

Diagnostic challenges and considerations of cyclical Cushing's syndrome in a 15-year-old female

Wyzwania diagnostyczne cyklicznego zespołu Cushinga u 15-letniej dziewczynki

¹Melissa An, ²Landon Hendricks, ¹Bert Bachrach

¹Pediatrics, University of Missouri School of Medicine, United States

²Pediatrics, University of New Mexico School of Medicine, United States

Abstract

Cyclical Cushing's syndrome (CS) is a rare disorder in which cortisol secretion is cyclical and intermittent. This phenomenon makes for a challenging diagnosis, as patterns of cycling can vary widely among patients and as patients with cyclical CS do not exhibit unique clinical features compared to those without cycling. Current research suggests that cyclical CS may be present in approximately 15% of adult cases, with an even lower reported prevalence in the pediatric population. In this case study, we describe a 15-year-old female with obesity and hypertension who was then diagnosed with cyclical CS after we pursued additional screening tests of urine creatinine and 24-hour urine cortisol, dexamethasone suppression tests, bilateral inferior petrosal sinus sampling, as well as MRI. We discuss the various diagnostic modalities in the challenging diagnosis of cyclical CS as well as the importance and modalities of post-operative monitoring in this patient population. From this case study, we emphasize that when CS is suspected and initial screening tests are negative, clinicians should be aware of the cycling phenomenon of CS in order to consider performing additional screening tests.

Key words:

obesity, Cushing's disease, hypercortisolemia.

Introduction

Cyclical Cushing's syndrome (CS) is a rare disorder, in which cortisol secretion is cyclical and intermittent. In such cases, clinical features of cortisol excess may be present, but measurements of plasma cortisol may yield normal results at one time point while yielding abnormal results at another. This phenomenon, known as cyclical CS or intermittent hypercortisolism, makes for a challenging diagnosis because patterns of cycling can vary widely among patients [1] and because patients with cyclical CS do not exhibit unique clinical features compared to those without cycling [2].

Establishing the diagnosis of cyclical CS requires evidence of cycling of excess cortisol secretion via three peaks and two troughs [3], although no specific scheme has yet been verified for the diagnosis of cyclical CS [1]. Treatment is based on aetiology and is equivalent to that of patients with non-cyclical disease [1]. Because a unifying set of diagnostic criteria has not yet been established, we illustrate a case that we believe demonstrates the cycling phenomenon of Cushing's syndrome and addresses the additional diagnostic investigation and monitoring needed in this pathology.

Case description

A 15-year-old female was referred to paediatric endocrinology by her primary care provider for hypertension and obesity. She had a past medical history of celiac disease diagnosed seven years earlier; her blood pressure in the clinic was 123/84, with systolic and diastolic blood pressures for age at the 95th and 87th percentiles, respectively. The patient's weight was 114.5 kg and height was 165 cm, with a BMI of 42 kg/m² – at the 100th percentile based on age and gender. On exam, the patient was alert and active with no active distress; her neurological exam was grossly normal and had appropriate mood and affect. Physical exam was significant for facial flushing and acanthosis nigricans. The physical exam was otherwise unremarkable, and the patient did not demonstrate any other signs or symptoms of CS. Notably, the patient presented with obesity and did not present with any signs of growth failure that could prompt CS in the differential diagnosis.

Work-up for obesity and hypertension was initiated, which included screening for CS with measurement of the urine cortisol to urine creatinine ratio (UCCR). Initial testing showed a UCCR of 8.16 µg/g, which was within the normal range for a 17-year-old female (1.0–42 µg/g). However, subsequent testing two days later revealed a UCCR of 59.69 µg/g; three days after the initial test, her UCCR was 161.54 µg/g (see Table I). Both of these values were greater than the normal range and demonstrated an adequate elevation for a diagnosis of CS. With this diagnosis high on the differential, cyclical CS was thought to explain the initial UCCR within the normal range.

In order to identify the aetiology of the patient's CS, an overnight screening dexamethasone suppression test was performed. Previous to giving dexamethasone, the patient's

ACTH was 94 pg/ml and her cortisol was 24.4 µg/dl, revealing inappropriately elevated ACTH, suggesting ACTH-dependent hypercortisolaemia. She was given 1 mg of dexamethasone in the evening and the following morning, her ACTH was 40 pg/ml and cortisol was 9.0 µg/dl. This, interestingly, did not demonstrate adequate suppression, which may again be due to the cyclical nature of this patient's CS. Given our high index of clinical suspicion, a high-dose dexamethasone suppression test was performed over three days, in which 2 mg of dexamethasone was given every six hours. The urine-free cortisol levels were measured each morning (shown in Table II), which demonstrated a significant reduction and pointed to a pituitary pathology. At this point, a brain MRI was performed. The paediatric neurosurgery team reviewed the MRI of the sella without and with contrast and identified a mass in the right pituitary gland, although no measurement was documented. Specifically, MRI of the sella with and without contrast showed a hypointense area on the right side of the pituitary gland with the stalk tilted slightly to the left. Initial imaging is shown in Figure 1.

