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CASE REPORT

Congenital adrenal hyperplasia in siblings - case report

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Abstract

We report two cases, siblings, diagnosed with congenital adrenal hyperplasia due to 21-hydroxylase deficiency in the simple classic virilizing form. The female patient had her research started early after birth because of ambiguous genitalia, while the older sibling had her diagnosis delayed, since her clinical manifestations were noticed at around the age of 4. Patients were diagnosed with hormonal dosages and molecular analysis was performed, followed by treatment. This, a challenge, since patients required adjustment of glucocorticoid dose and mineralocorticoid association. In addition to the description of the cases, we present what is discussed in the literature about the disease, its classifications, clinical presentations, therapeutic options and follow-up.

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INTRODUCTION

The endocrine system has several components, among them adrenal glands, also called suprarenal glands, which have this nomenclature due to their anatomical location, above the upper pole of the kidney. Each gland has an approximate weight of 4g and it is made up of two parts, one medullar, responsible for the production of epinephrine and norepinephrine, and a cortical one, responsible for the production of steroids derived from cholesterol that depend on the proper functioning of enzymatic pathways, to guarantee the hormonal biosynthesis.[1]

Defects in these enzymatic pathways that block the cortisol synthesis, end up suspending the negative feedback responsible for the control of pituitary adrenocorticotrophic hormone (ACTH) production, resulting in increased levels of it. This increase of ACTH generates a chronic stimulus to the adrenals, provoking its hyperplasia.[2]

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease in which 95% of the cases result from mutation in the CYP21A2 gene, which encodes the 21-hydroxylase enzyme, affecting 1: 7,500 to 1: 10,000 live births[3].

There may be several degrees of enzymatic activity affected, the presentation of the signs and symptoms becomes variable, and the CAH can be divided into classic forms, with the salt-losing subtypes (HACPS) and simple virilizing (HACVS) not classical.[3,4]

HACPS is the most severe form, where aldosterone and cortisol deficiency occurs, as well as disordered and excessive production of androgens, resulting in virilization of female fetuses. The loss of salt crisis is characterized by dehydration, weight loss, hyponatremia, hyperkalemia and acidosis in the second week of life.[5]

The virilization of the female fetus occurs by androgenic action during the period of 7 to 12 weeks of gestation, causing ambiguous genitalia. Newborn males have normal genitalia, which usually ends up delaying the diagnosis and increasing the mortality rate due to loss of salt. These children present virilization even in the first years of life.

Individuals with a diagnosis of non-classical CAH do not present virilization at birth and remain without apparent clinical manifestations until the end of pre-school, adolescence or even adulthood. Possible manifestations include premature pubarche, hirsutism, acne, menstrual irregularity and infertility.[5]

The genital ambiguity of the female neonate may range from clitoromegaly to fully virilized genitalia, indistinguishable from males except for non-palpation of the gonads. This degree of virilization can be classified through the Prader scale (figure 1)[2,6].

An important form of early CAH diagnosis is through the neonatal screening test. The inclusion of CAH screening in the so-called foot test which occurred in phase IV of its implantation in Brazil in 2014, extending to the whole national territory and aiming at the early detection of the affected individuals, which is fundamental for the prevention of loss-of-salt crisis, since this is a cause of death and even for the correct designation of sex in children born with ambiguous genitalia.[3]

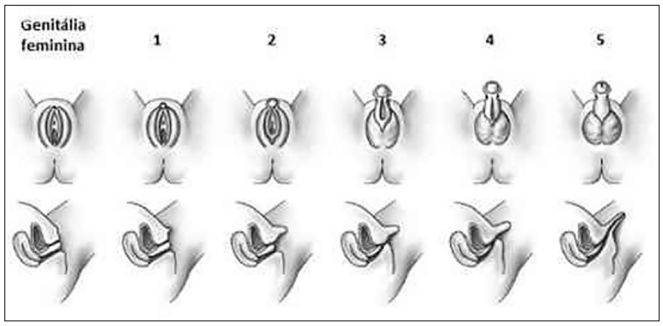


Figure 1. Female genitalia. Prader scale, female genitalia viewed from above (upper row) and cross section (lower row according to Turcu, 2015).

CASE REPORT

Patient 1, still without a civil registry, 27 days old, from RJ, born vaginally, at term, suitable for gestational age, referred to endocrinology for diagnosis of ambiguous genitalia. Mother attended the consultation without the exams collected at the maternity hospital and during follow-up the child was recalled to collect a new sample of neonatal screening test for alteration as a result of 17-hydroxyprogesterone (17OHP). On physical examination, the patient had ambivalent grade IV genitalia on the Prader scale, with no palpable gonads and no other changes. Family history reported a four-year-old brother with "very large penis for age". Result of karyotype collected on 07/07/17 46 XX, making possible a civil registry in the female sex at two months of age. Female genitalia surgery to be scheduled and the patient was followed up by pediatric endocrinology.

