

Diagnosis of Cushing's Disease in an Adolescent Male: A Case Report

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Received date: 08 November, 2018; Accepted date: 16 January, 2019; Published date: 25 January, 2019

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Citation: Taha HR, Albasri EE, Alyusuf E, Khamdan F (2019) Diagnosis of Cushing's disease in an adolescent male: A case report. Endocrinol Metab Vol.3 .No.1:113.

Abstract

Cushing's syndrome (CS) is a rare endocrine disorder caused by prolonged exposure to an excessive amount of glucocorticoids. Identifying the cause begins with determining whether hypercortisolism is adrenocorticotrophin (ACTH)-dependent (from the pituitary or ectopic sources) or ACTH-independent (from an adrenal source). Cushing's disease (CD) is the most common cause of endogenous CS and it represents a rare cause of short stature in children and adolescents.

The diagnosis of CS is often challenging because most of the symptoms and signs are nonspecific. These symptoms are common in individuals who do not have hypercortisolism (e.g., patients with diabetes, hypertension, or weight gain). Instead, various dermatological manifestations (such as purple striae, easy bruising, and skin atrophy) are more specific to CS.

Here, we report a case of a 17-year-old male who presented with progressive weight gain, and dermatological findings consisting of multiple purple striae 1 year prior to referral to our clinic from the dermatology clinic. He had typical features of CS, which were missed by his primary physician.

Keywords: Adrenocorticotrophic Hormone; Cortisol; Cushing's syndrome; Hyperpigmentation; Striae; Bruise

Abbreviations:

CS: Cushing's syndrome; CD: Cushing's disease; ACTH: Adrenocorticotrophic hormone; IPSS: Inferior petrosal sinus sampling; BMI: Body mass index; MRI: Magnetic resonance imaging; SIADH: Syndrome of inappropriate antidiuretic hormone secretion

Introduction

Endogenous CS results from either ACTH-dependent or ACTH-independent causes. CD which results from the autonomous

secretion of ACTH by a corticotroph adenoma of the pituitary gland is the cause of CS in more than two-thirds of patients [1].

CD presents more frequently in women compared to men and it more often occurs between the ages of 20 and 40 (except for prepubertal children for whom CD predominates in boys) [2].

Common nonspecific features of CS include obesity, hypertension, diabetes, and menstrual irregularities. Moreover, truncal obesity, ecchymoses, plethora, wide purple striae, proximal muscle weakness, and osteoporosis are useful discriminant indices for CS [3]. Growth failure and weight gain are frequently observed in pediatric patients suffering from ACTH-dependent hypercortisolism, while in ACTH-independent CS, the secretion of adrenal androgens may lead to an acceleration of bone aging and eventually compromise growth potential [11]. Early diagnosis and successful treatment of CS avoid the stunted linear growth associated with prolonged childhood disease.

The diagnosis of CD is based on biochemical testing, and the disease is defined by excess levels of glucocorticoids. The initial test includes assessing overnight dexamethasone suppression, 24-hour urine-free cortisol (UFC), and late-night salivary cortisol. All three tests have similar diagnostic utility. The 24-hour UFC and salivary cortisol tests should be performed at least twice to ensure the reproducibility of results [3].

Once ACTH-dependent CS is confirmed biochemically, a pituitary MRI is typically obtained. If no pituitary tumor or a tumor less than 6 mm is visualized, an inferior petrosal sinus sampling (IPSS) is recommended before exploratory pituitary surgery.

Trans-sphenoidal selective adenectomy is the most widely accepted primary therapy for pituitary-dependent CD. When performed by a specialist neurosurgeon, long-term remission rates up to 70% can be achieved [4]. Ultimately, the successful treatment of CD is associated with normal long-term survival [5].

Case Report

The patient was a 17-year-old male, who presented at the local health center with skin discoloration over his lower abdomen and upper arms. He had noticed an increase in body

weight over the previous 6 months, which was associated with generalized weakness. He was reassured by his primary care physician that the skin discoloration was stretch marks secondary to his increase in weight.

After 6 months, he returned to his primary care physician complaining of back pain, generalized bone pain, additional weight gain, and further skin discoloration. He was then referred to the dermatology clinic for assessment.

The patient was seen in the dermatology clinic 6 months later and he was urgently referred to the endocrine clinic to rule out CS because he displayed extensive multiple wide purple skin striae. He was immediately seen in the endocrine clinic, and upon physical examination, he weighed 62 kg (50th centile) (compared to 50 kg 1 year before). At a height of 157 cm, his final estimated target height was 166 cm (~25th centile). With a BMI of 25.2, he was plethoric with a round face, dorsocervical and supraclavicular fat pads, truncal obesity, and extensive purplish wide skin striae over his lower abdomen, arms, and thighs (**Figure 3**). His blood pressure was normal. He displayed signs of puberty, and his bone age was consistent with his chronological age. His clinical history did not include the use of glucocorticoids, and no family history of endocrine diseases was reported.

