Congenital Adrenal Hyperplasia due to 11-Beta-hydroxylase Deficiency

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The objective of this article is to relate the diagnostic and clinical evolution of a 15 year old patient with a congenital adrenal steroidogenesis dysfunction that can present as hypertension diagnosed later in life (adolescence), virilization or salt wasting (birth and childhood).

Congenital Adrenal Hyperplasia, due to the inability to synthesize cortisol, frequently presents clinically by signs of androgen overproduction (masculinization of the female external genitalia). Some patients also develop signs and symptoms due to aldosterone deficiency such as hyponatremia, hyperkalemia and hypovolemia, that if left untreated lead to shock and death after a few weeks of life. However, it was only after the 1950's that it was recognized that a small percentage of these patients develop hypertension that responds to glucocorticoid therapy. This subpopulation were affected by a distinct metabolic disorder, the 11-ß hydroxylase deficiency; while patients without hypertension presented the well known deficiency of 21-hydroxylase.

Case Report

A fifteen year old male mulatto adolescent was admitted to the Goiânia Urgent Care Hospital (GOUH) emergency ward due to a sudden severe parietal headache attack, vertigo, and ptosis of the eyelid and an asymmetrical smile both on the left side of the face. A hypertensive peak was recorded (blood pressure 250 over 160 mmHg in upper right limb with the patient supine). A computerized axial tomography (CAT scan) of the cranium was performed which showed intraparenchymal and left periventricular hemorrhaging but no surrounding mass effect was reported (fig. 1).

After the administration of symptomatic medication, he was transferred to the intensive care unit of the São Bernardo Hospital (Aparecida de Goiânia/GO). His past medical history given by his father described normal childhood development up to age three when he began to present gynecomasty, precocious puberty and early development of axillary hair as well as acne at age six.

Admission medical exam: acyanotic, eupneic, flushed, hydrated, no fever. Acne on the upper torso (fig. 2), near arms and face (fig. 3). When admitted to the intensive care unit, his blood pressure was 190 over 125 mmHg (controlled by oral nifedipine treatment) and a heart rate of 77 beats per minute. Thyroid impalpable. Heartbeat displaced to the left, palpable in the left 7th intercostal space, located near the axilla anterior wall. Normal heart rhythm, in two beats, with hyperresonant sounds, no murmurs or extra-systole. Respiratory system normal. No visceromegalies or bruits detected in the abdominal region. No edema in the lower limbs. Discrete dysarthria, ptosis of the eyelids and asymmetrical smile (both on the left side of the face). Normal muscle tone and strength. Superficial and deep tendon reflexes normal. Isochorich pupils, reacting to light. Height: 1.85 m Weight: 61.7 kg. BMI: 18.02. Arm span: 1.83 m. Crotch Height: 94 cm. Puberty Stage: pubic hair (Tanner Stage 5), genitalia (Tanner Stage 5).

Admission laboratory tests - Hct = 39.8%; RBC = 4.35tera/l; Hgb = 14g/dl; MCV = 91fl, MCH = 32.18pg; MCHC = 35.18g/dl; RDW = 14%. WBC: 6500; MY/ME/BA/SEG 0/0/1/62; BAS/EOS/LYMP/MON 0/5/26/6; U = 60; Cr = 1.3; Na^{+} = 136; K^{+} = 3.0; Ca^{++} = 10.6; Mg^{++} = 2.4; GOT = 31; GPT = 27; PT = 12.5s; Factor II = 100%; Cholesterol = 148; HDL = 38; LDL = 96; VLDL = 13.2; Routine urine test: uric acid crystals +++; 24-hour urine creatine clearance: 49 ml/min/1.73m^2; 24-hour urine protein test: 442 mg; EKG: Sinus rhythm, strain on left ventricle; Chest x-ray: cardiomegaly.

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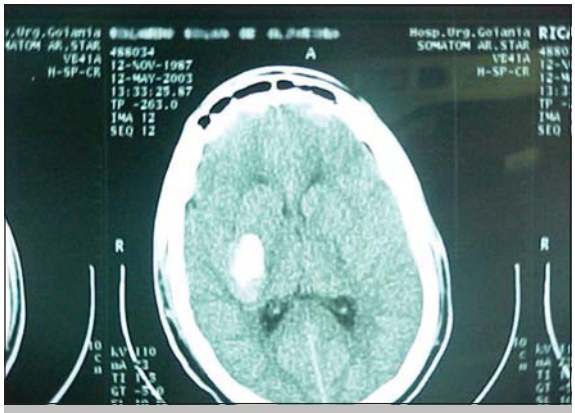

