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Primary Pigmented Nodular Adrenocortical Disease (PPNAD) Presenting as ACTH-Independent Cushing's Syndrome: A Case Report

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ABSTRACT

Cushing's syndrome diagnosis in childhood is a challenge, due to its atypical presentation. Primary Pigmented Nodular Adrenocortical Disease (PPNAD) is a rare cause of ACTH- independent Cushing's Disease. We present the case of a four-year-old patient evaluated for Cushing's Syndrome due to a rapid onset of obesity, pubarche and hirsutism with a characteristic phenotypic appearance. Initial biochemical examinations were compatible with ACTH- independent Cushing's Syndrome, but imaging studies were confusing (pituitary MRI detected an image compatible with adenoma). The study was completed with tests which confirmed independence from ACTH and finally the patient underwent a bilateral adrenalectomy. The anatomopathological findings of adrenal glands confirmed the diagnosis. Replacement hormonal treatment was applied, leading to the progressive recovery of a normal phenotype.

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Abbreviations

- **PPNAD:** Primary Pigmented Nodular Adrenocortical Disease.
- **CS:** Cushing Syndrome
- **CT:** Computed Tomography
- **MR:** Magnetic Resonance

Introduction

Cushing's syndrome (CS) englobes a set of signs and symptoms derived from a prolonged exposition to glucocorticoids. It is classified as ACTH-dependent or ACTH-independent. ACTH-dependent CS causes are mainly Cushing's Disease (pituitary adenoma) and ectopic secretion of ACTH. On the other hand, ACTH-independent CS causes are exogenous exposition (prolonged corticoid therapy), adrenal adenoma, adrenal carcinoma and primary adrenal hyperplasia (genetic variants), being the most common presentation in children the presence of Primary Pigmented Nodular Adrenocortical Disease (PPNAD) [1].

PPNAD may be sporadic (33%) or familiar (66%), in some cases as part of the Carney Complex (myxomas, mucous and skin lentigines and endocrine tumors) [2]. The most frequent form of presentation is growth retardation, although it can also manifest as a typical CS. However, it can be diagnosed later in life as its clinical course may be cyclic with remission periods [2-3].

Case Presentation

A four-year-old girl consulted due to weight gain and pubarche in the last 7 months, associating asthenia and exercise intolerance.

History revealed she was born in a controlled twin pregnancy without incidents. A caesarean section was practiced at 36 weeks of gestational age, with normal somatometry at birthtime. Neonatology intensive care unit admission was required due to a transient respiratory distress after birth. There was no family history of interest.

Physical examination revealed central obesity (weight 27.7 kg, +3.99 SD; height 102 cm, -0.75 SD; BMI 26.37 kg/m^2, 6.48 SD) associated to buffalo hump and moon face. Additionally, androgenic distribution of hair and Tanner III pubarche was observed. Vital signs: Blood pressure 126/95 mmHg (>p95), heart rate 121 bpm. In that moment, she was admitted into a hospital care unit to complete the evaluation.

Image 1: Physical examination one day after the adrenalectomy: central obesity, moon face, buffalo hump, hirsutism and Tanner III pubarche. No skin lentigines or other skin lesions were seen; no shortening of the 4th or 5th metacarpal.

Basal hormonal blood tests were performed, showing a suppressed ACTH as well as high-normal cortisol. Hypercholesterolemia and polyglobulia was also observed.

- Blood test: hemoglobin 16,3 g/dL; haematocrit: 47,5%. Triglyceride 54 mg/dl; cholesterol 235 mg/dl; (LDL 152 mg/dl; HDL 72 mg/dl); normal liver and kidney profile. Cortisol 25.02 µg/dL (normal range: 9-23), ACTH <5 pg/ml; 17-OH-P 2.33 ng/mL; DHEA 313 ng/mL; PRL 9.5 ng/ml. FSH/LH 0.3/<0.1 mU/ml, Estradiol <24 pg/ml. TSH 2.8 mU/l. Hb1Ac 5.3%.
- Blood test: cortisol 22 ug/dL; ACTH < 5 pg/mL
- Blood test: cortisol 17,10 µg/dL; ACTH: < 5,0 pg/mL Cortisoluria was elevated.
- Cortisoluria (1): 478 ug/24h; Cortisoluria (2): 824,0 µg/24h; Cortisoluria (3): 1.307,2 µg/24h
- A study of the circadian rhythm was carried out by measuring serum cortisol at 11 p.m. and salivary cortisol at night. Both suggested loss of circadian rhythm. No suppression was found in the Nugent test (Low-dose dexamethasone suppression test).
- Serum cortisol (11 p.m.): 19,50 µg/dL.
- Salivary cortisol (8 a.m.): 1,11 µg/dL; Salivary cortisol (11 p.m.): 0,90 µg/dL
- Test de Nugent (after 1 mg dexamethasone at 11 p.m.): Cortisol 18,20 µg/dL

An ultrasonography and an abdominal computed tomography (CT) scan were performed without reporting any relevant findings. The evaluation was completed with an abdominal magnetic resonance (MR) which showed the presence of normal adrenal glands, and a pituitary MR where a focal absence of enhancement consistent with a pituitary adenoma was found.

