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Case Report

Cushing's Disease in Pediatric Age: A Diagnostic and Therapeutic Challenge

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Abstract

We present the case of a 16-year-old male with Cushing's disease (CD) who faced diagnostic challenges due to the absence of an image on magnetic resonance imaging (MRI) of the sellar region. Despite undergoing surgical intervention, clinical and biochemical cure was not achieved. Inferior petrosal sinus sampling (IPSS) was performed for the first time in the country within this age group. The procedure proceeded without complications, leading to the establishment of a CD diagnosis. Pharmacological treatment with ketoconazole was initiated as a bridge therapy until definitive treatment; however, the patient did not tolerate ketoconazole. Due to an underdeveloped sphenoidal sinus, surgery was deemed inappropriate, and radiotherapy was administered. Performing PSC is crucial, as it is established as the gold standard for differentiating etiologies when other diagnostic studies are inconclusive.

Keywords: Cushing's Syndrome, Cushing's Disease, Petrose Sinus Catheterization.

Introduction

Cushing's disease (CD) is characterized by hypercortisolemia resulting from excessive adrenocorticotropic hormone (ACTH) secretion due to a pituitary corticotroph adenoma. While relatively rare in children and adolescents, it stands as the predominant cause of endogenous Cushing's Syndrome (CS), particularly in individuals above five years old [1-3]. Pediatric CD accounts for 75-80% of cases of CS in this age group, with corticotroph adenomas representing 54.8% and 29.4% of all pituitary adenomas in the 0-11 and 12-17 age groups, respectively [4]. Notably, a male prevalence of 63% has been documented [5,6]. The peak incidence occurs during the peri-adolescent period, typically presenting between 12.3 and 14.1 years [1]. Classic symptoms observed in adults are infrequent among children and adolescents, emphasizing the importance of considering CD in obese individuals with decelerated growth velocity [7]. The challenge in diagnosing pediatric CD is compounded by the common absence of adenoma visualization in imaging studies within this age group [7, 8]. The condition carries an increased risk of cardiovascular, metabolic, psychiatric, and infectious diseases, contributing to a heightened mortality rate in cases of persistent CD. Consequently, it poses a significant diagnostic and therapeutic challenge [3].In this article, we present a clinical case of CD in an adolescent patient. The absence of adenoma visualization in cranial MRI prompted the exploration of

alternative diagnostic techniques. Notably, we employed inferior petrosal sinus sampling, a novel approach in our country for an adolescent patient.

Clinical Case

A 16-year-old male teenager, characterized by a deficit in socioeconomic and cultural background, presents with a medical history marked by attention deficit during school years, bilateral multiple complicated renal lithiasis in 2021, and a familial predisposition to obesity. The anticipated genetic height for this individual is 178 cm. Referred to our center due to severe obesity, he has been progressively gaining weight since the age of 9, experiencing reduced growth velocity and shortened stature. Notably, he was previously of thin build. Initial consultation occurred at the age of 14, revealing the following physical examination findings: weight of 130 kg, height of 1.75 m, BMI of 42, and blood pressure of 120/70 mmHg. Physical manifestations included facial plethora, dorsal hump, wide red striae on the abdomen and chest, and gluteal muscle atrophy. Genital examination revealed inguinal intertrigo, a buried penis within a suprapubic fat pad measuring 5 cm in length, Tanner III pubic hair, and normal testes, both 8 cc (Tanner III). Work-up exams confirmed the presence of hypercortisolism, with a 1 mg overnight dexamethasone suppression test (Nugent test) result of 16.8 ug/ml (reference value (RV) <1.8); 24-hour urinary free cortisol (UFC) of 280 ug/24 hrs (RV 20-100 ug/24 hrs); and salivary cortisol of 363 ug/ml (RV < 100 ng/ml). The ACTH-dependent origin was substantiated with an ACTH level of 85.2 pg/ml (RV: 7.2-63.3 pg/ml). A 1.5 Tesla nuclear magnetic resonance of the sellar region revealed a normal signal and homogeneous enhancement of the adenohypophysis with gadolinium, without clear nodular images. Further investigation using an overnight high dexamethasone test exhibited a basal cortisol level at 8 hours of 13.8 ug and post-suppression cortisol of 8.3 ug (39.8% suppression). Subsequently, a PET-CT of the skull with methionine revealed abnormal radiotracer uptake in the pituitary gland. A subsequent 3 Tesla sellar region MRI identified a 5 mm nodular lesion in the adenohypophysis, situated at the left lobe and adjacent to the cavernous sinus (Figure 1).