Following the imaging, bilateral inferior petrosal sinus sampling (IPSS) was conducted to determine the location of the tumour, with the goal of isolating the mass and preserving as much of the pituitary tissue as possible for surgical planning. Specifically, in the IPSS protocol, we obtained two ACTH baseline levels on the right petrosal sinus, left petrosal sinus, and peripheral at –5 and 0 minutes. Next, we gave an injection of CRH 1 µg/kg. We then obtained ACTH levels from the right, left, and petrosal sites at 3 minutes, 5 minutes, 10 minutes, and 15 minutes. The results are shown in Figure 2. Notably, no gradient was identified between the central and peripheral sites, or between the left and right petrosal sinuses. It is suspected that no gradient was identified because the testing was done on a day when the disease was not active. Nocturnal reported similar findings during IPSS testing but were able to identify a gradient when re-administering the test on a day when the disease was active [9].

Table I. UCCR values over time

Day 0	Day 2	Day 3
8.16 µg/g	59.69 µg/g	161.54 µg/g

Table II. Urine-free cortisol levels (µg/24 h) after high-dose dexamethasone suppression test

Day 1	Day 2	Day 3
121	24	2

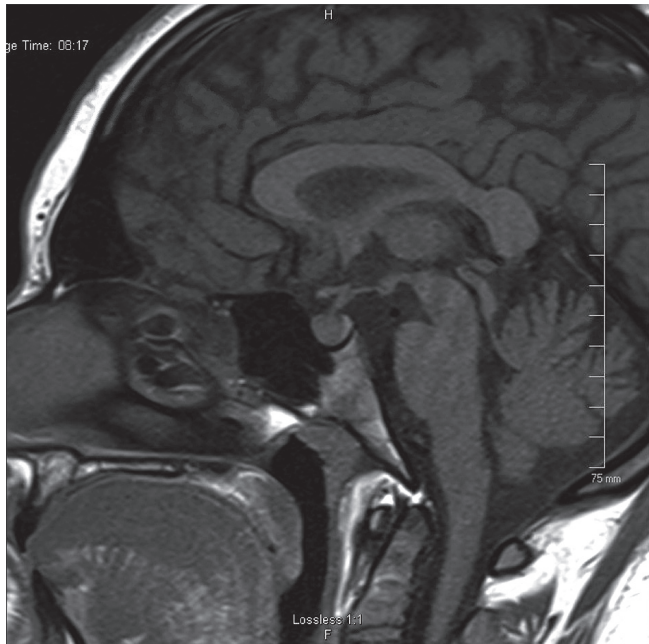


Figure 1. MRI of initial adenoma

Regarding treatment, the patient underwent trans-sphenoidal resection of the pituitary mass seen by neurosurgery on the brain MRI. The pathology was found to be consistent with pituitary adenoma. As follow-up, the patient had monthly 24-hour urine cortisol measurements and quarterly dexamethasone challenge tests. Seven months after surgery, the patient had slightly elevated urine cortisol levels of 57 $\mu\text{g}/24\text{ h}$ and 58 $\mu\text{g}/24\text{ h}$. Additionally, the dexamethasone challenge test did not appropriately suppress her cortisol level, as the patient was found to have a recurrence of her adenoma. Clinically, the patient did not report any significant symptoms of Cushing's syndrome. MRI of the brain demonstrated a 3 mm cystic appearing focus in the posterior superior pituitary and an oval 8 × 5 mm hypo-enhancing area on the right side of the pituitary (imaging shown in Figure 3). She then underwent repeat trans-sphenoidal surgery at an outside institution to remove the recurrent tumour 10 months after her initial surgery. The patient continues to be followed in a clinic.

