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An Interesting Case of Primary Amenorrhea

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Abstract : Congenital adrenal hyperplasia (CAH) is caused by deficiency of enzymes involved in glucocorticoid synthesis. The classic form of 21 hydroxylase deficiency (21-OHD) is the most common cause of CAH. It is the most common cause of androgenization in 46 XX females. Mutations in CYP21A2 is responsible for 90-95 percent of cases. The mildest mutations result in the least severe clinical phenotype non-classical CAH, usually presenting during adolescence and early adulthood and with preserved glucocorticoid production.We are presenting the case report of a 17 year old female who presented with masculine features. she had not attained menarche. On examination she had masculine look, male pattern pubic hair, female external genitalia with clitoromegaly, acanthosis nigricans and acne. On further evaluation, she was found to have elevated serum testosterone with elevated androstenedione and dehydroepiandrosterone (DHEAS). Her serum cortisol, aldosterone and electrolytes were within normal limits at the expense of elevated serum ACTH. Her serum 17-hydroxy progesterone levels (17-OH progesterone) were elevated. This lead to the diagnosis of non-classical CAH.

Keyword : Primary amenorrhea, Elevated adrenal androgens , Normal cortisol, aldosterone and elecrolytes, Elevated ACTH, Elevated 17 hydroxy progesterone, Non-classical congenital adrenal hyperplasia

CASE SUMMARY:

17 yr old female born of 3rd degree consanguineous marriage came with complaints of having a masculine look for the past few months. She had not yet attained menarche. She had two younger brothers of age, 12 years and 10 years who were apparently healthy. There was no similar complaints in the first or second degree relatives.

On examination, she weighed 55 kg, her height was 135 cm, and breast tanner stage was 1 on the right; 2 on the left. Her secondary sexual characters were such that axillary hair was present and pubic hair was of male pattern. She had female external genitalia with clitoromegaly. She also had acanthosis nigricans and acne. Even on repeated measurement her blood pressure was normal. Her baseline investigations were normal including serum

electrolytes (Na-144 meq/L K-3.9 meq/L Cl-103 meq/L). Her initial picture was as shown below.

Picture taken before treatment

Her karyotyping was 46 XX. Ultrasonogram of the pelvis showed that both ovaries, uterus and tubes were normal for age. There was no evidence of any adrenal mass.On hormonal assay, her serum TSH, FSH and prolactin values were normal. Serum testosterone was highly elevated and serum estradiol was within normal limits. We proceeded with analysing her serum DHEAS and androstenedione levels which were well elevated, confirming adrenal source of androgens. Her serum cortisol and aldosterone levels were within normal limits. 17 OH progesterone level was estimated which was well elevated. Her serum ACTH was also elevated.

Hence she had elevated adrenal androgens, elevated 17 OH progesterone, normal cortisol and aldosterone at the expense of elevated ACTH. This lead to the diagnosis of late onset congenital adrenal hyperplasia due to 21 hydroxylase deficiency.

She was started on tablet dexamethasone 0.25mg/d at night. There was a gradual reduction of her masculine features. On follow up at the end of 3 months, her 17 OH progesterone level was 13.04 ng/ml, testosterone level was 152.55 ng/dl and androstenedione level was 272.6 ng/dl. As the hormonal levels did not reach the normal reference range we increased the dose of dexamethasone to 0.5 mg/d.

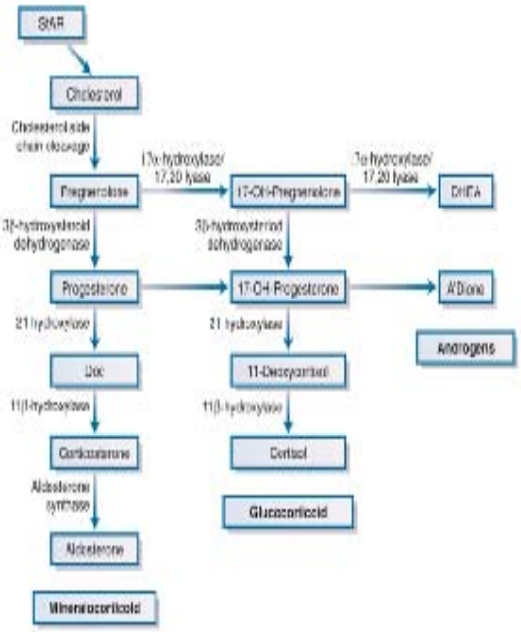
At the end of 5 months she attained menarche. Her follow up picture was as shown below. The patient is in regular follow up in our endocrine outpatient department.

Picture taken after treatment

DISCUSSION :

Congenital adrenal hyperplasia (CAH) is caused by mutations in genes encoding steroidogenic enzymes involved in glucocorticoid synthesis. Ninety percent of cases of CAH are due to 21-hydroxylase deficiency[5]. In Western societies, the incidence of 21-OHD varies from 1:5000 to 1:15,000 live births[1]. Recent studies have demonstrated that this disorder is extremely common in certain ethnic groups, occurring in approximately 0.3 percent of the general white population, 1.6 percent of Yugoslavs, 1.9 percent of Hispanics, and 3.7 percent of Jews of Eastern European (Ashkenazi) origin[6,7]. 21-OHD is inherited as an autosomal recessive trait. The gene encoding the enzyme 21-hydroxylase, CYP21, is a microsomal cytochrome P450 located on the short arm of chromosome 6, in the human lymphocyte antigen (HLA) complex[1]. Studies of HLA haplotypes show an association between the uncommon A3, Bw47, DR7 haplotype in the classical salt-losing form, whereas in the non-classical late-onset form, there is a strong association with HLA-B14, DR1[2]. Mutations in CYP21A2 are responsible for 90–95% of cases of CAH[4].