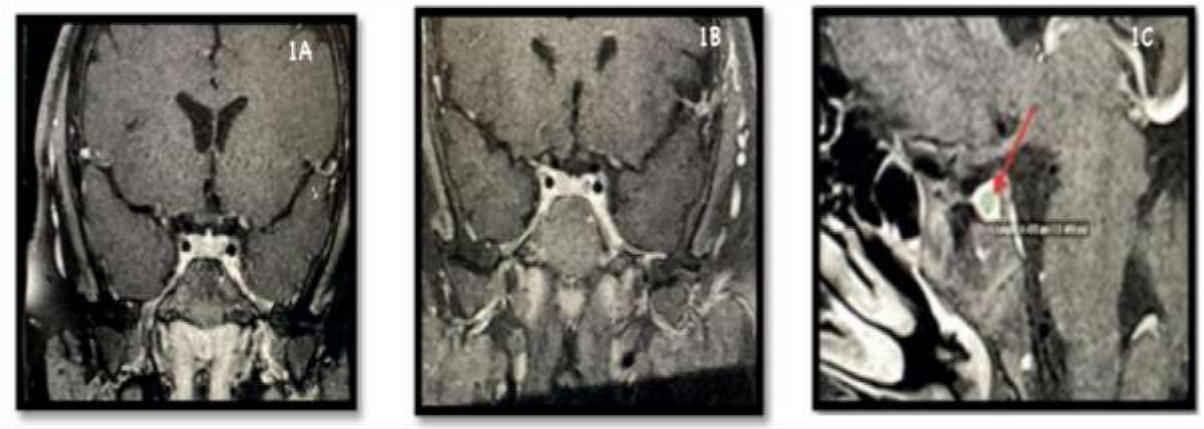

Figure 1. 1A, 1B, and 1C. Figure 1 presents nuclear magnetic resonance images of the skull with a sellar focus. In Figure 1A (T1 with contrast) from 2021, no pituitary adenoma is observed. However, Images 1B (coronal section, T1 with contrast) and 1C (sagittal section, T1 with contrast) clearly reveal the presence of a pituitary adenoma (red arrow) measuring less than 6 mm. In 2021, transsphenoidal surgery was successfully conducted without complications, targeting a suspected pituitary microadenoma. Pathological anatomy and immunohistochemistry confirmed a lesion consistent with a pituitary adenoma, characterized by intense and diffuse ACTH staining and sporadic mitoses. Postoperative follow-up, however, revealed persistent Cushing's disease (CD), both clinically and biochemically, with no indications of cure. Whole-body PET with methionine reported radioisotope uptake in the pituitary gland, more pronounced on the right. No abnormalities were identified in the rest of the body exploration. A subsequent 3 Tesla skull MRI revealed a subtle alteration in the upper contour of the pituitary gland's right lateral side, accompanied by a small underlying nodular image exhibiting differential enhancement compared to the rest of the gland. This nodular image measured 4.3 mm in diameter, suggesting the possibility of a second microadenoma. Faced with diagnostic challenges, IPSS was performed. Hypercortisolism was confirmed in the morning of the procedure with a cortisol level exceeding 10 µg/dl. Venous blood samples, obtained from both the petrous sinuses and a peripheral vein at baseline (10 and 5 minutes before desmopressin administration), were subjected to ACTH, cortisol, and prolactin measurements. Subsequently, a 10 µg intravenous desmopressin infusion was administered, and additional samples were collected for the same measurements at 3, 5, 10, and 15 minutes post-desmopressin administration. A baseline petrous gradient exceeding 2 and a post-desmopressin stimulus gradient exceeding 3 were evident, consistent with a diagnosis of Cushing's disease (CD). At the basal level, a gradient between the petrosal sinuses of more than 1.4 on the left suggested a 50-70% probability of left lateralization. Additional laboratory results include glucose at 107 mg/dl, A1C at 5.9%, calcium at 9.8 mg/dl

(with normal albumin), a normal lipid profile, LH at 4.4 mIU/ml, FSH at 7.0 mIU/ml, and total testosterone at 0.4 ng/ml (normal range: 2.68 - 5.56 ng/ml). Bone age aligns with the chronological age. Currently, the patient is undergoing treatment with metformin and vitamin D. Although oral ketoconazole was initiated, the patient experienced intolerance. Given the underdevelopment of the sphenoidal sinus, surgery was deemed unsuitable, and radiotherapy was administered.

