Specially interesting clinical case
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Hypercortisolism and hyperandrogenism as manifestations of adrenal adenoma. Report on a Mexican girl and review of the literature

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ABSTRACT

Background: Adrenal cortex tumors (ACT) are extremely rare in children and adolescents. Only 0.2% of all the new cases of cancer diagnosed in the United Stated and Europe are adrenal cortex tumors. The international incidence is not well defined, since it differs demographically. Due to the rarity of these tumors in children, little is known about their natural history.

Case report: 11 months old female patient who developed, at the age of nine months, acne in forehead and thorax, also, weight gain, facial hair, apocrine activity, appearance of pubic hair, and hirsutism, increase of appetite, altered sleep-vigil cycle, increased height with accelerated growth velocity. From a biochemical standpoint, alterations in cortisol, showed an increase in morning and evening cortisol levels, as well as androgens. CT scan showed an adrenal mass on the right side not dependent of the kidney, which was completely resected. The histopathology report was of adenoma of the adrenal cortex. Currently, the patient is asymptomatic and is followed at the Endocrinology Service with dose reduction of steroid.

Conclusion: Because adrenal cortex tumors are extremely rare in children, a small percentage appears with virilization data and Cushing's syndrome. For this reason, we should be aware of their existence in order to make the diagnosis and treat them as soon as possible.

Keywords: Tumor, adrenal cortex, hirsutism, cortisol, androgens, virilization.

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Adrenal cortex tumors (ACT) are extremely rare in children and adolescents. A majority of children who develop them are almost always healthy and with normal development. Such tumors account for 3 to 6% of all carcinomas and it is assumed that one third of them are adenomas. In the United States it is estimated that each year there are 25 to 30 cases in individuals under 20 years; the incidence increases with age.[1]

The incidence of adrenal cortex tumors is highly variable. In Denmark 0.2 cases per million are reported and in Brazil 3.4 to 4.2 cases per million children under 15.[2] Approximately 95% of patients have virilization; of those, almost half suffer from hypercortisolism.[2]

CLINICAL CASE

Girl 11 months of age, who was taken to Hospital Infantil de Tlaxcala on referral from a rural healthcare center to receive specialized care due to clinical signs of virilization of external genitalia.

Her in utero evolution was normal and she was born from the mother's second pregnancy; she presented marginal placenta previa, and therefore was delivered by Cesarean section, without complications. Weight 3.200 kg, height 52 cm. Apgar score unknown. Immediate neonate normal.

Personal non-pathological, pathological, and nutritional antecedents were not considered relevant.

The present disorder first appeared at 9 months, with acne on the forehead and chest, weight gain and generalized increase of facial hair, apocrine gland activity, appearance of pubic hair and hirsutism; increased appetite manifested by irritability. Patient was taken to her community's healthcare center. Abdominal ultrasound showed a right adrenal nodular mass, for which she was referred to Hospital Infantil de Tlaxcala. The initial assessment performed there found somatometry and vital signs within normal parameters; full moon face, generalized increase of facial hair, hirsutism on the back and limbs, hyperpigmentation of genitals, with a 1 cm phallus; the rest of the examination found no alterations (Figure 1).

Based on the clinical findings reported by physicians of the endocrinology service, quantifications were made of concentrations of: cortisol, ACTH, and androgens due to suspected diagnosis of Cushing's syndrome or Cushing's disease (Table 1). Data compatible with non-ACTH dependent hypercortisolism, hyperandrogenism, and Cushing's syndrome. In view of these findings image studies were requested, which revealed an adrenal mass on the right side, not dependent on the kidney, without calcifications (Figure 2). Physicians at the Oncological Sur-

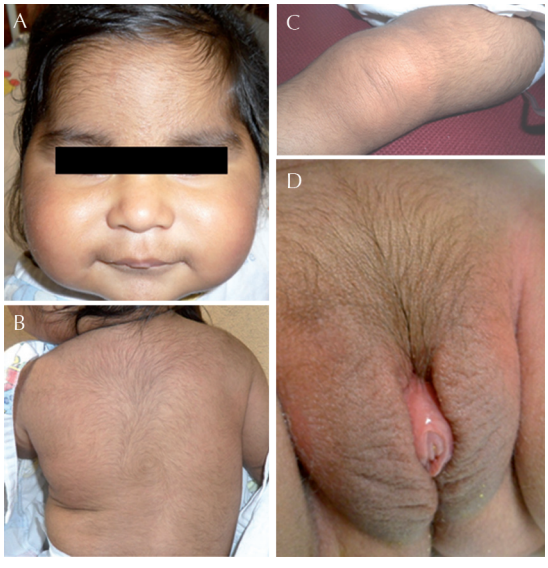


Figure 1. A) Full moon face, B y C) Hirsutism. D) 1 cm phallus.

