.* – Retrospective comparative study of subjects seen in a tertiary care unit (November 2008 to July 2011). *Methods.* – Thirty-six patients with PCS and 32 patients with CD underwent 4-mg IV dexamethasone infusions from 11 am to 3 pm. Areas Under ROC Curves (AUCs) were estimated and compared for ACTH and cortisol measured at 4 pm the same day (day 1) and 8 am the next day (day 2). The ROC curve of the marker with the highest AUC was used to determine the threshold with the highest specificity for 100% sensitivity. *Results.* – The AUC of ACTH at 8 am on day 2 was estimated at 98.4% (95% CI: [92.1–100]), which is significantly greater than that of ACTH at 4 pm on day 1 ($P = 0.04$) and that of cortisol at 8 am on day 2 ($P = 0.05$). For ACTH at 8 am on day 2, the threshold with the highest specificity for 100% sensitivity was estimated at 14.8 ng/L. At this threshold, the sensitivity was estimated at 100% [89–100] and the specificity at 83.3% [67–94]. *Conclusion.* – The 4-mg IV DST is an easy and accurate tool in distinguishing CD from PCS. It deserves thus a better place in establishing the diagnosis of CD.

Keywords: Cushing disease; Pseudo-Cushing syndrome; Dexamethasone suppression test; ACTH; Pituitary tumor

Résumé

Contexte. – Le diagnostic différentiel entre une maladie de Cushing (MC) et un pseudo-Cushing (PCS) est difficile mais peut être facilité par l'utilisation du test de freination à la dexaméthasone 4 mg intraveineuse (DXM-IV 4 mg). *Objectif.* – Évaluer la performance du test DXM-IV 4 mg dans le diagnostic différentiel entre le CD et PCS chez les patients présentant au moins un test de première ligne positif.

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Design. – Étude comparative rétrospective des sujets vus dans une unité de soins tertiaires (novembre 2008 à juillet 2011). *Méthodes.* – Trente-six patients avec PCS et 32 patients avec MC ont été perfusé de 11–15 heures avec 4 mg de dexaméthasone. Les aires sous la courbes ROC (AUC) de l'ACTH et de cortisol mesurées à 16 heures le même jour (j1) et 8 heures le lendemain (j2) ont été analysées. *Résultats.* – L'AUC de l'ACTH à 8 h à j2 a été estimée à 98,4 % (IC 95 % : [92,1–100]), ce qui est nettement supérieure à celle de l'ACTH à 16 h à j1 ($p = 0{,}04$) et du cortisol à 8 h à j2 ($p = 0{,}05$). Pour l'ACTH à 8 h à j2, le seuil avec la plus grande spécificité pour 100 % de sensibilité a été estimé à 14,8 ng/L. À ce seuil, la sensibilité est de 100 % [89–100] et la spécificité à 83,3 % [67–94]. *Conclusion.* – Le test de freination par DXM-IV 4 mg est de réalisation simple et performant pour distinguer une MC d'un PCS. Ce test mérite d'être utilisé pour le diagnostic de CD.

Mots clés : Maladie de Cushing ; Pseudo-Cushing ; Test de freination ; Dexaméthasone ; ACTH ; Tumeur hypophysaire

1. Introduction

The diagnosis of Cushing disease (CD) remains a great challenge, especially regarding its differentiation from pseudo-Cushing syndrome (PCS). Actually, PCS is still not clearly understood; it would result from a physiological hyperactivation of the hypothalamic axis that produces symptoms of glucocorticoid overproduction. Besides, PCS is considered typically associated with alcoholism, depression, anorexia, and obesity [1].

The classical phenotype of Cushing syndrome (with cardiovascular, metabolic, dermatological, musculoskeletal, and psychiatric manifestations) is rather easy to diagnose but remains uncommon. In fact, the clinical manifestations of Cushing syndrome (CS) are variable and differ widely in severity depending on the degree and duration of the hypercortisolism. This leads to a clinical overlap with PCS.

Despite the fact that some symptoms (ecchymosis, purple striae, and proximal myopathy) are more specific of CD than PCS [2], the diagnosis of CD is still dependent on laboratory results.

For the diagnosis of CD, the Endocrine Society Clinical Practice guidelines recommended one of the following tests: at least two 24-hour urinary free cortisol tests, 1-mg overnight dexamethasone suppression test, or two measurements of late salivary cortisol [3,4]. The Endocrine Society consensus considers the 2 mg/d for 48 h dexamethasone suppression test as a first step test. Once CD is suspected, the second step consists in performing a Dexamethasone/Corticotropin-Releasing Hormone (DEX/CRH) test, or a midnight serum cortisol test.

Nearly 30 years ago, our group demonstrated the interest of a 4-mg intravenous (IV) Dexamethasone suppression test (DST) in differentiating obese subjects from CD patients [5]. The test was based on beta-lipotropin and cortisol measurements. In 2010, Jung et al. [6] evaluated the performance of a 4-mg IV DST based on plasma cortisol and ACTH measurements in differentiating CS from control subjects (normal and overweight) and from patients with low probability of CS. Here, we evaluate the diagnostic accuracy of the 4-mg IV DST based on ACTH and cortisol measurements in a large and carefully characterized cohort of patients already classified as CD or PCS patients on the basis of stringent clinical and biological criteria.

2. Materials and methods

2.1. The patients

The present retrospective observational study was conducted in a tertiary care unit of Hospices Civils de Lyon (France). It included all 32 patients with Cushing disease diagnosed between July 2004 and July 2011. In this CD group, the pituitary adenoma was confirmed by histopathology after transsphenoidal surgery.

This CD group was compared with a PCS group that included 36 patients seen between November 2008 and July 2011. In this PCS group, the diagnosis was based on biochemical features compatible with CS; i.e., 24-hour urinary free cortisol higher than the reference values of the laboratory and/or lack of plasma cortisol suppression after administration of 1 mg DST (plasma cortisol post-test > 50 nmol/L), and at least one year of clinical and biochemical follow-up (Median of follow-up was 2.49 years [1–4.2]). MRI was performed in 11 patients and was normal in 10 and revealed a Rathke Cleft Cyst in one case.

The study excluded initially patients with ACTH-independent Cushing Syndrome or recurrent CD. Four patients with ectopic ACTH-producing tumors were excluded from the analysis; they had either neuroendocrine tumors or unidentified tumors that caused Cushing paraneoplasic syndrome.

The study was approved by the local ethics committee though, in accordance with the current French legislation, an observational study that does not change the routine management of patients does not need to be declared or submitted to the opinion of a research ethics board.

2.2. The 4-mg intravenous DEX infusion

Two IV catheters were placed at 08:30 am: one for blood sampling and another for DEX infusion. DEX phosphate (4 mg; Soludecadron®) was dissolved in 40 mL 0.9% saline and infused at 1 mg/h for 4 h using an IV infusion pump, starting at 11 am. Blood samples for cortisol and ACTH measurements were withdrawn at 9 am, 11 am, 4 pm, 8 pm, and midnight on day 1 then at 8 am on day 2 [5].