Discussion

Cushing's syndrome is a rare condition in children and adolescents, yet it is associated with significant morbidity, including hypertension, cardiovascular disease, hyperglycemia, osteoporosis, and psychiatric conditions such as depression or cognitive dysfunction, and can even lead to mortality [9,10]. Pediatric cases account for only 10-15% of all diagnoses [1]. The most common cause of endogenous glucocorticoid overproduction in this age group is the presence of a pituitary corticotroph microadenoma, typically < 6 mm in diameter. These microadenomas are often hypodense on MRI and typically do not enhance with gadolinium contrast [7]. In children, Cushing's syndrome commonly manifests as slowed growth velocity and/or short stature associated with obesity, mirroring the presentation observed in our case. The average duration between symptom onset and diagnosis is approximately 2.5 years [5]. Classic adult symptoms like facial plethora, red-violet striae, and muscle atrophy are less frequent in pediatric cases, but our patient exhibited these symptoms, likely due to the prolonged duration of the disease [6]. Hypercortisolism and increased adrenal androgen production, along with the suppression of gonadotropin secretion, contribute to the disruption of normal sexual development [5,7]. It is crucial to consider ruling out Multiple Endocrine Neoplasia 1 (MEN1), which encompasses primary hyperparathyroidism (HPP), pituitary adenomas, and pancreatic tumors, as a potential etiology. Tumors secreting ACTH are generally rare in MEN1, accounting for only about 2% of cases [5,12]. In the presented case, the patient has a history of multiple bilateral renal stones. With normal calcium levels with normal vitamin D levels, primary hyperparathyroidism is ruled out. Interestingly, renal stones have been noted as a less-recognized clinical symptom of Cushing's syndrome, suggesting that it might be an underappreciated complication of the disease [11]. The characteristic absence of adenoma visualization in cranial MRI (observed in 50% of cases) presents a notable diagnostic and therapeutic challenge [13]. The gold standard for differentiating ACTH-dependent Cushing's syndrome is IPSS [14], which confirms the central origin of hypercortisolism and, particularly in children, often provides a higher incidence of lateralization [10,13,15]. It is recommended when pituitary MRI is negative despite

confirmed ACTH-dependent hypercortisolism [15]. This technique enables the differentiation between pituitary and ectopic cortisol sources. In the procedure, intermittent ACTH secretion is addressed by administering either CRH (corticotropin-releasing hormone) or a 10 mcg intravenous desmopressin, both of which stimulate ACTH production and enhance study sensitivity [14,15]. IPSS is a minimally invasive diagnostic technique, involving blood sample collection from catheterized petrous sinuses and a peripheral vein at baseline for ACTH and cortisol measurements. Following this, an infusion of 1 μg/kg intravenous CRH or 10 μg intravenous desmopressin is administered, with subsequent measurements taken at 3, 5, 10, and 15 minutes after the stimulus [15]. While ectopic ACTH secretion in children is exceedingly rare, the primary goal of IPSS is to localize adenomas by demonstrating ACTH secretion lateralization [15]. The procedure exhibits a sensitivity of over 92.8% for diagnosing Cushing's syndrome. With the intrapetrosal ACTH index > 1.4, the sensitivity to detect lateralization of an adenoma was 60 to 88% [13,16]. Potential complications include hematoma and bleeding at the puncture site, with central venous thrombosis being less common [5]. Transsphenoidal surgery (TSS) is regarded as the first-line therapy, boasting a remission rate of 70-80% [17,18].Selective microadenomectomy poses technical challenges in children, often leading to a notable failure rate, even in the hands of experienced neurosurgeons. The recurrence rate after transsphenoidal surgery (TSS) in this population is approximately 11.5%, occurring at a median of 44 months [19].