There was a marked increase of urinary free cortisol combined with non-suppressible serum cortisol after a low-dose dexamethasone suppression test and a detectable ACTH value, which confirmed a diagnosis of ACTH-dependent CS.

Hormonal laboratory evaluations were as follows:

8 AM cortisol: 904 nmol/L

24 hr urine cortisol values: 642 nmol/d, 853 nmol/d (normal is less than 152 nmol/d)

Cortisol level after a 1-mg dexamethasone suppression test: 369 nmol/L (normal <50 nmol/L)

ACTH: 11.1 pmol/L

The patient also displayed mild polycythemia (hematocrit 52.9%) and dyslipidemia (**Table 1**). MRI of the pituitary was normal (**Figures 1 and 2**), and we proceeded for a CT of the chest, abdomen, and pelvis to rule out an ectopic source of hypercortisolism, which was negative.

Table 1 Biological parameters.

Type	Number	Normal range
8AM cortisol	904 nmol/L	193-690 nmol/L
24H U Cortisol 1	642 nmol/d	13.8-152 nmol/d
24H U Cortisol 2	853 nmol/d	13.8-152 nmol/d
LDDST	369 nmol/L	<50 nmol/L
ACTH	11.1 pmol/L	<10 pmol/L
Hemoglobin	16.4 g/dL	12-14.5
Hematocrit	52.90%	33-45
Platelets	144 x 10 ⁹ /L	150-400

Thyroid stimulating hormone	2.88 mIU/L	0.25-5
Thyroxine (T4) free	21.7 pmol/L	6-24.5
LH	3.8 IU/L	1.5-9.3
FSH	5.8 IU/L	1.6-11
Testosterone	8.64 mmol/L	1.38-24.3
Prolactin	11.44 ng/mL	0.7-16.8
LFTs	Normal	
UREA	5.3 mmol/L	3.2-8.2
Creatinine	92 mcmol/L	44-88
Sodium	142 mmol/L	132-146
Potassium	4 mmol/L	3.5-5.5
FBS	4.1 mmol/L	3.9-5.6
Cholesterol	5.9 mmol/L	3.6-5.2
LDL	3.76 mmol/L	1.7-3.4
Triglycerides	0.8 mmol/L	0.2-1.8

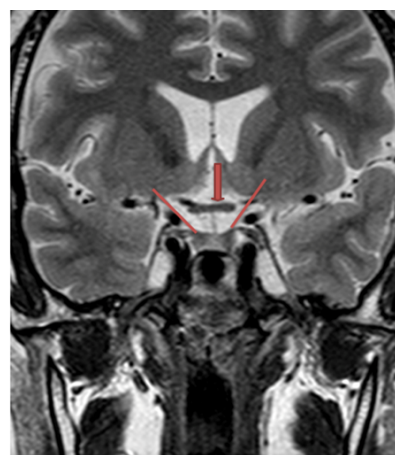


Figure 1 T2w coronal image at the level pituitary gland.

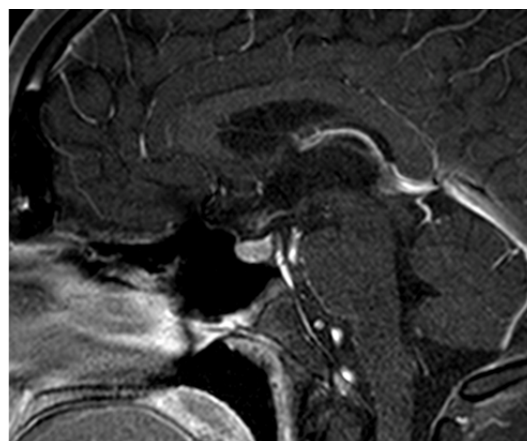


Figure 2 Post contrast sagittal image.

Bilateral inferior petrosal sinus sampling was performed, which showed that the pituitary was the source of the CS. The interpetrosal sinus ACTH gradient indicated lateralization of ACTH secretion to the right side. The patient underwent transsphenoidal surgery with selective microadenomectomy. The post-surgical histopathology analysis revealed abnormal pituitary tissue with ACTH expression in tumor areas. Postoperative levels of cortisol were low (27.9 µg/dL), but this returned to normal levels after 2 weeks. The patient did not develop any signs of diabetes insipidus or SIADH. The patient was discharged and advised to follow up with his endocrinologist. He was also given information regarding the signs and symptoms of hypocortisolism.