Fig. 1 *- CT of the cranium showing periventricular intraparenchymal hemorrhaging at the left*

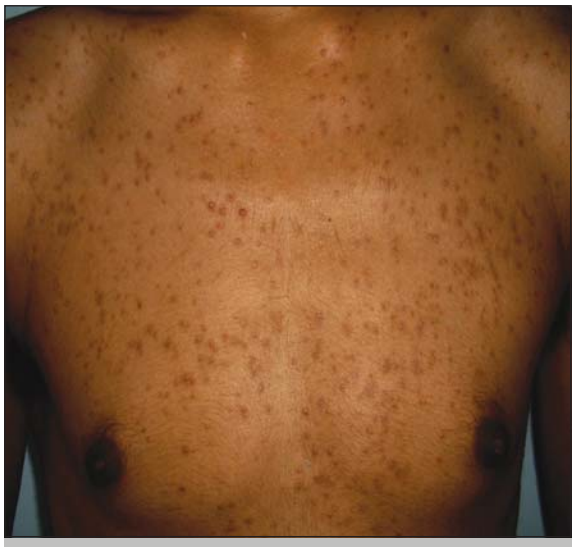

Fig. 2 *- Acne on the upper torso region*

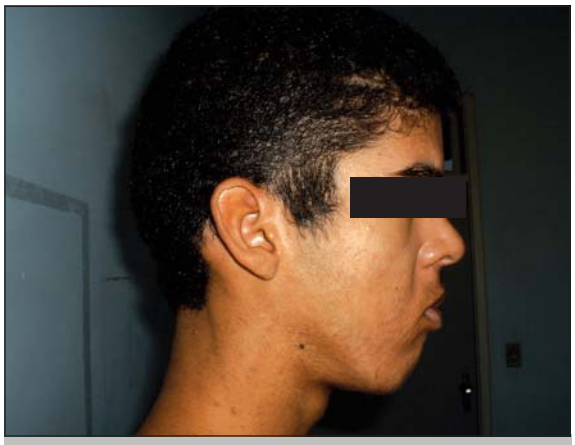

Fig. 3 *- Patient at admission: facial acne*

Clinical progression: Admitted to the intensive care unit for ten days. Intravenous nitroprusside and oral hypertension medications were administered during most of the stay. The following tests were requested: ACTH: 498 (N < 60 pg/ml); 11-deoxycortisol: 41 (N: 0 to 0.8 ng/ml); Androstenedione: 28 (N: 0.4 to 2 ng/ml); Total testosterone: 789 (N: 241 to 827 ng/dl); Free testosterone: 22 (N: 0.3 to 21 pg/ml); 17-OH progesterone: 109 (N: 50 to 300 ng/dl); DHEA-S: 421 (N: 4 to 68 mg/dl); 8H Cortisol: 3.5 (N: 4.3 to 25 mg/dl).

The test results confirmed the diagnosis of congenital adrenal hyperplasia due to 11-β-hydroxylase deficiency. Two oral antihypertensive medications (nifedipine and enalapril) as well as a 0.5 mg daily oral dosage of dexamethasone, physiotherapy to improve motor skills and a low sodium diet were prescribed.

The patient responded to the treatment with a total recuperation of the neurological symptoms (without any apparent relapses), the acne healed and blood pressure levels were maintained within a reasonable range. The patient was discharged fourteen days after the initial episode.

Discussion

This case demonstrated lesions of target organs, both acute (vascular hemorrhage disorder) and chronic (class III chronic renal insufficiency) due to elevated blood pressure levels indicating a secondary cause.

Hypertension should be treated as a secondary cause in the following situations[1]: Onset < 30 or > 50 years; Hypertension: severe or resistant to therapy; Pheochromocytoma triad; Abdominal masses or bruits; Asymmetric femoral pulses; Elevated creatine serum levels; Prescription drugs; Spontaneous hypokalemia (K^+<3.0 mEq/l); Abnormal urine sediment elements (hematuria or proteinuria); Facies (acromegaly, Cushing , hyperthyroidism).

The clinical signs that suggested hormonal imbalance as the basis of the entire process were the early appearance of acne and precocious puberty as well as gynecomasty indicating an overproduction of androgen that is associated with high blood pressure and hypokalemia (indicating an excessive circulation of mineralocorticoids).

Biochemistry of adrenal steroid biosynthesis - Cortisol is a hormone that is synthesized from cholesterol in the zona fasciculata of the adrenal cortex. This process requires five enzyme conversions (fig. 4). During the conversion of 11-deoxycortisol to cortisol a subtype of the enzyme 11-β-hydroxylase is involved. This enzyme has two isoforms: CYP11B1 and CYP11B2. These isoenzymes are mitochondrial P450 cytochrome enzymes which are located on the inner face of the membrane and the isoenzyme CYP11B1 is responsible for this process[2].

