Case Report

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A variable course of Cushing’s disease in a 7 year old: diagnostic dilemma

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Abstract: Cushing’s syndrome (CS) or hypercortisolism results from disruption of the hypothalamus-pituitary-adrenal (HPA) axis with the resultant increase in the circulating serum and urinary cortisol levels and lack of cortisol circadian rhythm. The resultant effects cause the physical manifestation of hypercortisolism. The appearance of Cushing’s disease in children is insidious, the most common features being growth failure, obesity, early puberty and facial appearance. We report a case of a 7-year-old male with a very unusual course of the disease, which could have led to diagnostic delays.

Keywords: Cushing’s disease; obesity; pseudoCushing’s.

Introduction

Cushing’s syndrome (CS) or hypercortisolism results due to excess glucocorticoid, the source of which could be endogenous or exogenous. Cushing’s disease (CD) refers to hypercortisolism due to excessive adrenocorticotropic hormone (ACTH) secretion from a pituitary lesion, it was first described by Harvey Cushing in 1932, and represents the most frequent cause of CS [1, 2].

A pituitary adenoma is the most common cause of CS in comparison to a carcinoma. The pituitary adenomas in 90% of cases are due to monoclonal slow growing microadenomas and only about 10% are macroadenomas [3].

CS is rare presentation in children and adolescents and very unlikely below the age of 7 years, however, isolated case reports have been reported across the pediatric age groups and some rare cases in infancy have been reported [4]. If undiagnosed or untreated it can lead to considerable morbidity and mortality, and the inability to detect a microadenoma on magnetic resonance imaging (MRI) can lead to a diagnostic dilemma leading to unnecessary delays in treatment initiation [5].

We report a case of a CD due to a pituitary microadenoma with a very variable course of the disease process, which caused a diagnostic dilemma.

Case presentation

A 7-year-old boy presented with complaints of excessive appetite and weight gain for the last 5 months. He was prepubertal weighing 46.8 kg and 127 cm tall and had a blood pressure of 124/80 mm of Hg. His body mass index (BMI) was 29 and was 0–1 standard deviation (SD) for height.

He had Cushingoid facies with plethora and predominantly abdominal obesity. No bruising or striae were present.

The child was evaluated for obesity with a provisional diagnosis of CS vs. pseudoCushing’s.

He had no history of any acute or chronic steroid intake. There was no history of any mood swings or sleep disturbances and no visual impairment. He was admitted for an overnight dexamethasone suppression test (with 1 mg dexamethasone given orally at 11 pm) and an oral glucose tolerance test (OGTT).

The 4 pm cortisol was 18 μg/dL and morning cortisol at 8 am following dexamethasone was 18 μg/dL. His low-density lipoprotein-cholesterol (LDL-C) was 194 mg/dL, triglycerides 93 mg/dL, very-low-density lipoproteins (VLDL) 18 mg/dL. A dynamic MRI of the pituitary (Figure 1) revealed no pituitary lesions. OGTT revealed 1 h and 2 h blood sugars – 140 mg/dL and 125 mg/dL; insulin levels 141.3 μIU/mL.

The rest of his biochemical results were within normal limits including the thyroid stimulating hormone (TSH).

The child was discharged with dietary advice and regular follow-up.

After 2 months later, he weighed 42.5 kg now having lost 4 kg weight, and was still 127 cm tall. However, he
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complained of headaches and some visual disturbances, and complained of several episodes of diplopia.

This posed a certain dilemma for us as a classical case of CD, the most significant characteristic is short stature which was not there in this case. The boy lost weight, which is also not characteristic of CD, as CD patients do not lose weight without any pharmacological therapy. But favoring CD was the development of neurological symptoms that were initially absent.

Hence he was re-valuated at his last visit for Cushing’s and an overnight dexamethasone suppression followed by a 2-day dexamethasone suppression was done with 0.5 mg dexamethasone given 6 hourly orally, starting at 9 am and given in a total of eight doses, after the last dose at 3 pm the next morning’s 9 am sample ACTH and cortisol was sent for testing.

A 24-h urinary cortisol was sent for testing and an MRI was repeated.

Urinary 24-h cortisol was 215.55 g/24 h in a 900 mL sample (normal 28.5–213.7 μg/mL).

Ophthalmology opinion was sought for diplopia, no fundal or any other abnormal changes were noted.

His evening (4 pm) basal ACTH was 60.4 pg/mL and cortisol was 30.5 μg/dL. The values after a 2-day suppression test were ACTH – 51.4 pg/mL, cortisol – 32.8 μg/mL. The second MRI now revealed a small microadenoma in the right lobe of the pituitary (Figure 2).

