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CASE REPORT

Diagnosis of Cushing's disease in a patient with consistently normal urinary free cortisol levels: a case report

Kelley J. Moloney[1], Jennifer U. Mercado[1], William H. Ludlam[2] & Frances E. Broyles[1]

[1]Seattle Pituitary Center, Swedish Neuroscience Institute, Seattle, Washington, USA
[2]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Correspondence
Kelley J. Moloney, Swedish Medical Center, Seattle Neurology and Endocrinology, 550 17th Ave, Suite 400, Seattle, WA 98122, USA. Tel: (206) 320-4844; Fax: (206) 320-2995; E-mail: Kelley.Moloney@swedish.org

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Key Clinical Message

The urinary free cortisol (UFC) test is widely used for the screening of Cushing's syndrome. This case study illustrates the potential failure of the UFC test to correctly diagnose Cushing's disease (CD), indicating that the use of other complementary tests may be necessary to diagnose this disease in some cases.

Keywords

Biological markers/urine, Cushing's syndrome, diagnosis, urinary free cortisol, pituitary ACTH hypersecretion.

Introduction

Cushing's disease (CD) is a condition characterized by the elevation in cortisol levels caused by an ACTH-secreting pituitary adenoma. Failure to accurately identify and treat patients with the disease could lead to an increased risk of mortality and worsened morbidity compared with the control population. Identification of patients may be complicated by nonspecific signs and symptoms of hypercortisolism that overlap with more common conditions such as hypertension, type 2 diabetes, obesity, and osteoporosis [1].

The screening tests recommended by The Endocrine Society's clinical practice guidelines for patients suspected of having CD include the urinary free cortisol (UFC) test, the late-night salivary cortisol test, the 1-mg overnight dexamethasone suppression test, and the longer low-dose dexamethasone suppression test [1]. The variability of screening tests is one factor contributing to the reduced reliability of diagnosis of CD [1, 2]. Further evaluation is recommended in patients with discordant UFC test results, which can be attributed to varying diurnal levels of cortisol throughout a 24-h period and to the low sensitivity of each screening test, which could lead to missed diagnoses [1]. Additionally, elevated cortisol levels can be caused by a variety of conditions such as physical stress, malnutrition, and intense chronic exercise. These conditions can also lead to false-positive screening test results, which necessitate further evaluation by an endocrinologist to confirm or exclude the diagnosis.

The UFC test is the most common screening method for the diagnosis of CD and, historically, elevation of 24-h UFC to two to three times the upper limit of normal (ULN) was considered the practicing standard for

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diagnosis [3]. However, initial UFC test results that are normal should not be a cause for dismissal of the diagnosis of the disease in patients if the clinical suspicion is high [1]. Therefore, The Endocrine Society's guidelines recommended that at least two cortisol measurements be obtained from the patient when using the urine or salivary cortisol test. These guidelines also recommended that patients with suspected CD be monitored by an endocrinologist and undergo additional serial testing. In this case study, we described a case of a patient suspected of having CD who had consistently normal 24-h UFC levels with repeated testing despite other biochemical markers of hypercortisolemia.

Case Presentation

A 31-year-old woman with a suspected diagnosis of CD underwent a physical examination and exhibited typical features of the disease, including precipitous central weight gain, hirsutism, acne, bruising, violaceous skin striae, and hypertension. After proper instruction regarding the collection and storage of 24-h urine samples, a total of eleven 24-h UFC tests at multiple testing sites were performed using high-performance liquid chromatography–tandem mass spectrometry. The results showed that UFC levels ranged from 7.2 to 19 μg/24 h, which were within the normal limits and well below the ULN of 50 μg/24 h (Fig. 1). The patient also had normal creatinine clearance and did not exhibit any renal impairment, which is known to potentially cause false-negative UFC results.

Additional laboratory studies showed that the patient had elevated overnight 1-mg dexamethasone-suppressed morning serum cortisol (14.1 μg/dL; normal level, <1.8 μg/dL; Table S1) and a positive dexamethasone-suppressed corticotropin-releasing hormone (CRH) stimulation test (dexamethasone level, 634.0 ng/dL; serum cortisol, 7.14 μg/mL 15 min after CRH stimulation; Table S2). Following a serum ACTH biochemical test, the patient's serum ACTH concentration was found to be slightly elevated (37 pg/mL; normal range, 5–27 pg/mL). The results of the biochemical screening tests indicated hypercortisolemia, and Cushing's syndrome was presumptively diagnosed despite the negative UFC results.