Three weeks after surgery, the patient's mother called to report that he was complaining of fatigue, nausea, and vomiting. Laboratory reports were obtained, but the results were all within normal ranges. The patient's parents were reassured that his symptoms were most likely related to cortisol withdrawal.

The patient was reviewed in the endocrinology clinic several times for his follow-up appointments. By six months after surgery, he had lost 10 kg, his skin striae were fading, and his face was thinner. His dorsocervical and supraclavicular fat pads were completely resolved (Figure 4). He denied fatigue or dizziness. Biochemical evaluation did not show any deficiency in terms of pituitary function. Patient's laboratory test results are presented in Table 2.



Figure 3 Typical wide violaceous skin striae over shoulders, lower abdomen, and flanks with monomorphic papules in the anterior chest, which goes with acniform eruption.

Table 2 Patient's laboratory test results

Type	Number	Normal range
ACTH	4.1 pmol/L	<10 pmol/L
8AM Cortisol	277 nmol/L	193-690 nmol/L
24H U Cortisol	13.4 nmol/d	13.8-152 nmol/d
Hemoglobin	12.8 g/dL	12-14.5
Hematocrit	40.40%	33-45
Platelets	256 x 10 ⁹ /L	150-400
Thyroid stimulating hormone	2.36 mIU/L	0.25-5
Thyroxine (T4) free	13 pmol/L	6-24.5
LH	3.3 IU/L	1.5-9.3

FSH	1.8 IU/L	1.6-11
Testosterone	11.11 mmol/L	1.38-24.3
Prolactin	10.16 ng/mL	0.7-16.8
FBS	4.4 mmol/L	3.9-5.6
Cholesterol	3.9 mmol/L	3.6-5.2
LDL	2.4 mmol/L	1.7-3.4
Triglycerides	1 mmol/L	0.2-1.8

The Patient underwent successful surgery and achieved remission from CD. He will be monitored throughout his life for possible recurrence of the disease [6-9].



Figure 4 Resolution of physical features of cushing's after surgery: (moon facies, supraclavicular fat pads, truncal obesity, and the skin striae). The picture in the middle (b) is before surgery, the other two pictures (a,c) are one year after surgery.

Discussion

CD is the most common cause of endogenous CS. Pediatric CD accounts for approximately 75–80% of all pediatric CS cases [10]. By comparison, 49–71% of adult CS cases are caused by CD [10].

Although CD predominates in female adults, studies show that pre-pubertal boys are affected more frequently than girls [3]. As children approach puberty, the sex distribution of CD equalizes, and the trend is reversed with female being more commonly affected during adulthood. The explanation for this is unclear but is perhaps due to the estrogenic milieu during puberty in females [2].

Diagnosis of CS is challenging, and it is often delayed because most of the signs and symptoms are nonspecific, commonly affecting the general population [3]. The most common presentation of CS in children is growth retardation and weight gain [13]. Thus, CS should always be considered during the evaluation of short stature in children. Bone age in children and adolescents with CS is consistent with chronological age in 81% of cases, but it is accelerated in 8% and delayed in 11%, correlating with early and delayed sexual development, respectively [11]. In the present case, the patient had already reached his adult height before diagnosis, so he did not display a short stature [12,13].

Hypocortisolism can cause alterations in body composition with an increase in visceral adiposity and decreased bone mass [14]. The most important clinical feature observed in our patient

was weight gain, purple striae, and fatigue, which led to a decrease in his tolerability for playing sports. However, muscle weakness was not present at the physical examination. In fact, this sign (which has high specificity in adult patients) may be less common in pediatric and adolescent patients [11].

Several striking features of CS (such as central obesity, moon facies, dorsocervical supraclavicular fat pads, and abdominal striae) can be more discriminatory. These features are seen in about half of patients with cortisol overproduction [12], and these were all observed in our patient upon physical examination [15].

The presence of purple (violaceous) striae >1 cm in diameter is substantially pathognomonic for CS. These striae are most commonly seen on the abdomen and lower flanks, but they can also occur on the shoulders, upper arms, axillae, breasts, buttocks, and upper thighs. In children with CD, the skin is affected at multiple sites; however, the severity of the manifestations does not correlate with biochemical indices of the disease. With the exception of striae, cutaneous effects of endogenous hypercortisolism completely heal within the first year after surgical intervention for the disease [7,16]. In the present case, the patient presented with extensive typical wide purple striae, which were gradually fading following his surgery for CD, but this was not completely resolved at the time of writing.

