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CONGENITAL ADRENAL HYPERPLASIA WITH ABNORMAL GENITALIA DUE TO 21-HYDROXYLASE DEFECTS

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Abstract

Congenital adrenal hyperplasia is one of common causes of genital ambiguity in female fetus, which becomes evident after birth. Congenital enzymatic deficiency specific to concrete synthetic process of steroidogenesis in congenital adrenal hyperplasia leads to cortisol and aldosterone insufficiency and excess of androgens during intrauterine period of genital development, as well as to bilateral hyperplasia of adrenal cortex. There are two forms of congenital adrenal hyperplasia due to 21-hydroxilaze deficiency: classic (salt-losing and simple virilizing) and non-classic. Classic salt-losing forms manifest with the features of cortisol and/or aldosterone deficiency in neonatal period, and simple virilizing form – only with virilization of external genitalia.

Herein a report of a case a girl with congenital adrenal hyperplasia with male external genitalia due to 21-hydroxylase deficiency is presented. It's a rare case of classic salt-losing form of CAH, the peculiarities of which is, that virilizing features were predominance against the clinical signs of cortisol and aldosterone insufficiency. The patient underwent surgical correction of external genitalia (vagino-urethro-clitoro-labioplasty) and hormone replacement therapy. Only absence of testes in the scrotum (supposed as bilateral cryptorchidism) served as a cornerstone for further hormonal, USG examination, and karyotyping.

The diagnosis of congenital adrenal hyperplasia supposes a multidisciplinary approach. Both proper prenatal diagnostics and adequate treatment allow girls to have normal external genitalia and neuropsychological family atmosphere. A high index of clinical suspicion is necessary when evaluating newborn children with sexual infantilism, with cryptorchidism, with ambiguous external genitalia.

Keywords: *congenital adrenal hyperplasia, abnormal genitalia, autosomal recessive diseases, surgical correction.*

Introduction

The term congenital adrenal hyperplasia (CAH) involves a group of autosomal recessive diseases as a result of enzymatic defects responsible for the synthesis of cortisol and/or aldosterone [*Vlaski J et al., 2008; Sahakitrungruang T et al., 2010; Scheys J et al., 2011*]. Separate zones of adrenal cortex synthesize specific hormones according to the selective expression of the genes encoding each enzyme in the synthesis of steroid hormones: mineralocorticoids, glucocorticoids and androgens, mainly dehydroepiandrosterone and androstenedione [*Babu P et al., 2000; Mnif M et al., 2013; Mula-Abed W et al., 2013*]. Cholesterol is the substrate for steroidogenesis. There are various genetic mutations determinating the enzyme deficiency of steroidogenesis pathognomonic for CAH [*Xu B et al., 2009; Kamrath C et al., 2012*]. Due to these enzyme defects, a scarcity of cortisol is produced and the negative feedback control on adrenocorticotropic hormone is lost. The result is the excess of adrenocorticotropic hormone level which in its turn stimulate adrenal cortex which results an overproduction and accumulation of androgens and steroid substrates prior to the enzyme defect. Permanent stimulation of adrenocorticotropic hormone also leads to the hyperplasia of adrenal cortex [*Othman M et al., 2014*].

Deficiency of 21-hydroxylase as a result of mutations or deletions of CYP21A is the most common form of CAH, accounting for more than 90% of cases [*Chan L et al., 2015*]. Numerous cases of 21- and 11β-hydroxylases combined defects are described in literature [*Speiser P et al., 2010; Flint J, Jacobson J, 2013*]. However, these reports are enigmatic. Chromosomal locations of concrete genes encoding these two enzymes are described here.

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CAH includes two forms: classic CAH that includes salt wasting, or simple virilization, and non-classic disease [*Witchel S, 2012*]. Clinical features of adrenal insufficiency in patients with the classical form of CAH develop earlier in neonatal period – salt-losing form or with virilization during infantile age [*Alka K et al., 2012*]. The classical form is the most severe form of CAH due to CYP21A2 deficiency. Females usually have genital ambiguity [*Pelletier G et al., 2001*] which is found after birth. Approximately 67% of classical CAH presents as salt-losing and only 33% – as nonsalt-losing or simple-virilizing reflecting the degree of aldosterone deficiency [*Belinda G et al., 2012*]. Non-classical or late-onset CAH deficiency presents with signs of androgen excess and without hermaphroditic constitution of external genitalia [*Mahdi Kamoun M et al., 2013*].

Incidence of CAH varies according to the race and populations, but is around 1:14 000 live births [*Koh J et al., 2013*]. CAH is the most common cause of hermaphroditic external genitalia in females at birth. Genital anomalies range varies from complete fusion of the labioscrotal folds and a phallic urethra to clitoromegaly up to partial fusion of the scrotal suture, clitoromegaly and shallow (interfacial) vagina accompanied by accelerated growth and skeletal maturation [*Aycan Z et al., 2009; Markosyan R et al., 2012; Markosyan R et al., 2013; Piaggio L, 2014*]. Current clinical case report generally focuses on classic CAH with virilizing features without clinical features of cortisol deficiency.