Discussion

This case is unique because it demonstrates the diagnostic challenges in identifying cyclical CS and the importance of additional diagnostic investigation and monitoring. Regarding the epidemiology of cyclical CS, while relatively unknown in the clinical community, current research suggests that cyclical CS may be present in approximately 15% of adult cases [2]. The aetiology is similar to that of non-cyclical CS, with 54% originating from a pituitary corticotroph adenoma, 26% from an ecto-

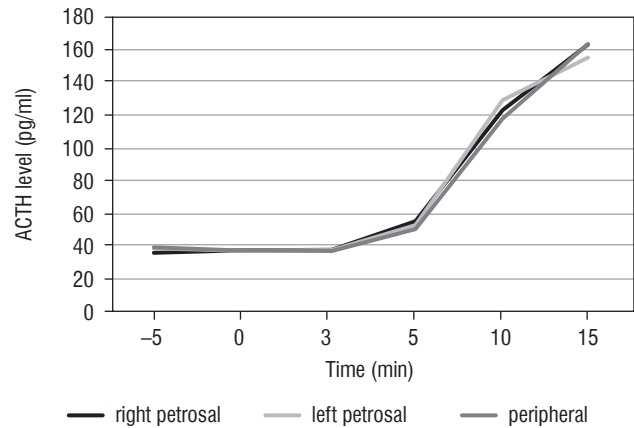


Figure 2. IPSS results

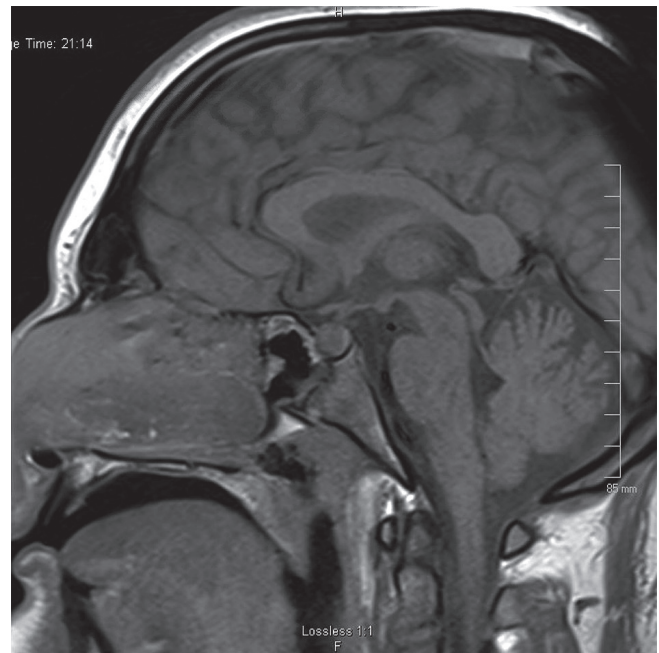


Figure 3. MRI of recurrent adenoma

pic ACTH-producing tumour, and 11% from an adrenal tumour. Within the paediatric population, CS is relatively rare in comparison to the disorders of growth, puberty, and thyroid that are commonly treated by paediatric endocrinologists. Alexandraki *a* analysed case records of 201 patients with CS for cyclical nature and variability and found that 17 of these patients were paediatric and only one paediatric case exhibited cycling [2]. Of 59 paediatric cases analysed by Magiakou *a*, only two demonstrated cycling [4]. Aetiologies for cyclical disease vary in the 10 reported paediatric cases in the literature. In these 10 cases, four are due to nodular adrenocortical disease [5–8], one is

due to corticotroph cell hyperplasia [9], three are due to pituitary adenoma [2, 4, 10], one is due to ectopic ACTH [4], and one case has unknown aetiology [11]. Although rarely reported in the literature, the prevalence of cyclical disease in the paediatric population is probably higher than suspected due to the pathology's challenging diagnosis and variability in presentation and cycling patterns.

When CS is suspected and initial screening tests are negative, clinicians should consider the cyclical phenomenon of CS in formulating their differential diagnosis and thus consider additional screening tests. Notably, it is important to recognise that patients with cyclical CS can often not fit the classic picture of CS; for example, this patient presented with obesity rather than growth failure. In this case study, additional measurements of urine creatinine and 24-hour urine cortisol raised the suspicion of cyclical CS and prompted further diagnostic investigation.

In addition, it is important to utilise multiple modalities in the diagnosis of cyclical CS. Inferior petrosal sinus sampling

is an excellent diagnostic test for CS; however, its results may not demonstrate a gradient due to the cyclical nature of the patient's CS; in this case, the patient failed to show a gradient because her disease was not active at the time of testing – a finding that was similarly demonstrated in the study by Noctor *a*. Therefore, it is essential to also explore imaging in the diagnostic investigation; this case study was able to identify the patient's pituitary adenoma and follow through with treatment due to the high sensitivity of MRI.

This case study also demonstrated the high recurrence rate that patients with cyclical CS may experience. Through longitudinal, post-operative monitoring of the patient, a recurrence of the pituitary adenoma was identified and treated. Specifically, the case study's monthly 24-hour urine cortisol measurements and quarterly dexamethasone challenge tests were adequate and appropriate monitoring measures to detect recurrence in a timely fashion.

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