11-β-hydroxylase deficiency - Congenital adrenal hyperplasia is caused by a defect in the cortisol synthesis process. Generally speaking, patients with this deficiency present signs of androgen overproduction such as virilization of the external genitalia in females or early puberty in males.

The first cases of this isoenzyme deficiency were reported in the 1950's[3,4]. The 11-β-hydroxylase deficiency

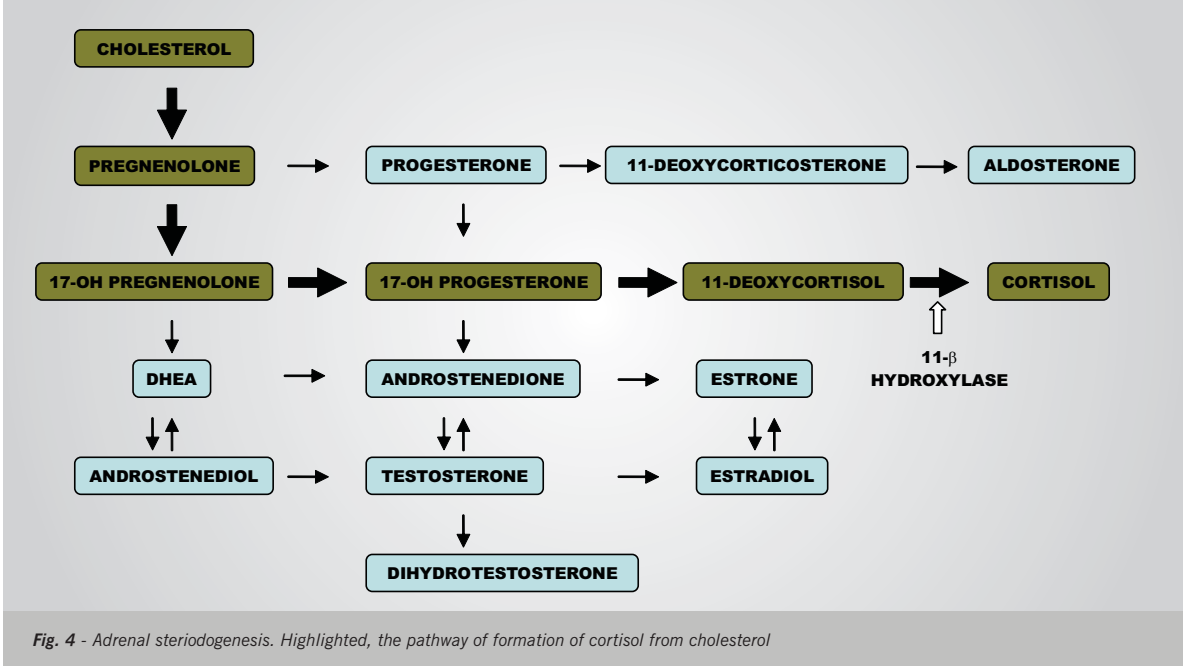

Fig. 4 *- Adrenal steriodogenesis. Highlighted, the pathway of formation of cortisol from cholesterol*

accounts for 5%-8% of the causes of congenital adrenal hyperplasia, with a prevalence of approximately one case in every one hundred thousand live births[5].

There are certain uncommon defects in the steroidogenesis that results in an exaggerated synthesis of adrenal enzyme precursors, particularly 11-deoxycortisol, inducing hypertension caused by mineralocorticoids. The reduced production of glucocorticoids results in an ineffective negative feedback to the hypothalamus and anterior pituitary gland, leading to an increased secretion of ACTH. This overstimulates the adrenal cortex and produces an excess of proximal cortisol precursors. These precursors have mineralocorticoid activity leading to high blood pressure among other abnormalities.

Laboratory diagnosis - The specific diagnosis of 11-β-hydroxylase deficiency can be determined using the high basal levels of deoxycorticosterone and/or 11-deoxycortisol serums or by the increased excretion of the tetra-hydrometabolites found in these compounds during a 24-hour urine test. This diagnosis should be suspected in patients with ACTH serum levels that are three or more times higher than the 95th percentile predicted for the patient's age. Even though the majority present elevated levels of all of these hormones, a small portion could present a selective elevation of just one hormone.

