PRIMARY PIGMENTED NODULAR ADRENOCORTICAL DISEASE (PPNAD) PRESENTING AS CUSHING SYNDROME IN A CHILD AND REVIEW OF LITERATURE

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Abstract

Cushing syndrome in the paediatric age group is very difficult to diagnose due to atypical presenting features in children. Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing syndrome in children and it has characteristic gross and microscopic pathologic features. We report a case of PPNAD in a 16-year-old boy who was evaluated in our hospital with chief complaints of poor height velocity and rapid weight gain for 2-3 years before presentation. Proper evaluation showed ACTH-independent Cushing syndrome with normal imaging. Total bilateral adrenalectomy was performed followed by hormones replacement. 6 months after surgery, significant acceleration of height velocity was noticed. Patient also lost body weight and developed secondary sexual characteristics.

Keywords: Cushing syndrome, Primary Pigmented Nodular Adrenocortical Disease, Height velocity.

INTRODUCTION

Cushing syndrome (CS) is classified into adrenocorticotrophic hormone (ACTH) dependent and adrenocorticotrophic hormone (ACTH) independent. The causes of ACTH-independent CS are factitious CS, adrenocortical adenoma or carcinoma, primary pigmented nodular adrenocortical disease (PPNAD) and primary macronodular adrenal hyperplasia (PMAH). PPNAD is a rare but an important cause of hypercortisolism especially in the paediatric age group with characteristic gross multiple small and pigmented nodules, and microscopic features such as synaptophysin positive, lipofuscin pigmented nodules, atrophic cortex in between nodules of the adrenal glands. It may occur independently or associated with Carney complex (1). We report a case of isolated PPNAD presenting with

poor height velocity under evaluation for short stature with relatively increased body weight.

CASE PRESENTATION

A 16-year-old boy presented to an endocrine outpatient clinic with complaints of gradually decreased height velocity for 3-4 years, weight gain over 2 years before presentation and lack of secondary sexual characteristics, noticed by parents. He was born out of non-consanguineous marriage, delivered vaginally with vertex presentation and without any history of perinatal crisis, prolonged jaundice or recurrent hypoglycaemia. There was no history of chronic diseases. The patient reportedly was not on any medication. There was no family history of similar problems in siblings or any other family members. Patient's auxology was as below: height 135 centimeter (<3rd percentile), height SDA -4.3 (suggestive of short stature), weight 45 kg, height for age 10 years (Patient's age 16 years), weight for age 13 years (Patient's age 16 years). On examination, he had mild facial fullness. There was no fat accumulation in the neck (buffalo hump), abdominal striae, hirsutism or proximal muscle weakness. His pulse rate was 78/minute, blood pressure was 100/70 mmHg and he was clinically euthyroid. There were no lentigines or blue nevi on skin examination. There were no features of Albright Hereditary Osteodystrophy (AHO) like brachydactyly (short finger bones) in 4th and 5th finger or subcutaneous ossification. Due to decreased height velocity and increased body weight with facial fullness, Cushing syndrome was suspected and investigations were carried out.

Investigations to find out the cause and the diagnosis are described in Table 1.

Contrast-Enhanced computed tomography

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Figure 1. Contrast Enhanced Computed Tomography scan of both adrenal glands with suspected beading in the limbs of adrenals.

(CECT) with the adrenal protocol was done to rule out adrenal pathology which was normal except for suspected beading in bilateral adrenal glands (Fig. 1). A sequential Liddle's test was done which revealed >50% of increased urinary cortisol levels from baseline (988 µg/day (reference range: <50 µg/day)) on day 2 after 0.5 mg dexamethasone every 6 hours for 48 hours followed by 2mg dexamethasone every 6 hours for another 48 hours (Table 1). On further investigations to evaluate for features of Carney complex, echocardiography and ultrasonography of neck and testes were done, all of which were normal. Laparoscopic bilateral adrenalectomy was performed. Postoperative period was uneventful. Gross examination of bilateral adrenal glands showed nodular appearance (Fig. 2) with nodules size ranging from 2

Figure 2. Gross appearance of both Adrenal glands after removal.

Figure 3. Large polygonal shaped cells with eosinophilic cytoplasm with some cells showing lipofuscin pigments.

Table 1. Further dynamic endocrinology testing

Test	Patient's value	Reference range	Interpretation
9 AM cortisol	16.1 µg/dL	5 to 15 µg/dL	Likely hypercortisolism
24 hours urinary cortisol levels	453 µg/day	54-408 µg/day	Increased, suggestive of excessive cortisol
1 mg overnight dexamethasone suppression test (ONDST) (Low Dose)	15 µg/dL	Appropriately suppressed level: (<5 µg/dL): Normal Inappropriately high levels (>15 µg/L): Cushing syndrome	Suggestive of excessive cortisol production due to 1. Pituitary causes 2. Adrenal causes 3. Ectopic ACTH production
Morning ACTH	5 pg/mL	7 to 60 pg/mL	Suggestive of ACTH independent Cushing syndrome
Liddle's test			
Baseline 24 hours urinary Cortisol levels	453 µg/day	54-408 µg/day	Increased, suggestive of excessive cortisol
Urinary cortisol levels at day 2 after 0.5 mg dexamethasone every 6 hours for 48 hours.	988 µg/day	<50 µg/day	Paradoxical rise in urinary cortisol levels
Urinary Cortisol levels at day 4 after 2 mg dexamethasone every 6 hours for another 48 hours.	950 µg/day	<50 µg/day	Paradoxical rise in urinary cortisol levels
Urinary cortisol levels at day 6	937 µg/day	<50 µg/day	Paradoxical rise in urinary cortisol levels

to 4 mm. Histological examination showed nodules in the adrenal cortex. The cells were large polygonal, abundant eosinophilic cytoplasm, small vesicular nuclei and prominent nucleoli. Some cells showed the presence of lipofuscin pigment in their cytoplasm. All features were suggestive of primary pigmented nodular adrenocortical disease (Fig. 3). Immunohistochemistry study was positive for synaptophysin. Genetic testing was planned for the correct diagnosis but could not be done because of non-availability at our centre and the refusal of parents. The patient was put on lifelong steroid supplements in forms of hydrocortisone and fludrocortisone. On further follow-up, increased height velocity and pubertal features were observed.