Despite blood test results were compatible with ACTH-independent CS (adrenal origin was suspected), the image results suggested further investigations should be conducted. A high-dose dexamethasone suppression test was performed, observing an absence of cortisol suppression. Furthermore, a CRH hormone test was conducted where neither ACTH nor cortisol levels were suppressed after 120 minutes. Both these results indicate an ACTH-independent CS. Finally, classical Liddle test showed a paradoxical rise in free urinary cortisol in the second sample, which was suggestive of PPNAD.

- High-dose dexamethasone suppression test (after 4 mg dexamethasone at 11 p.m.): basal cortisol: 17,10 µg/dL; post-test cortisol 20,00 µg/dL.
- CRH test (after CRH 30 mcg IV): No suppression of ACTH or cortisol (table 1).
- Classical Liddle test (DXM 0.5mg/6h 2 days, DXM 2 mg/6h 2 days): basal cortisoluria 1.307,2 µg/24h; post-test cortisoluria 1.741,5 µg/24h

Table 1: CRH test results

Basal ACTH	<5 pg/mL	Basal cortisol	21 µg/dL
15' ACTH	<5 pg/mL	15' cortisol	19.3 µg/dL
30' ACTH	<5 pg/mL	30' cortisol	15.3 µg/dL
60' ACTH	<5 pg/mL	60' cortisol	18.5 µg/dL
90' ACTH	<5 pg/mL	90' cortisol	17.6 µg/dL
120' ACTH	<5 pg/mL	120' cortisol	16.8 µg/dL

As high blood pressure was verified during inpatient stay, treatment with captopril was initiated.

As the finding of an adenoma in the pituitary MR was not concordant with the rest of the results, the MR was repeated, which showed no abnormalities, stablishing the hypothesis that the previous image was due to the contrast wash.

Finally, surgeons performed a laparoscopic unilateral adrenalectomy with extemporaneous biopsy of the surgical sample. Once confirmed the existence of adrenal hyperplasia (Image 2), bilateral adrenalectomy in the same surgical time was completed. Replacement hormonal treatment consisted of both hydrocortisone and fludrocortisone. The results of the histological study were compatible with primary pigmentary nodular adrenocortical disease (PPNAD). Since surgery, the patient underwent a progressive but slow recovery of her phenotype (image 3).

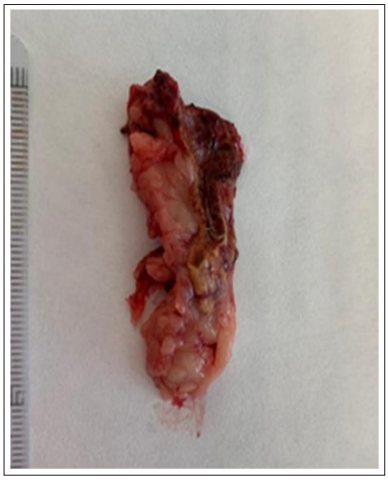

Image 2: Adrenal gland removed during laparoscopic surgery

Image 3: Clinical course after surgery

Genetic test (PRKAR1A, PDE11A and PDE8B genes) was negative.

As part of the investigation of a possible Carney Complex, a thyroid ultrasound and an echocardiogram study were performed, which showed no abnormalities. There were no lesions suggestive of Sd. McCune Albright in the skeletal survey either.

Discussion

The incidence of CS is 0.7-2.5 cases per million inhabitants/year and pediatric cases are infrequent (10% from total). In children with an age under 5 years adrenal origin (adrenal tumors and genetic variants) is predominant [1].

PPNAD is caused by cortisol hypersecretion by multiple pigmented nodules, independently from ACTH stimulation. It is a rare cause of CS (<1 %), despite 50% of its incidence takes place before 15 years of age and it is more frequent in women [2].

