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A Case Of Pediatric Cushing Disease: Diabetic Ketoacidosis

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ABSTRACT: Objective: Cushing syndrome (CS) is very rare in pediatric patients. The major cause of endogenous CS is Cushing disease (CD), which is due to excessive adreno-corticotropic hormone (ACTH) secretion from pituitary cells. CS that presented with diabetic ketoacidosis (DKA) has rarely been reported in adults.
Methods: A case report and literature review.
Results: A 12-year-old female suffering from polyuria and polydipsia for 3weeks was admitted with amenorrhea. Due to her hyperglycemia, ketonuria, glucosuria, and metabolic acidosis on arterial blood gas, she was diagnosed with DKA. Oral moniliasis, acanthosis nigricans, moon face, central obesity, and striae were detected on physical examination. Based on the results of overnight and low-dose dexamethasone suppression tests, the patient was diagnosed with CS. In a high-dose dexamethasone suppression test (HDDST), her urinary free cortisol (UFC) excretion rate was suppressed by 71.3%. Brain magnetic resonance imaging (MRI) revealed a 3-mm pituitary microadenoma. Because serum cortisol and24-hour UFC levels were not sufficiently suppressed by the HDDST and the diameter of adenoma in the MRI was <5mm, bilateral inferior petrosal sinus (BIPS) sampling was performed. A diagnosis of CD was confirmed by determining a high central/peripheral ACTH ratio of 11.
Conclusion: Although very rare in childhood, CS should be considered in pediatric patients with obesity, acanthosis nigricans, moniliasis, and striae. DKA may be the presenting clinical feature in patients with impaired glucose metabolism.

1. INTRODUCTION

Cushing syndrome (CS) is a rare endocrine disorder in childhood with an incidence of 2 to 5 per million. The incidence of CS is similar between sexes, and children account for 10% of all cases (1). CS results from prolonged exposure to supraphysiological levels of circulating glucocorticoids that are endogenously or exogenously derived. The most common cause of CS in childhood is the administration of high-dose topical, inhaled, or oral corticosteroids (1,2). Childhood CS can be divided into 2 subgroups: ACTH-dependent and ACTH-independent forms. CD accounts for 75% of CS in children >7 years of age, and the remaining
25% of pediatric cases are ACTH-independent CS (mostly adrenal tumor or adrenal adenoma), which is commonly observed in children <7 years of age. Ectopic ACTH syndrome (small cell lung cancer, carcinoid tumor, pheochromocytoma, medullary thyroid cancer, etc.) is quite rare in children, accounting for <1% of cases (1).

In patients with CS, various complications such as hypertension, diabetes mellitus (DM), osteoporosis, infec- tion, thromboembolic events, sleep disturbance, and neuropsychological disturbances (e.g., depression, irritability, cognitive defects) are encountered (3). DM accompanying CS is frequently (20-60%) reported in adult studies (3-5); however, this association is unusual in childhood. Age, genetic predisposition, and the degree and duration of hypercortisolemia are important risk factors for the development of DM in CS (4). This report describes a 12-year-old obese female who presented with clinical signs of DKA and was diagnosed with CD due to hypophyseal microadenoma.

2. CASE REPORT

A 12-year-old female presented with the complaints of polyuria, polydypsia, weight gain, oral moniliasis, and amenorrhea. She had experienced polyuria and polydypsia for the past week, and weight gain and amenorrhea for the past year. There was no chronic disease or a history of continuous drug use. The family history was unremarkable except that her paternal grandmother had type 2 DM. On physical examination, she weighed 85 kg (>95th percentile, 2.19 SD), with a height of 154 cm (10-25 percentile,−0.71 SD), a body mass index of 37.1 kg/m2 (>95th percentile, 2.32 SD), blood pressure of 129/89 mm Hg, and a heart rate of 136 beats/minute. The rest of the physical examination revealed dry skin, moon face appearance, buffalo hump, purple-colored striae on the skin, and acanthosis nigricans, but hirsutism and virilization were not present. Her laboratory examination results were notable for hyperglycemia (venous blood glucose: 559 mg/dL) and metabolic acidosis (pH: 7.12, HCO3: 7.6 mmol/L) with ketonuria (3+) and glucosuria (3+). Other values were as follows: glycated hemoglobin (HbA1c), 10.6%; serum C-peptide level, 11.2 ng/mL (normal, 0.9-7.1); triglyceride level, 200 mg/dL (normal, 40-128); cholesterol (C) level,186 mg/dL (normal, 125-212); high-density lipoprotein-C level, 44 mg/dL (normal, 35-65 mg/dL); and low-density lipoprotein-C, 89 mg/dL (normal, 50-170). Diabetes anti-bodies for anti-insulin and anti-glutamic acid decarboxylase were negative. Based on these clinical and laboratory findings, the patient was diagnosed with DKA. After the recovery of ketoacidosis by intravenous hydration and regular insulin infusion (0.1 IU/kg/hour), intensive insulin treatment with insulin lispro and insulin glargine was initiated and metformin was added.

