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ORIGINAL ARTICLE

Desmopressin test in the diagnosis and follow-up of cyclical Cushing's disease

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PALABRAS CLAVE
Enfermedad de Cushing cíclica;
Prueba de desmopresina;
Hipercortisolismo

Abstract
Objective: To assess the utility of the desmopressin (DDAVP) test in the diagnosis and follow-up of a cyclical Cushing's disease (CCS) case.
Material and methods: Laboratory tests included morning and midnight serum cortisol levels, 24 h urine free cortisol excretion, midnight salivary cortisol levels, serum cortisol levels after low (1 mg) and high (8 mg) dexamethasone, plasma ACTH and serum cortisol levels after DDAVP. Magnetic resonance imaging (MRI) was used to assess the presence of a pituitary adenoma. The resected tumor specimen was studied by histological, immunohistochemical and cell biology techniques.
Results: A patient was referred to our unit with a diagnosis of Cushing's syndrome (CS) for further evaluation and treatment. However, no biochemical evidence of hypercortisolism was observed in the follow-up evaluations. Furthermore, the typical features of CS fluctuated throughout this period. A consistent positive response to the DDAVP stimulation test was observed during the diagnostic work-up, even when overt clinical features of CS were not apparent, raising suspicion for CCS. After two years of follow-up a definitive diagnosis of hypercortisolism was established. An MRI scan revealed a pituitary adenoma, as the source of ACTH production. After transphenoidal surgery, clinical signs of CS resolved and the response to DDAVP

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became negative. DDAVP induced a significant increase in ACTH levels in cultured pituitary adenoma cells, consistent with the in vivo DDAVP test results.
Conclusions: Our case illustrates the utility of the DDAVP test in the evaluation of patients with suspected CCS. The DDAVP test could facilitate the management of CCS by shortening the time of diagnosis.

KEYWORDS
Cyclical Cushing's disease;
Desmopressin test;
Hypercortisolism

El test de la desmopresina en el diagnóstico y seguimiento de la enfermedad de Cushing cíclica

Resumen
Objetivo: Evaluar la utilidad de la prueba de la desmopresina (DDAVP) en el diagnóstico y seguimiento de un caso de enfermedad de Cushing cíclica (ECC).
Material y método: Se realizaron mediciones de cortisol sérico diurno y nocturno, cortisol libre en orina de 24 h, cortisol en saliva nocturno, cortisol sérico tras dosis elevadas y bajas de dexametasona, ACTH plasmática y cortisol tras la DDAVP, y resonancia magnética (RM) para valorar la presencia de un adenoma hipofisario. El tumor extirpado fue analizado mediante técnicas histológicas, inmunohistoquímicas y de biología celular.
Resultados: Se presenta una paciente enviada a nuestra unidad con el diagnóstico de síndrome de Cushing (SC) para evaluación más completa y tratamiento. No obstante durante un periodo de seguimiento de 2 años no se encontró evidencia alguna de hipercortisolismo en los análisis realizados en nuestro laboratorio. Durante este tiempo, la paciente mostró fluctuaciones de los síntomas y signos típicos del SC. De manera interesante, la prueba de DDAVP mostró hiperrespuesta de cortisol y ACTH en todas las evaluaciones. La exploración por RM mostró un adenoma hipofisario que tras extirpación resultó ser positivo para ACTH. El SC se resolvió tras la cirugía y la respuesta a la prueba de DDAVP desapareció en las evaluaciones de seguimiento posquirúrgico. Se incubaron muestras del tumor mostrando este un aumento en la secreción in vitro de ACTH.
Conclusiones: Este caso ilustra la utilidad de la prueba de DDAVP en la evaluación de pacientes con sospecha de SCC. Esta prueba podría facilitar el manejo del SCC acortando el tiempo de diagnóstico.

Introduction

Cyclical Cushing's syndrome (CCS) is a rare form of hypercortisolism characterized by repeated episodes of cortisol excess and normal cortisol secretion. These episodes or cycles of hypercortisolism and the associated clinical signs and symptoms can fluctuate over days, months or even years. Due to this cyclical pattern, hypercortisolism might be difficult to detect in CCS patients through biochemical tests commonly used to assess endogenous hypercortisolism in Cushing's syndrome (CS), such as 24-h urinary free cortisol (UFC) and midnight serum or salivary cortisol.[1] In addition, these biochemical tests have intrinsic methodological difficulties and concerns about their precision and accuracy have been recently raised.[2] New procedures, such as the measurement of hair cortisol levels, are now becoming available for the diagnosis of CS.[3] However, evidence about the utility of this test to assess CCS is still limited. The combination of all these factors makes the diagnosis of CCS a significant challenge for endocrinologists.

The desmopressin (DDAVP) stimulation test has been proposed as a useful diagnostic tool for Cushing's disease (CD). DDAVP, a long-acting vasopressin analog, stimulates ACTH and cortisol production in the majority of patients with CD, but generally not in healthy subjects, pseudo-Cushing's, adrenal and ectopic Cushing's patients.[4–7] The positive ACTH response to DDAVP after surgery is associated with increased risk of CD recurrence[8,9] and thus, the DDAVP test might also be useful for the follow-up of CD patients. Here we report a case of CCS in which the positive response to the DDAVP test provided a strong suspicion for the presence of Cushing's disease, warranting further evaluation until a firm diagnosis of hypercortisolism was made. The DDAVP test was also useful to confirm the pituitary origin of excess ACTH as well as to monitor the postsurgical follow-up of CCS. In addition, a cellular and molecular characterization of the pituitary adenoma was performed revealing molecular features similar to those found in most human corticotroph tumors.

Material and methods

Hormone assays

ACTH levels were determined by electrochemiluminescence immunoassays in E170 Modular Analytics (Roche Diagnostic, Manheimn Germany), with intra-assay and inter-assay coefficients of variability (CVs) of 3.1–9.6% and 5.1–9.2%, respectively (for values between 2.3 and 1121 pg/mL). The normal range value was 7.2–63.3 pg/mL and the lower