Patient # 2, G.S.O., male, four years old, born in RJ. Seen in an outpatient pediatric endocrinology outpatient clinic for "large penis" complaint, according to those responsible. He was born vaginally, at term, with adequate weight for gestational age, without problems. Neonatal screening test without changes, but it was always noted that the patient's penis was larger than expected for age and, with the younger sister's suspected diagnosis, was referred to specialist. No history of other diseases. The physical examination had a Tanner G3P2 classification, testicles with a volume of 1mL and a penile length of 9cm; a value above the 90th percentile for age.[7] During follow-up, the patient was identified as an eight-year old through bone age.

Blood samples were collected for hormonal dosages of both patients as shown in Table 1. In addition, samples were collected for molecular analysis that diagnosed CAH due to 21-hydroxylase deficiency in the simple virilizing form due to mutation in pI172N and IVS-13A/G, with composite heterozygosity. Image exams such as pelvic and abdominal ultrasonography had normal results in patients.

Table 1. Exams collected for diagnosis collected when patient # 1 was one month and patient # 2 was four years old.

	17OHP[1]	Testosterone	Androstenedione
Patient n° 1	12660 ng/dL	44ng/dL	> 5.5 ng/mL
Patient n° 2	9957 ng/dL	74.8 ng/dL	9.8 ng/mL

[1] 17-hydroxyprogesterone.

The patients were treated with prednisolone at a dose of 2.5mg/m²/day, orally, adjusted as needed. Fludrocortisone 0.1 mg/day was associated with increased plasma renin activity. Current photographs of sibling genitals can be seen in Figure 2.



Figure 2. A and B-Patient # 1, one year and 10 months old; C- Patient # 2, five years and eleven months old.

DISCUSSION

The reported patients portray a constant example in the literature, where the diagnosis of girls with CAH is precocious when compared to that of boys, since the virilization already detected in the delivery room triggers diagnostic investigation, whereas with males, the earliest manifestation is the salt loss crisis in those who have HACPS. In the case of patient # 2, the late diagnosis despite the neonatal screening test was probably due to the fact that this type of screening was developed for the detection of severe cases, such as HACPS, taking into account higher cutoff levels for 17-OHP as diagnostic reference.

When the diagnosis is confirmed, treatment should be initiated immediately, consisting of glucocorticoid replacement in all patients with the classic form, with hydrocortisone in doses of 10 to 15mg/m²/day, fractionated in three doses orally. Patients diagnosed with HACPS with clinical manifestations or high plasma renin activity, as was the case in the patients reported, should also initiate mineralocorticoid replacement, in the form of fludrocortisone acetate, at the dose of 0.05 to 0.2 mg/day. In the unavailability of hydrocortisone, one can use prednisolone, in the dose of 2 to 4mg/m²/day. The use of fludrocortisone is also indicated in patients with non-classical form with high plasma renin activity, explained by a possible subclinical aldosterone deficiency. Replacement of glucocorticoid with dexamethasone should be avoided during childhood and adolescence, because it has a very long half-life, with consequent Cushing's syndrome.[8]

It is recommended to provide the patient with an identification of their condition, such as a card or bracelet, containing a dose of stress in the case of surgery or in febrile conditions, where the glucocorticoid dose should be increased two to three fold until resolution of the condition. During follow-up, several aspects, such as growth and development, the possibility of the onset of Cushing's syndrome iatrogenic, blood pressure levels, bone age, plasma renin activity, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, periodic assessment of bone mineral density.[8]

In the case of the patients in question, the early diagnosis of patient # 2 would have made it possible to begin treatment at an earlier and timelier fashion, preventing the progress of physical maturation, reflected in the advancement of bone age. This early physical maturation can result in short stature in adulthood. It would also have made her sibling's prenatal treatment possible, minimizing virilization. This treatment consists of the administration of dexamethasone at a dose of 20 µg/kg/day orally in pregnant women whose first child from the same partner has been diagnosed with CAH and should be started as soon as the pregnancy is diagnosed. This prenatal approach; however, has been controversial. Some authors claim risk for pregnancy, and memory impairment and school difficulties are reported in children undergoing treatment.[1,9,10]

During the follow-up of female patients, the feminizing surgery of the genitalia is indicated, aiming at aesthetic and functional correction. This consists of clitoroplasty and vaginoplasty in patients with a Prader stage greater than or equal to three, as in patient 1; however, more and more has been discussed about the age most suitable for performing these procedures, since there is no consensus regarding the benefit of early intervention. Each case must be individualized and studied according to its clinical manifestation and the family must have an active participation in the decision regarding the most opportune moment for the surgical intervention, always considering psychosocial aspects.[2,6]

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