Test results for obesity and etiology of secondary amenorrhea were as follows: Thyroid function tests were normal (free thyroxine, 1.3 ng/mL; thyroid-stimulating hormone, 3.47 mIU/mL), follicle-stimulating hormone,
3.71 mIU/mL; luteinizing hormone, 17.83 mIU/mL; estradiol, 126 pg/mL; dehydroepiandrosterone sulfate, 331.2 mg/dL; 17-hydroxyprogesterone, 1.3 ng/mL; cortisol [8:00 am], 36.7 mg/dL [normal, 5-25 mg/dL]; and cortisol (11:00 pm), 28.3 mg/dL (3-10 mg/dL). The patient had consistently elevated urinary free cortisol (UFC) levels (>70 mg/m2/ day) in 3 different measurements. Plasma ACTH level was 42.7 pg/mL. After an overnight 1-mg dexamethasone suppression test and a low-dose dexamethasone suppression test (4 × 0.5 mg for 2 days), serum cortisol levels were inadequately suppressed (serum cortisol >1.8 mg/ dL). Thus, the patient was diagnosed with CS. In order to determine the etiology of CS, a high-dose dexamethasone suppression test (HDDST) (4 × 2

mg for 2 days) was performed; the patient's serum cortisol level was suppressed by ~70% (9.87 mg/day), and 24-hour UFC was suppressed by ~71.3% (30 mg/m2/day) (suppression >90% suggests CD) (1). Pituitary magnetic resonance imaging (MRI) showed a microadenoma with a diameter of 3 mm (Fig. 1). Because her serum cortisol and 24-hour UFC levels were not sufficiently suppressed by the HDDST and the diam- eter of adenoma in the MRI was <5 mm, bilateral inferior petrosal sinus (BIPS) sampling was performed to make an accurate diagnosis. After intravenously administering 1 mg/kg corticotropin-releasing hormone , levels of peripheral and central ACTH were measured at 0, 1, 3, 15, and 30 minutes. However, adequate sampling could not be performed from the left petrosal sinus because of a vascular malformation. As a result, no evidence of lateralization could be obtained. A diagnosis of CD was confirmed by determining a high central/peripheral ACTH ratio. After glycemic control was achieved, a transsphenoidal adenomectomy was per- formed. Histopathologic examination of the biopsy specimen revealed findings compatible with a ACTH-secreting pituitary adenoma. Three days after the operation, hydro-cortisone was started at a dose of 10 mg/m2/day because the patient had clinical features of adrenal insufficiency (profound muscle weakness and fatigue, depression) with a concurrent morning cortisol level of 5 mg/dL. The evaluation of other pituitary hormones revealed normal findings. Two weeks after transsphenoidal surgery (TSS), the patient was weaned off insulin, and her DM was under control with diet and metformin treatment. Three months after surgery she had lost 9 kg, and normal blood glucose and insulin responses to an oral glucose tolerance test (OGTT) were observed; thus, metformin was discontinued without any glycemic deterioration.

3. DISCUSSION

During childhood, patients with CS are frequently asymptomatic, and the beginning of clinical signs is insidi- ous. The most important signs of CS in childhood are weight gain and short stature (1). Linear growth is almost always severely diminished and may be useful in differentiating between childhood obesity and CS (9). Facial plethora, headache, hypertension, hirsutism, amenorrhea, fatigue, weakness, delayed sexual development, and virilization may also be seen (1,3,9). Skin atrophy, acne, purple striae, easy bruising, and acanthosis nigricans are common (1,9). In the present patient, dry skin, moon face, buffalo hump, purple striae, and acanthosis nigricans were observed, but she showed no signs of hirsutism or virilization. Because the patient has already reached her adult height before the diagnosis, she did not have short stature.

Due to the poor discrimination of laboratory tests, the diagnostic process for CS is usually difficult. Although laboratory and imaging techniques are essential for an accurate diagnosis, they may not always be distinguishing. The initial laboratory signs for the diagnosis of CS are high morning and midnight cortisol levels and loss of diurnal cortisol rhythm (1). It was reported that a single morning plasma ACTH level was also important for the diagnosis of CS, and a value >29 pg/mL had a sensitivity of 70% for the diagnosis of ACTH-dependent CS (1,10). The morning plasma ACTH levels in the present case were >29 pg/ mL, which suggested a diagnosis of ACTH-dependent CS (10). Different opinions regarding the interpretation of diagnostic tests for the etiology of CS have been reported in

the literature (1,3,9). After HDDST, approximately 85% of patients with CD will exhibit suppression of serum cortisol, UFC, and 17-hydroxysteroid values, whereas less than 10% of patients with ectopic ACTH secretion will have suppression (1,3,9). In CD, UFC values should suppress to 90% and 17-hydroxysteroid excretion should suppress to less than 50% of baseline value after HDDST (1). In the present case, the expected suppression (>90%) did not occur after HDDST in the 24-hour UFC level, and ectopic ACTH syndrome could not be ruled out.