The treatment of CAH usually includes replacement therapy with exogenous glucocorticoids to reduce hyperplasia and supersecretion of androgens [*Newell-Price J et al., 2008; Mnif M et al., 2013; Miller W, 2015*]. Females with abnormal genitalia require plastic correction [*Joint LWPES/ESPE CAH Working Group, 2002*]. Clitoral recession is indicated in early neonatal period followed by vaginoplasty after puberty in accordance with the expressiveness of virilization [*Poppas D, 2011*]. This sequence is very important for avoiding psycho-neurological complications of patient and his/her family [*Auchus R, Miller W, 2012*]. Some authors believe that plastic correction of external genitalia should be conducted in single-stage [*Gonzalez R, Ludwikowski B, 2014*]. The prognosis is good with joint adequate medical and surgical therapy, however, the cases of infertility after puberty period are not rare [*Seyam R et al., 2013; Trapp C, Oberfield S, 2012*]. Various studies have shown a fertility rate of 35–60% in classic virilization of CAH [*Flint J, Jacobson J, 2013*].

CASE REPORT

A 2.5-month-old "boy" presented to the primary pediatrician for absence of testes in the scrotum, who mentioned that testes weren't found during palpation, however, no other clinical signs and complaints were noted, he had gained enough weight after birth. For that time the child had already got metrics with male sex and male name. After having ultrasonography picture of ovaries and uterus, the infant was transferred to the Endocrinology Department of "Mouratsan" University Hospital. Hormonal and biochemical analyses were organized, which showed increase of 17-OH progesterone, adrenocorticotropic hormone and decrease of cortisol levels, with hyperkalemia and hyponatremia. The presumptive diagnosis was salt-wasting congenital adrenal hyperplasia. The paradox was that within 15 days mother argued against any hormonal therapy, however, hormones regulated by themselves without treatment: the adrenocorticotropic hormone reduced from 452 *pg/ml* to 228.8 *pg/ml* (N=7.2-63 *pg/ml*), cortisol from 146 *nmol/ml* to 238 *nmol/ml* (N=171-450 *nmol/ml*), and 17-OH progesterone from 4.7 *ng/ml* to 1.0 *ng/ml* (N= 0.2-0.9*ng/ml*). Hyperkalemia and hyponatremia were found to be stable. If we add to this picture that he didn't have any other clinical signs except testes absence and ovaries presence, it becomes obvious why the prescription of therapy was difficult.

Birth history hadn't revealed any significant event during pregnancy and delivery. Patient is the first child in this family. The height was 51 *cm* (65th percentile) and the weight was 3.05 *kg* (37th percentile) at birth. Apgar scores were 8-9. Light hyperpigmentation of the scrotum was noted at birth. Palpably testes were absent in the scrotum. Hypoglycemia wasn't noted after birth in postpartum period. He was discharged on the third day of life.

Physical examination upon arrival to our hospital revealed normal vital signs and a blood pressure of 70/45 *mmHg*. No dysmorphic features were noted. Genital exam revealed normal male genitalia without both testes descended. Phallus was normal in length and caliber with the urethral meatus at the tip. Physical exam wasn't remarkable for bronzing of the skin.

The main arguing factor was that there were no clinical features of cortisol insufficiency. Only ultrasound examination of the pelvis showed normal uterus and ovaries with no testis. This served as a cornerstone for the later examination of child. Investigation revealed female karyotype (46XX). Furthermore, genetic testing was sent for CYP21A gene – results were positive, which shocked parents, and the whole family were in psychological stress, taking into account that none of relatives had such problem characters. A reanalysis of 17-hydroxyprogesterone and adrenocorticotropic hormone after a month without treatment showed increase in its level, and then parents started treatment with hydrocortisone, which was administered before. The hormonal testing results before and after treatment are shown in table.

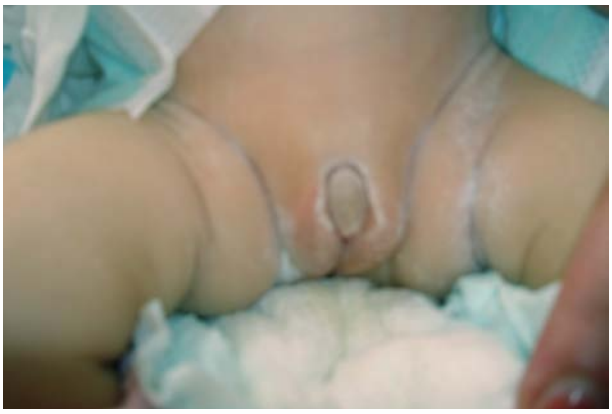
Table 1.