Although in the case that we present symptoms were typical, in general the diagnosis of PPNAD can be complex since it frequently presents as an atypical CS. Atypical CS is characterized by an asthenic habit (rather than obese), severe osteoporosis and short stature, with a normal or almost normal cortisoluria but with loss of a circadian cortisol rhythm. There are also patients who can associate a cyclical course of the disease, with remission periods,

which means that the diagnosis can be delayed for years. Ruder HJ et al describe in their review two patients who were diagnosed with severe osteoporosis due to the long evolution of their disease [1, 3]. In typical CS presentation, the symptoms are usually weight gain with central obesity, arterial hypertension and, in some cases, growth retardation [4, 5].

The histological study shows small nodules (<4 mm) in the adrenal cortex, consisting of polygonal cells with eosinophilic cytoplasm. Some of them present staining with lipofuscin. The immunohistochemistry study is usually positive to synaptophysin, which suggests the neuroendocrinological origin of these cells [6].

PPNAD may be sporadic (33%) or familial (66%). Family cases may appear as isolated cases or as part of a Carney Complex [2].

Carney Complex is an autosomal dominant disease characterized by the presence of pigmented skin and mucosal lesions, multiple endocrine neoplasia (PPNAD, adenoma/thyroid tumors, pituitary adenomas) as well as other non-endocrine tumors (cardiac myxoma, osteochondromyxoma) [7]. For its diagnosis, criteria are exposed in table 2 [8]. Mutations in the gene PRKAR1A, which codes for the regulatory type 1A (R1A) subunit of the protein kinase A (PKA) enzyme are responsible for most of the cases, including isolated PPNAD [9]. Other genetic studies that must be performed in similar cases include the following genes: PDE11A (2q31.2) and PDE8B (5q13.3) in cases of non-pigmented adrenal micronodular disease, MYH8 (Carney Complex variant without adrenal disease), B-catenin and PRKACA.

Table 2: Diagnostic criteria for Carney Complex [8]. Reproduced from: Almeida MQ, Stratakis CA (2010). Carney complex and other conditions associated with micronodular adrenal hyperplasias. Best Pract Res Clin Endocrinol Metab. 24:907.

Major diagnostic criteria (with histological confirmation for *)
1. Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa).
2. Myxoma (cutaneous and mucosal)*.
3. Cardiac myxoma*.
4. Breast mixomatosis* or fat-suppressed MRI findings suggestive of this diagnosis.
5. PPNAD* or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test.
6. Acromegaly due to GH-producing adenoma*.
7. LCCSCT* or characteristic calcification on testicular ultrasonography.
8. Thyroid carcinoma* or multiple, hypoechoic nodules on thyroid ultrasonography in a young patient.
9. Psammomatous melanotic schwannoma*.
10. Blue nevus, epithelioid blue nevus (multiple)*.
11. Breast ductal adenoma (multiple)*.
12. Osteochondromyxoma*.
Supplemental criteria
1. Affected first-degree relative.
2. Inactivating mutation of the PRKAR1A gene.

For a biochemical demonstration of PPNAD, hypercortisolism must be proven in at least 3 different 24-hour urinary cortisol samples (as the main test for screening), night blood cortisol or salivary cortisol. Once hypercortisolism is demonstrated, it must be proven whether it is ACTH-dependent or independent, and request the appropriate radiology studies. In our case report, absence of dexamethasone suppression and basal hormonal studies made initial diagnosis to seem compatible with ACTH-independent CS. Finally, a CRH test confirmed ACTH- independence and the classical Liddle test revealed a paradoxical increase in cortisoluria, typical of this disease. This paradoxical rise is explained as dexamethasone stimulates paradoxically cortisol secretion in the micronodules throughout an effect in the catalytic PKA subunits of the glucocorticoid receptor [10].

Given the micronodular affectation, it is usual that appearance of the adrenal glands in TC/RM is interpreted as normal. For this reason, it is important to maintain a high index of suspicion [11].

The treatment of this disease is bilateral adrenalectomy. In some cases, unilateral adrenalectomy was performed, although finally a second surgery was required to remove the contralateral gland. Pharmacological treatment (ketoconazol, metirapone) may be used as pre- surgery treatment, but it does not cure the disease [2, 4, 12].

Yearly evaluation including echocardiography, thyroid, and testicular echography must be performed to evaluate the presence of a Carney Complex [2].

Conclusions

In conclusion, although PPNAD is a rare cause of CS, it must be considered in the differential diagnosis of ACTH-independent CS, especially in a pediatric patient with normal adrenal imaging. After initiation of treatment, clinical outcomes are usually favorable, although it is important to maintain treatment and periodic evaluations over time in order to rule out the possibility of a Carney Complex.

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