MRI is the examination of choice for diagnosing CD. However, ACTH-secreting pituitary adenomas are usually hypodense on MRI and often fail to enhance with gadulinium contrast. Besides in as much as 50% of cases they do not exceed the diameter of 5 mm (11). Dynamic contrast-enhanced pituitary MRI may detect only 50 to 60% of ACTH-producing pituitary adenomas, perhaps because corticotroph adenomas tend to be microadenomas with sig- nal and enhancing characteristics similar to normal pituitary tissue (1,3). BIPS, which is considered the gold standard technique that is helpful in the differential diagnosis of ectopic ACTH syndrome and CD, should be performed in cases where pituitary adenomas cannot be determined by imaging techniques (1,13). The diagnostic accuracy of BIPS sampling can reach up to 100% if performed in experienced centers (1). It is suggested that small pituitary lesions (<5 mm) should be viewed in context with dynamic testing. BIPS sampling is also recommended to increase diagnostic accuracy in cases where dynamic test results are uncertain; ectopic ACTH syndrome cannot be ruled out; and adenoma diameter is <5 mm on pituitary MRI (3). In the present study, CD was diagnosed by using BIPS sampling for all of these reasons. The treatment of choice for almost all patients with ACTH-secreting pituitary adenoma (CD) is TSS. In most specialized centers with experienced neurosurgeons, the success rate of the first TSS is 90% or higher (2). 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, syndrome of 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% (1). In the present case, a hypophyseal adenomectomy was performed via TSS. No complications related to other pituitary hormones developed during the postoperative period. Hydrocortisone replacement therapy is recommended in cases with CD if serum cortisol levels are below

2 mg/dL or signs of adrenal insufficiency appear during the postoperative period. It is also administered if there are clinical signs of adrenal insufficiency at serum cortisol levels between 2 and 10 mg/dL (2). In the present case, the patient had symptoms of adrenal insufficiency with a concurrent morning cortisol level of 5 mg/dL 72 hours after surgery, and hydrocortisone replacement was initiated. Obesity, hypertension, and DM are the most common complications in CS, and their frequencies and severities are related to disease duration. The reported incidence rate of DM associated with CS ranges from 16.7 to 63% (10,14). Hypercortisolism promotes hyperglycemia and decreases carbohydrate tolerance by increasing hepatic glucose production and decreasing glucose uptake and utilization by peripheral tissues (15). Pancreatic beta cells possess glucocorticoid receptors that cause beta cell dysfunction and reduce insulin sensitivity (16). DM occurs as a consequence of an insulin-resistant state together with impaired insulin secretion, which

are both induced byglucocorticoid excess (17). Age, genetic predisposition, and lifestyle, in combination with the duration and degree of hypercortisolism, strongly contribute to the development of DM in patients with CS (4). DKA has long been considered a hallmark of type 1 DM; however, it can also occur in type 2 DM. Individuals with the latter are more likely to develop a hyperosmolar hyperglycemic state (HHS). In patients with HHS, a concomitant illness (infection, altered mental status, or dehydration) that leads to reduced fluid intake is usually present, and sufficient insulin production prevents lipolysis, leading to ketosis and acidemia (18). There are 3 proposed mechanisms of DKA in type 2 diabetics:
(1) insulinopenia, (2) elevation of counter regulatory stress hormones and, (3) increased levels of free fatty acids. The predominant mechanism is the deficiency or decrease in insulin secretion. In the current patient, her serum C-peptide level was elevated in response to hyperglycemia; therefore, we can only hypothesize about the possible role of increased counterregulatory hormones (cortisol), which are thought to cause an acute halt of insu- lin secretion by temporary pancreatic beta islet dysfunction in addition to insulin resistance (19). To our knowledge, there are few reports of adult CS cases accompanied by DKA (6-8). Commonly, infectious diseases or the ingestion of large volumes of sugar-containing soft drinks are proposed to lead to ketosis or DKA in DM patients with CS. Two weeks after surgery, she was weaned off insulin, and 3 months after surgery metformin was no longer needed because of marked weight loss, and normal blood glucose and insulin responses to an OGTT were observed. On the basis of these results, it was assumed that the main cause of obesity and obesity-related type 2 DM in our patient was CS. In addition, we propose that hypercortisolemia is the most important risk factor for the development of DKA in our patient.

4. CONCLUSION

In conclusion, although rare in childhood and adolescence, CS should be considered in the differential diagnosis of pediatric patients who present with signs of obesity and DM. With this report, we emphasize that related to the duration of hypercortisolemia, children with CS may also present with DM and DKA.

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