DISCUSSION

Cushing syndrome is an endocrine disorder characterised by chronic and inappropriately excessive exposure to glucocorticoids which leads to the development of classical features of hirsutism, central obesity, moon face, proximal muscle weakness, abdominal striae, impaired blood pressure regulation and glucose metabolism. Cushing syndrome in the paediatric age group is a rare entity and most of the time there is a significant delay and difficulty in diagnosing it because of atypical presenting features like decrease in height velocity and increased body weight (2). These features in paediatric Cushing syndrome are due to the suppressive effects of glucocorticoids on long bones. The suppressive effect of glucocorticoids on growth may be due to 1. An indirect excessive secretion of somatostatin, 2. Indirect inhibition of IGF-1 production, 3. Direct action on epiphyseal cartilage to inhibit sulfation, mineralization and cell proliferation (3). Depending upon source of excessive cortisol production, paediatric Cushing Syndrome can be classified into A. ACTH dependent Cushing syndrome (where there is excess production of ACTH either from pituitary, hypothalamic sources or ectopic ACTH production), B. ACTH independent Cushing syndrome (where excessive cortisol is due to either excessive intake or excessive production due to adrenal cortex pathology)(1). The causes of ACTH independent Cushing syndrome can be due to excessive glucocorticoid administration, micro or macronodular hyperplasia of adrenal cortex, adrenocortical tumor or primary pathology or as a part of McCune Albright syndrome complex (4). Amongst the causes of ACTH independent Cushing syndrome, PPNAD is a rare (found in less than 1% of patients with Cushing syndrome) but an important differential

diagnosis. It can occur as either sporadic (approximately 33% of cases) or familial (approximately 66%). Familial cases may occur as isolated PPNAD or as a part of Carney Complex (5).

Cushing syndrome secondary to PPNAD can present with typical or atypical features, but there are a number of clinical features that can help towards the diagnosis. Patients usually present at younger age with more female adolescent patients developing Cushing Syndrome compared to males (6). Osteoporosis and avascular necrosis of the hip can sometimes be prominent features (7,8). Patients may have mild features which can be missed easily or they can have cyclical/periodic hypercortisolism which can be difficult to diagnose. PPNAD may also occur as a part of Carney Complex. Carney Complex is an autosomal dominant multiple neoplasia characterised by skin pigmentation, multiple endocrine neoplasia (PPNAD, thyroid adenoma or tumor, sertoli cell calcification, ovarian cyst, and/or growth hormone secreting pituitary adenoma), non-endocrine tumors including atrial myxoma, cutaneous myxoma, osteochondromyxoma (9).

Pathologically, most nodules are small in size (usually <4 mm) and surrounded by atrophic cortex. Cells are usually large with clear or eosinophilic cytoplasm with many of them containing large amounts of coarse brown lipofuscin pigments. They have high Synaptophysin expression and it is suggestive of its neuro-endocrine nature (7).

Initial biochemical evaluation should be carried out the same way as evaluating any other patients with Cushing syndrome to confirm excessive cortisol. 24 hours free urinary cortisol levels, 1 mg overnight dexamethasone suppression test, night salivary cortisol can be done which suggest unequivocally and reproducibly high cortisol. The second step is to establish whether it is ACTH dependent or ACTH independent. A low ACTH level with high cortisol level in a patient with Cushing syndrome is suggestive of ACTH independent of Cushing syndrome. Sequential low-dose-high-dose dexamethasone suppression test (Liddle's test) can be useful to differentiate PPNAD from other primary adrenocortical lesions. The test consists of dexamethasone administration at the dosage of 0.5 mg every six hours for 48 hours and 2 mg every six hours for another 48 hours and collection of 24 hours of urine for determination of cortisol excretion baseline and every 2 days. Paradoxical rise in urinary cortisol excretion of more than 50% is indicative of PPNAD (10).

Appearance of adrenal gland in CT scan with PPNAD is often interpreted as normal (in contrast to

the other adrenal hyperplasia) and sometimes it gives appearance of a string of beads because of the presence of multiple small nodules in otherwise atrophic adrenal cortex.

Bilateral adrenalectomy is the treatment of choice for Cushing syndrome due to PPNAD. The laparoscopic approach is associated with lower morbidity rate compared with the open technique, less post-operative pain, shorter hospitalization time and lower overall cost.

In conclusion, even though PPNAD, sporadic or familial, is a rare cause of Cushing syndrome, it should be included in the differential diagnosis of ACTH-independent Cushing syndrome, especially in paediatric age group and when adrenal imaging is apparently normal. Every patient diagnosed with PPNAD should be screened for CNC (Carney complex) and monitored closely on a long-term basis by annual echocardiogram, thyroid and testicular ultrasound at regular intervals.

Conflict of interest

The authors declare that they have no conflict of interest.

Consent

Consent has been obtained from the patient to publish the case report.

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