Table 1. Hormonal profile

Hormonal profile	Presurgical	Postsurgical	Follow up. 1	Follow up. 2	Follow up. 3
17-Alpha hydroxyprogesterone	2.35 ng/mL				
Morning plasma cortisol	31.2 µg/dL		1.19 µg/dL	10.70 µg/dL	10.30 µg/dL
ACTH	5.0 pg/mL		21.60 pg/mL	33.60 pg/mL	14.40 pg/mL
Total testosterone	1840 ng/dL	7.18 ng/dL*	4.9 ng/dL**		
Androstenedione	17.2 ng/dL		0.30 ng/dL		
Dehydroepiandrostenedione sulphate	1021 µg/dL		15.0 µg/dL		

*Substantial reduction following the surgical event.
**Low levels were maintained in follow up.

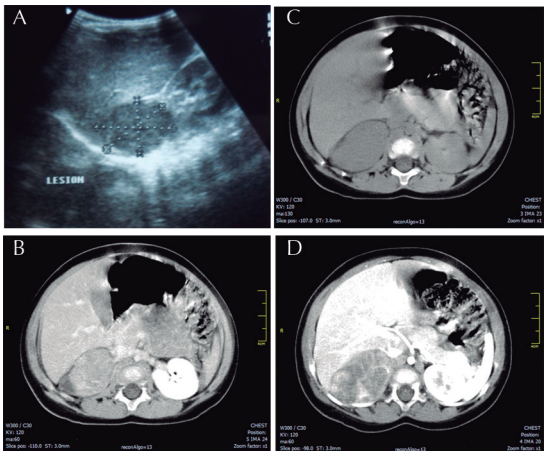


Figure 2. A) Ultrasound: adrenal nodular lesion located on the upper pole of the right kidney, measuring 41 × 29 × 38 mm B, C, and D) CAT: adrenal mass on the right side dependent on the kidney without calcifications.

gery service performed adrenalectomy without complications.

The patient was given hydrocortisone thirty minutes before surgery and halfway through the procedure, and afterwards maintenance doses. During her internment she maintained hemodynamic stability and electrolyte balance. On the third day after surgery, measurement of androgens (Table 1) showed substantial reduction, as did serum electrolytes in view of the risk of imbalance due to aldosterone deficit.

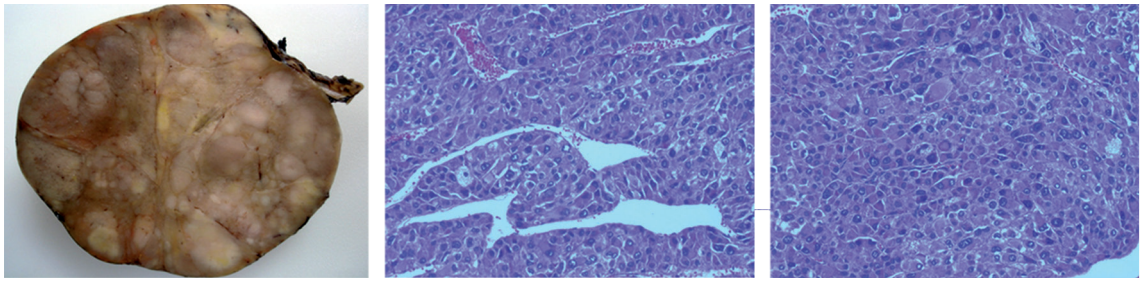
The pathology report was: adenoma of right adrenal cortex (Figure 3). The patient returned home five days after the operation with glucocorticoid reduction regimen; she was monitored by outpatient services. Three months after surgery, the patient's evolution was favorable with improvement of clinical signs and hormonal profile (Table 1).

ANALYSIS

Tumors of the adrenal cortex can appear at any age; however, they are more common in adults and extremely rare in children.[3-6] In the United States, the incidence in persons under 25 years of age is 14 to 20 cases per year.[3,7] Cases have even been reported in newborns, which suggests the existence of congenital tumors.[8] Our patient can be considered in the latter category, due to the early age of onset.