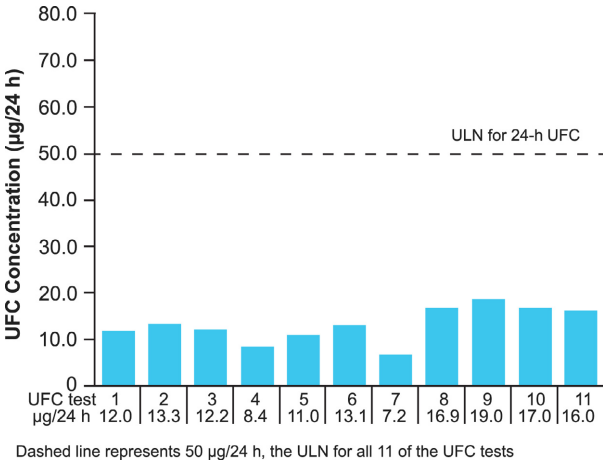

Figure 1. Results from multiple UFC tests demonstrate 24-h cortisol concentrations well below the normal. The dashed line represents 50 μg/24 h, the ULN for all 11 of the UFC tests. UFC, urinary free cortisol; ULN, upper limit of normal.

Magnetic resonance imaging of the pituitary revealed a 4-mm hypoenhancement and a left-sided pituitary microadenoma (Figure S1). Inferior petrosal sinus sampling (IPSS) showed an elevated ACTH concentration (mean basal sampling; left, 171 pg/mL; right, 43 pg/mL; peripheral, 13 pg/mL) and an elevated IPSS ratio (mean basal sampling; left, 13.2 pg/mL; right, 3.3 pg/mL), which indicated lateralization to the left side of the pituitary gland (Table S3). The patient received a transsphenoidal adenomectomy, and a white milky semisolid adenoma was removed. Histopathological examination of the resected tissue showed a continuous sheet of corticotropic pituitary adenoma cells with the loss of the reticulin architecture, which is normally seen in adenohypophyseal tissue (Figure S2A). Immunohistochemical staining revealed strong ACTH staining of corticotropic pituitary adenoma cells (Figure S2B). Three days after surgery, the patient's serum cortisol decreased to 0.58 μg/dL, which was consistent with the complete tumor removal. On follow-up, the patient underwent symptomatic and physical changes consistent with the remission of CD, including a 30-lb weight loss over 3 months. There were no new endocrinopathies noted after surgery.

Discussion

In the case presented here, the patient had consistently normal UFC test results with repeated testing despite exhibiting other symptoms and signs of CD. A recent study demonstrated a high rate of normal UFC test results in patients with Cushing's syndrome, which suggests that negative UFC test results are not uncommon despite the presence of hypercortisolism-related disease [4]. Moreover, drugs such as carbamazepine, fenofibrate, and carbenoxolone have been reported to increase the cortisol levels and interfere with the accurate interpretation of UFC results [1]. These observations have important clinical implications because they suggested that the UFC screening method can fail to indicate disease and that complementary tests are potentially needed to help with the diagnosis of CD. Furthermore, current clinical practice guidelines recommend additional testing and

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further evaluation by an endocrinologist to confirm or exclude the diagnosis of CD in individuals with normal UFC test results [1]. In this case study, CD was diagnosed after further biochemical screening, including a positive dexamethasone suppression test. Histopathological evaluation revealed corticotroph adenoma with ACTH expression.

Conclusions

Taken together, our results indicate that clinical symptoms and biochemical and pathological evaluations are important factors in diagnosing CD, even in the absence of elevated cortisol. Therefore, test results from the UFC analysis should be complemented with additional serial testing as needed. This case study supports the recommendation of clinical practice guidelines that initial normal UFC test results should not be cause to dismiss the diagnosis of CD in patients if clinical suspicion is high.

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Conflict of Interest

KJM, JUM, and FEB have nothing to declare. WHL was employed by Novartis and is currently employed by Chiasma, Inc.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Dynamic 1.5-T pituitary magnetic resonance imaging revealed a 4-mm region of hypo-enhancement, demonstrating a left-sided pituitary microadenoma (red arrow).
Figure S2. Features of the resected tissue confirm a corticotropic adenoma. (A) Histopathological and (B) ACTH immunochemical staining of the resected pituitary microadenoma.
Table S1. Biochemical screening tests show lack of cortisol suppression.
Table S2. Dexamethasone/CRH test shows elevated serum cortisol within 15 min after CRH stimulation and remained elevated for the duration of the test.
Table S3. Results of IPSS show an elevated ACTH concentration and elevated IPSS ratio on the left side of the pituitary gland.

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