Adrenal testing results before and after 3 months after the treatment with hydrocortisone.

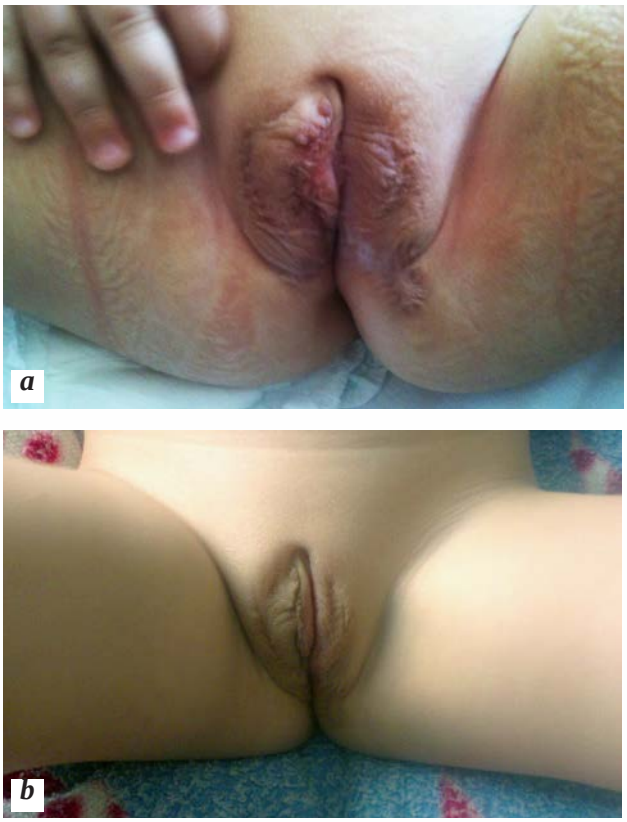
Hormones	Before treatment	After treatment	Normal ranges
17-OH progesterone, ng/ml	4.7	0.8	0.2 – 0.9
Cortisol, nmol/ml	146	350	171–450
ACTH, pg/ml	452	68	7.2 – 63
Renin, pg/ml	250	46	4.0 - 21.0
DHEA-S, mg/dl	580	390	31.6 – 431
K+, 6.4 mmol/l		3.7	3.5 – 5.2
Na^{+}, mmol/l	134	141.8	135-155

Notes: ACTH- Adrenocorticotrophic hormone, DHEA-S – Dehydroepiandrosterone sulfate.

Patient underwent to surgical correction of ambiguous genitalia – vagino-urethro-clitoro-labioplasty (Fig. 1, 2). Child has changed his name to female name and passport of birth with female sex. On follow up, improvement of her hormonal levels and external genitalia become evident after several months of treatment.



Ficure 1. *The external genitalia of the girl with congenital adrenal hyperplasia before surgery.*



Ficure.2. *The external genitalia of the girl with congenital adrenal hyperplasia after surgery.*
a *- after 1 month ,* ***b*** *- after 1 year*

Discussion

Congenital adrenal hyperplasia has a wide field of clinical severity and manifestation depending on the enzyme deficiency and the residual enzyme activity [*Achermann J et al., 2001; Flint J, Jacobson J, 2013*]. It is possible to diagnose CAH prenatally by villous sampling or amniocentesis for mutational study or by amniotic fluid levels of 17-OHP [*Martinerie L et al., 2009; Meyer-Bahlburg H, Dolezal C, Haggerty R et al., 2012; Hirvikoski T, Nordenstro A, Wedell A et al., 2012*]. That is especially important if there is an affected child in family and the parents plan for future child [*Vos A, Bruinse H, 2010*]. Diagnosis at birth is also possible to do by 17-OHP levels at the 3rd day of birth, but unfortunately not in all countries prenatal screening test is done for early diagnosis of preclinical stage of CAH [*White P, 2009; Trapp C,*

Oberfield S, 2012; Held P. et al., 2015].

A case showing the difficulty of anatomical and psychological issues of diagnosis and proper treatment of a child and which can be avoided by implication of prenatal screening tests is described here [*Yau M. et al., 2015*].

Each newborn boy with true bilateral cryptorchidism should be carefully evaluated and followed up by multidisciplinary team but not only by family doctor. Adequate replacement therapy, close clinical and laboratory monitoring, if needed, early surgical correction, early and regular fertility assessment and continuous psychological management are acquired to improve outcomes in patients with CAH [*Achermann J et al., 2000; Torre J et al., 2006; Belinda, G et al., 2012; Seyam R et al., 2013*].

This is one of the reported cases of congenital adrenal hyperplasia with virilization of external genitalia to V stage by Pradder's scale in absence of clinical other manifestations and cortisol insufficiency. A high index of clinical suspicion is necessary when evaluating newborn children with sexual infantilism, with cryptorchidism, with ambiguous external genitalia.

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