Most tumors of the adrenal cortex which appear in patients of pediatric age are functional and 80 to 90% have endocrine manifestations at the time of diagnosis; the most common clinical manifestation is virilization, and 94% present hormonal hypersecretion; such findings also coexisted in our patient.[7]

Tumors of the adrenal cortex are divided in adenomas and carcinomas; both secrete hormones or may be hormonally inactive. The



Macro: Nodular tumor measuring 6 × 5 × 4 cm and weighing 53.7 g. With light brown, lobulated surface; section shows encapsulation, dependent on adrenal cortex, with light brown and light yellow multinodular surface, with no hemorrhage or necrosis and of a rubbery consistency.

Micro: (H-E) encapsulated neoplasm, formed by cords, trabeculae, and nests of cells with abundant eosinophilic cytoplasm, large nuclei with pseudoinclusions, cells with light vacuolated cytoplasm, round nuclei and open chromatin. These nests are separated by slender and sinusoid fibrovascular septums. There is non-confluent necrosis and 5 mitoses in 50 high-dry fields; there is no capsular or vascular invasion.

Figure 3. Macro and microscopic description.

hormones secreted include: cortisol, aldosterone, androgens, estrogens, and intermediaries of steroid biosynthesis. Adenomas are more efficient in producing steroidal hormones than carcinomas.[8,9] This coincides with our patient, who, at diagnosis, had extremely high testosterone levels for her age and gender. Despite the production of hormones, adenomas are often benign, whereas carcinomas present malignant behavior.

In any boy or girl with signs of extemporaneous heterosexual or isosexual virilization or feminization this pathology should be suspected and appropriate laboratory and examining room studies performed promptly for early and timely detection, in addition to assiduous physical examination to look for any abdominal mass, which may be found even in 50% of patients at the time of diagnosis to prevent delay, which may be up to 10 months with limits from 3 days to 61 months between the first clinical manifestation and the definitive diagnosis.[1,7] In our patient, the diagnosis was established two months after the onset of virilization, which was the first clinical manifestation.

Laboratory evaluation in patients with suspected tumors of the adrenal cortex should include, according to Ribero,[1] the studies indicated in Table 1. This hormonal group not only contributes to the diagnosis, it is also helpful in detecting recurrences.

Magnetic resonance, computed tomography (CAT), and ultrasound are used to confirm a tumor and its staging, to plan surgical treatment, and to view the invasion of adjacent structures.[4,8]

Tumors of the adrenal cortex originate in any of the three layers that cover the adrenal cortex, and therefore are considered epithelial tumors and histologically it is difficult to differentiate by light microscopy between adrenal adenoma and carcinoma; for that reason immunohistochemical reaction methods, such as vimentin and cytokeratin, have been used. In this regard, Wick et al.[10] studied 30 patients and found no significant differences between immunostaining profiles for adrenocortical carcinoma versus adenoma. They concluded that such a distinction should be based on clinical and morphological criteria.

Table 2. Histological criteria for diagnosis of adrenocortical neoplasms in children (modified from the criteria of Weiss et al.) [1,11]

Diagnosis	Mitotic index*	Necrosis	Atypical mitoses	Nuclear grade**
ACA	0-5	Absent	Absent	1-2
Low grade ACC	6-20	Present	Present	3
High grade ACC	>20	-	-	-

* Mitotic figures per 50 high power fields .
**Grade 1: mild pleomorphism. Grade 2: moderate pleomorphism. Grade 3: severe pleomorphism.
ACA = adrenocortical adenoma.
ACC = adrenocortical carcinoma.

For their part, Weiss and Hough[11] (Table 2) formulated a classification system based on the clinical, microscopic, and macroscopic characteristics coexisting at the time of diagnosis in adults. Consequently, and because both clinical manifestations and biological behavior are different in children, Weineke et al.[12] studied 83 children with tumors of the adrenal cortex to determine whether the clinical and histological characteristics proposed by the first authors could be applied to pediatric patients. They found that the characteristics with the highest probability of corresponding with a tumor with malignant histology were: weight over 400 grams, diameter greater than 10.5 cm, capsular or vascular invasion, spreading to periadrenal tissues, severe cellular atypia with more than 15 mitoses per 20 high power fields, and confluent necrosis.[3,12] In our patient immunostaining techniques were not used and morphologically the tumor measured 6 × 5 × 4 cm; weight 53.7 grams; there was no vascular invasion or spreading to extension adjacent tissues, nor did histological analysis find nuclear atypia and mitoses were less than 15 per 20 high power fields. All this, added to the natural history following surgical exeresis, indicates that it was an adenoma.

CONCLUSION

Tumors of the adrenal cortex are extremely rare in children; a high percentage manifest with signs of virilization. In order to establish a diagnosis and offer opportune treatment, we must be alert and perform appropriate studies.

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