Following this a trans-sphenoidal surgery was planned, but was deferred by the surgical team. The child was then planned for a Gamma Knife suite and Leksell Stereotactic Frame, which was successfully performed. Two shots were given using 8 and 4 mm collimators each. One hundred percent of the tumor volume (0.07 cubic cm) was treated with a dose of 15.0 Gy at 50% isodose configuration. The maximum dose at the reference point was 30 Gy.

His cortisol and ACTH levels were serially monitored after the microadenoma was removed and returned to normal after 6 weeks.

This case had posed some challenges for us due to the variable course of the presentation, the absence of growth delay, weight loss without any medical interventions and normal value of 24 h urinary cortisol value, which are very unlike a true CD. Hence, this suggested a high degree of suspicion and regular follow-up in cases with absent lesions on MRI and appearance of new symptoms.

**Discussion**

CD is characterized by a disruption of the hypothalamus-pituitary-adrenal (HPA) axis with the resultant increase in the circulating serum and urinary cortisol levels and lack of cortisol circadian rhythm [3]. The resultant effects cause the physical manifestation of hypercortisolism.

CD mostly presents with weight gain with central obesity, fatigue with proximal myopathy, skin thinning with purplish striae and diffuse bruising.

However, the appearance in children is insidious, most common features being growth failure, obesity, early puberty and facial appearance [6].

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**Figure 1:** First MRI showing no lesion

**Figure 2:** Second MRI showing adenoma marked with arrow
Although most of the cases in the pediatric population have no underlying germline genetic defects, somatic mutations of the USP8 deubiquitinase gene in corticotroph adenomas have been implicated in the molecular pathogenesis of CD, mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene also are known to predispose to familial pituitary adenomas [7].

CS is very rare in children and the most common cause in children is exogenous or iatrogenic Cushing’s. There are certain conditions, which can present similar to CS and needs to be borne in mind while diagnosing CS: obesity, stress, uncontrolled diabetes mellitus and polycystic ovarian syndrome (PCOS). These are known as pseudo-Cushing’s, as they only have partial signs of hypercortisolism. And the differentiation between these two are not always very clear-cut.

For our case, we needed to differentiate between CS and obesity. It was very challenging, as the child did not present with growth failure, one of the common presentations in children.

The tests employed to diagnose CS are [8, 9]:
- 24-h urinary free cortisol, repeated at least twice; values should be above 220–330 nmol/24 h
- cortisol response to 1 mg-overnight dexamethasone suppression test: cortisol value <50 nmol/L (<2 μg/dL) excludes Cushing’s
- cortisol response to low dose dexamethasone suppression test (0.5 mg dexamethasone every 6 h during 48 h): cortisol value <50 nmol/L (<2 μg/dL) excludes CS with a sensitivity and specificity close to 100%
- late night salivary cortisol: a cortisol value >2 ng/mL (5.5 nmol/L) has a 100% sensitivity and 96% specificity.

Once diagnosed as CS the mainstay of therapy includes removal of the pituitary adenoma, which can be done using trans-sphenoidal surgery, newer forms of stereotactic radiotherapy are now available for ACTH-secreting pituitary tumors. The Photon Knife (computer-assisted linear accelerator) or the Gamma Knife (GK, cobalt 60) are the newer approaches [10]. Different modalities have been developed and employed to irradiate pituitary tumors, including: 1) conventional radiotherapy (CRT), a technique delivering ionizing radiation to target small tumors; and 2) stereotactic radiotherapy (SRT), a technique delivering large ionizing radiation to the target tumors by stereotactic methods, while sparing the surrounding tissue. SRT can be delivered by two methods: 1) a single treatment (stereotactic radiosurgery [SRS]); or 2) a fractionated treatment (stereotactic conformal radiotherapy [SCRT]). SRS can be performed with different techniques, including a multiheaded cobalt unit (GK), a linear accelerator (LINAC) system [LINAC SRS], or a proton-beam system [Proton-beam SRS].

Pharmacotherapy can be used in post-operative patients or while awaiting surgery due to inability to identify the site of lesion. There are various agents that block the steroidogenesis in the adrenals: ketoconazole, metyrapone, mitotane, trilostane, aminoglutethimide. Certain other drugs with pituitary actions are used to inhibit the ACTH production: serotonin antagonists, dopamine agonists. However, these drugs can only be used for limited time periods only.

Conclusions

CD is a rare condition in children and most commonly presents with short stature and obesity. However, it can have a variable course of presentation with no neuroimaging findings and hence requires a high index of suspicion to differentiate from pseudo-Cushing’s. Such cases need to be followed-up closely as a pituitary adenoma may be detectable at a later time and would need surgical intervention.

Learning points

- CD may initially present only with obesity and may not be associated with short stature. Despite short stature being the most common presentation in children.
- MRI findings of the pituitary may be inconclusive in the beginning of the disease process and should be borne in my mind during further follow-up.
- In cases where a clear-cut diagnosis may be difficult, a diligent follow-up is required to ascertain the course of the disease and to make timely diagnosis.

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