Clinical presentation - Hypertension: Approximately two thirds of the patients diagnosed with 11-β-hydroxylase deficiency have hypertension[6], which is generally detected during the first few years of life. Even though blood pressure is only slightly to moderately elevated in the majority of cases, left ventricular hypertrophy and/or hypertensive retinopathy has been detected in one third of the patients as well as death caused by stroke. Other signs of excessive mineralocorticoids such as hypokalemia or muscle weakness are seen in a minority of patients and are not correlated to blood pressure levels. The cause of hypertension is not clear. It could possibly be due to an excess of deoxycorticosterone serum[5].

Salt loss - Even though hypertension is the classic sign of 11-β-hydroxylase deficiency, occasionally during childhood some patients can develop signs of mineralocorticoid deficiency such as hypokalemia, hyponatremia and hypovolemia. The explanation in some cases is glucocorticoid therapy. In other cases this mineralocorticoid deficiency appears before treatment due to mechanisms that are still in the discovery stages and are attributed to the loss of peripheral sensitivity to these metabolites[5].

Virilization - New-born females with 11-β-hydroxylase deficiency present some degree of virilization at birth. This process starts from the sixth week of gestation. Clitoromegaly can be so severe that it may be mistaken for a penis[6-8]. The urinary meatus and genital opening are displaced to the front and can blend into the urogenital sinus. In extreme cases the labia may be fused presenting no differences from a masculine scrotum.

Unlike the external genitalia, gonads and internal structures (ovarian tubes, uterus and cervix) that are derivatives of the Mullerian ducts are preserved since the substance that normally causes the involution of these structures in men (mullerian inhibiting factor) is not produced by the fetal ovary.

Other signs of androgen overproduction include rapid somatic growth during childhood and early closing of the skeleton epiphysis (short stature). This was not noted in the related patient due to the tall stature of his parents. There could be amenorrhea or low spermatogenesis due to the dysfunction of the hypothalamic-pituitary-gonadal axis as well as hirsutism and acne.

Treatment - Glucocorticoid therapy - Glucocorticoid administration restores the cortisol deficit and reduces the secretion of ACTH. This therapy should be evaluated by monitoring the growth curve, bone age advancement, adrenarche and measurements of cortisol androgen precursors such as 4-androstenedione. Oral hydrocortisone is the preferred therapy during childhood. If the epiphysis closing is complete, the therapeutic treatment could be changed to prednisone or dexamethasone.

Hypertension Therapy - Spironolactone or amiloride can be used to correct hypokalemia and treat slight hypertension (not present in this case). If these agents do not prove to be sufficient or they are not available calcium channel blockers such as nifedipine or verapamil can be used[9].

A prenatal diagnosis can be made by injecting a dose of 11-deoxycortisol into the amniotic fluid[10]. Ambiguous genitalia can be corrected with surgery.

References

1. Sociedade Brasileira de Hipertensão, Sociedade Brasileira de Cardiologia, Sociedade Brasileira de Nefrologia - Investigação clínico-laboratorial & Decisão terapêutica – IV Diretrizes Brasileiras de Hipertensão Arterial, 2002, 1:8.
2. Yanagibashi K, Haniu M, Shively JE, Shen WH, Hall P. The synthesis of aldosterone by the adrenal cortex. J Biol Chem 1986; 261:3556-62.
3. Shepard TH, Clausen SW. Case of adrenogenital syndrome with hypertension treated with cortisone. Pediatrics 1951; 8:805-13.
4. Wilkins L, Gardner LI, Crigler JF. Further studies on the treatment of congenital adrenal hyperplasia with cortisone. J Clin Endocrinol Metab 1952; 12:1015-30.
5. Zachmann M, Tassinari D, Prader A. Clinical and biochemical variability of congenital adrenal hyperplasia due to 11 betahydroxylase deficiency. A study of 25 patients. J Clin Endocrinol Metab 1983; 561:222-9.
6. Rosler A, Leiberman E, Sack J et al. Clinical variabilitv of congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency. Horm Res 1982; Ib:133-41.
7. Harinarayan CV, Ammini AC, Karmarkar MG et al. Congenital adrenal hyperplasia and complete masculinization masquerading as sexual precocity and cryptorchidism. Indian Pediatr 1992; 29:103-6.
8. Bistritzer T, Sack J, Eshkol A, Zur H, Katznelson D. Sex reassignment in a girl with 11-beta-hydroxylase deficiency. Isr J Med Sci 1984; 20:55-8.
9. Marg A, Kuban RJ, Behlke J, Dettmer R, Ruckpaul K. Crystallization and X-ray examination of bovine adrenodoxin. J Mol Biol 1992; 227:945-7.
10. Rosler A, Weshler N, Leiberman E et al. 11-Beta-hydroxylase deficiency congenital adrenal hyperplasia: update of prenatal diagnosis. J Clin Endocrinol Metab 1988; 66:830-8.