It is important to diagnose CS early because it is associated with increased morbidity and mortality. Delays of a median of 2 years in diagnosing CS have been reported according to recent studies [6]. In fact, before reaching the correct diagnosis of CS, general practitioners were consulted 76% of the time, endocrinologists 25% of the time, gynecologists 24% of the time, rheumatologists 11% of the time, and dermatologists 8% of the time [6]. It is important to specifically train family physicians and general practitioners to look for rare diseases or symptoms that are not age-appropriate, such as typical striae, a buffalo hump, proximal muscle weakness, plethora, and signs of osteoporosis in patients with weight gain. Early referral of these patients to an endocrinologist will facilitate their diagnosis and treatment.

A reasonable approach for confirming the existence of inappropriate cortisol secretion is based on urinary free cortisol, midnight serum, salivary cortisol levels, or serum cortisol levels after a low-dose dexamethasone suppression test [17].

In our patient, first-line tests confirmed inappropriate cortisol secretion, and ACTH levels were suggestive of ACTH-dependent CS. While a “detectable” ACTH value (>2.22 pmol/L) in adult patients is suggestive of an ACTH-dependent CS, a cut-off value of 6.44 pmol/L in children has been reported to have a sensitivity of 70% for identifying an ACTH-dependent form of CS (15). In our case, an ACTH value of 11.1 pmol/L was clearly suggestive of ACTH-dependent CS. MRI is the test of choice for diagnosing CD. However, ACTH-secreting pituitary adenomas are usually hypodense on MRI and often fail to enhance with gadolinium contrast. Furthermore, in as many as 50% of cases, they do not exceed a diameter of 5 mm [1]. Dynamic contrast-enhanced pituitary MRI may detect only 50–60% of ACTH-producing pituitary adenomas, possibly because corticotroph

adenomas tend to be microadenomas with signal and enhancing characteristics similar to normal pituitary tissue [18,19]. Colombo et al. reported that the accuracy of MRI in detecting corticotropin-secreting microadenomas as small as 2 to 3 mm is 65–75% [20]. Successful treatment of ACTH-secreting adenomas requires accurate diagnosis and exact localization. IPSS, which is considered the gold standard technique for a differential diagnosis of ectopic ACTH syndrome and CD, should be performed in cases in which pituitary adenomas cannot be determined using imaging techniques [18]. The diagnostic accuracy of BIPSS sampling can reach up to 100% if performed in experienced centers [18]. IPSS sampling is also recommended to increase diagnostic accuracy in cases where dynamic test results are uncertain. Ectopic ACTH syndrome cannot be ruled out, and the adenoma diameter is <5 mm on a pituitary MRI [19]. In the present case, CD was diagnosed using BIPSS because the patient’s imaging studies were all negative. There was a clear central-to-peripheral gradient and a right-to-left gradient, indicating a right ACTH-secreting microadenoma.

Successful surgery requires precise localization of the adenoma because the majority of lesions are small and pituitary imaging studies fail to visualize an adenoma in up to 50% of cases of documented CD [11].

IPSS can be used to guide the initial pituitary gland exploration if the MRI is negative, but if an adenoma is not discovered, the entire pituitary gland must be thoroughly explored. The studies demonstrate that 31% of patients would likely harbor an untreated ACTH-secreting adenoma within the remaining gland if it were left unexplored [9].

Transsphenoidal surgery with selective microadenomectomy is now the first-line treatment for both adult and pediatric CD [17]. In most specialized centers with experienced neurosurgeons, the success rate of the first TSS is 90% or higher [18]. The aim of the procedure is selective removal of the microadenoma while preserving normal pituitary tissue. This is essential for the future development of the pediatric patient [20].

Treatment failures are most commonly the result of a macroadenoma or a small tumor invading the cavernous sinus. Postoperative complications include transient diabetes insipidus and, occasionally, syndromes associated with inappropriate antidiuretic hormone secretion, central hypothyroidism, growth hormone deficiency, hypogonadism, bleeding, meningitis, and pituitary apoplexy. The mortality rate is extremely low at less than 1% [18]. In our patient, a hypophyseal adenomectomy was performed via TSS. No complications related to other pituitary hormones developed during the postoperative period. Flu-like symptoms (malaise, joint pain, anorexia, and nausea) during the post-operative months indicated remission, as some of these symptoms have been related to high levels of circulating interleukin-6 [8].

Conclusion

Although rare during childhood and adolescence, CS should be considered in the differential diagnosis of pediatric patients presenting with signs of obesity.

Statement of Ethics

The authors have no ethical conflicts to disclose. The patient's parents have given their informed consent, including the use of the photographs.

Disclosure Statement

The authors have no conflicts of interest to disclose. No funding support was obtained for this work.

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