HORMONE (Normal reference range)	PATIENTS VALUE
Serum TSH 0.3-5.5 µIU/ml	3.05 µIU/ml
Serum FSH Follicular : 2.5 – 10.2 m IU/ml Luteal : 1.5-9.1 m IU/ml	5.18 m IU/ml
Serum Prolactin 2.8-29.2 ng/ml	23.65 ng/ml
Serum Testosterone 6-82 ng/dl	**693.8** ng/dl
Serum Estradiol Follicular : 12.5-166 pg/ml Luteal : 43.8 – 211pg/ml	65.08 pg/ml
Serum DHEAS 10-14 yrs 33.9-280 µg/dl 15-19 yrs 65.1-368 µg/dl	**409.60** µg/dl
Serum Androstenedione 50-250 ng/dl	**349.5** ng/dl
Serum Cortisol 7-10 am 6.2-19.4 mcg/dl 4-8 pm 2.3-11.9 mcg/dl	 14.10 mcg/dl 4.84 mcg/dl
Serum Aldosterone 2-9 ng/dl	5.21 ng/dl
Serum ACTH 7.2- 63.3 pg/ml	**159.4** pg/ml
Serum 17 OH Progesterone Follicular : 0.11-1.08 ng/ml Luteal:0.95-5.00 ng/ml	**19.58** ng/ml



StAR- steroidogenic acute regulatory protein, A'Dione- Androstenedione, DHEA- dehydroepiandrosterone, Doc-deoxycorticosterone.

21-OHD causes defective conversion of 17-hydroxy progesterone to 11-deoxycortisol. Reduced cortisol biosynthesis results in reduced negative feedback drive and increased ACTH secretion. As a consequence, adrenal androgens are produced in excess. Seventy-five percent of cases have mineralocorticoid deficiency because of failure to convert progesterone to deoxy corticosterone in the zona glomerulosa[1].

Clinically, several distinct variants of 21 hydroxylase deficiency have been recognized. Major loss-of-function mutations result in combined glucocorticoid and mineralocorticoid deficiency (classic CAH, neonatal presentation), whereas less severe mutations affect glucocorticoid synthesis only (simple virilizing CAH, neonatal or early childhood presentation). The mildest mutations result in the least severe clinical phenotype, non-classical CAH, usually presenting during adolescence and early adulthood.

Patients with non-classic 21-OHD produce normal amounts of cortisol and aldosterone, but at the expense of producing excess androgens[4]. Non-classical 21-OHD, is much more common than the classical form, with an incidence as high as 1:27 in Ashkenazi Jews. This disorder was first described in 1957 by Decourt et al [8]. It can cause premature development of pubic hair, advanced bone age and accelerated linear growth velocity in both males and females. In females, hirsutism (60%), oligomenorrhea (50%), and acne (30%) are the most common presenting features[2]. Menarche in females may be normal or delayed, and secondary amenorrhea is a frequent occurrence. Polycystic ovarian syndrome (PCOS) may also be seen as a secondary complication in these patients. So, it is important to recognize non-classical 21 OH deficiency in women with PCOS because low dose steroid therapy may improve fertility, menstrual rhythm and hirsutism in these patients.[10] In males, early balding, acne or infertility may prompt the diagnosis of non-classical CAH. Males may have small testes compared to the phallus, which results from suppression of the hypothalamic-pituitary-gonadal axis from adrenal androgens. They may also develop intratesticular adrenal rests, which can cause infertility. Gold standard for the diagnosis of late onset congenital adrenal hyperplasia is the measurement of serum 17-hydroxyprogesterone levels [6].ACTH stimulation (0.25 mg cosyntropin IV) with assays for 17- OH progesterone at baseline and 30 minutes may be useful for detecting non-classic 21-OHD and heterozygotes. Prenatal prediction of CAH attributable to classic 21-OH deficiency is possible by the determination of amniotic fluid

hormone levels, human leukocyte antigen (HLA) typing of chorionic villus cells and/or amniotic fluid cells, and molecular genetic studies of chorionic villus cells and amniotic fluid cells.[3]

Older adolescents and adults often are treated with prednisolone or with dexamethasone at night to provide more complete ACTH suppression. In children, hydrocortisone is given in divided doses. Dexamethasone should not be given before end of puberty to avoid oversuppression and reduction in linear growth. Treatment needs to be carefully titrated against clinical features of disease control. In childhood, optimization of growth and pubertal development are important goals of glucocorticoid treatment. In adults, the focus shifts to preserving fertility and preventing side effects of glucocorticoid overtreatment.

Acute salt-wasting crises require fluid resuscitation, IV hydrocortisone, and correction of hypoglycemia. Otherwise salt-wasting conditions are treated with mineralocorticoid replacement. Plasma renin activity and electrolytes are used to monitor mineralocorticoid replacement. Plasma renin should be kept within the upper half of the normal reference range. Mineralocorticoid requirements diminishes with ongoing maturation of the kidney. Biochemical monitoring should include Androstenedione and Testosterone, aiming for the normal sex-specific reference range. In very severe cases, adrenalectomy has been advocated but incurs the risks of surgery and total adrenal insufficiency, patients might also develop feedback ACTH-secreting pituitary tumours.[9] Girls with significant genital androgenization can undergo vaginal reconstruction and clitoral reduction. Fecundity is achieved in up to 90% of women, but ovulation induction is frequently required. Prenatal treatment of 21-OHD by the administration of dexamethasone to mothers is still under evaluation[4]. Non-classical CAH is an important cause of primary amenorrhea with virilizing features. We presented this case since non-classical CAH is a less frequently encountered endocrine disorder causing primary amenorrhea which is well amenable to therapy.

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