Alternative therapeutic options for such cases include a second surgery, medical treatment with various drugs, and radiotherapy [5].Drug therapies for children with Cushing's syndrome are limited and not well studied [16]. In this case, ketoconazole is initiated as it is not tolerated. Pharmacological treatment aims to reduce circulating cortisol. Drugs that suppress adrenal steroidogenesis can be divided into potential long-term therapy, such as ketoconazole, mitotane, and metyrapone, and short-term therapy, such as etomidate. Ketoconazole is indicated when TSS is expected, after failed TSS, and during the post-radiotherapy period [1, 2, 5, 16]. The dose is 300 to 1200 mg/day, and 45-50% of patients show long-term control with continuous use. However, it has not received FDA approval due to the risk of severe liver damage and interactions with other drugs [16]. For patients who do not respond to initial treatments, there are therapies targeting the pituitary tumor directly such as cabergoline, pasireotide, and radiotherapy. Cabergoline is a dopamine agonist, and its role in treating Cushing's syndrome has been debated. Functional D2 receptors have been observed in corticotropin-secreting pituitary tumors. The presence of functional D2 receptors in 60% and the demonstration of short-term cabergoline treatment efficacy in normalizing ACTH and cortisol secretion in 40% of corticotropin-secreting pituitary tumors strongly support the potential therapeutic use of this drug in

managing persistent, recurrent, or radiologically undetectable Cushing's syndrome [20,21]. Pivonello et al. demonstrated in their study that cabergoline treatment is effective in controlling cortisol secretion for at least 1–2 years in more than 33% of a limited population of patients with Cushing's syndrome (20 patients aged 24–60 years with CD after failed surgery) [20]. Currently, cabergoline is not FDA-approved for Cushing's syndrome treatment [2,16,21]. The use of pasireotide in children is limited to individual cases, and there are no studies summarizing treatment effects in this patient group [16]. Failure to control hypercortisolism will increase morbidity and mortality, leading to multiple systemic repercussions due to sustained elevation over time. Jeong I. et al. reported a 16-year-old male patient with Cushing's syndrome, facing similar diagnostic and therapeutic difficulties as our case. The patient underwent transsphenoidal surgery, but hypercortisolism persisted. Subsequently, a second surgery was performed with disease remission and postoperative hypopituitarism [9]. In cases where surgery is not possible or TSS fails, radiotherapy (RT) or chemotherapy are effective second-line treatments to address residual tumor tissue. Limited studies have reported on efficacy and long-term outcomes in children. Conventional fractionated RT has better cure rates in children (50-100%) compared to 56-83% in adults. The onset of action is faster (average cure time: 0.75-2.86 years) than in adults (range: 1.5-5 years) [1]. Another recent study reported better efficacy and a lower adverse effect profile of stereotactic radiosurgery in 24 pediatric patients with Cushing's syndrome, who received this modality as first-line treatment (7 patients) or after a failed TSS. An endocrine remission rate of 80% was achieved within a median time of 12 months, and tumor control was observed in 87.5% of cases with a median follow-up of 46 months. In 20.8% of patients, multiple new pituitary hormonal deficiencies emerged over an average interval of 18 months, while tumor recurrence was observed in 21% of patients after an average interval of 9.5 months [2]. Cranial irradiation may lead to various complications, including the development of hypopituitarism, cranial neuropathies, cerebrovascular events, the formation of second intracranial tumors, and cognitive effects. Patients are at risk of developing growth hormone deficiency, as well as hypogonadism, either independently or with other anterior pituitary hormonal deficiencies, necessitating thorough and regular evaluation. Notably, recovery of the somatotropic axis has been documented, highlighting the importance of sequential reevaluation [2,16].

Conclusion

In conclusion, managing pediatric Cushing's disease presents significant challenges in achieving optimal growth, body composition, bone health, reproductive capacity, and overall quality of life. Recognizing the

unique characteristics of Cushing's syndrome in the pediatric age group is crucial to avoid diagnostic delays. Inferior petrosal sinus sampling (IPSS) stands as the gold standard for diagnosing the etiology of ACTH-dependent Cushing's syndrome when previous studies yield inconclusive results. Lifelong follow-up is imperative due to the risk of clinical, biochemical, and imaging recurrence, along with associated morbidity and mortality."

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