

Late Onset Congenital Adrenal Hyperplasia Presenting at Puberty with Ambiguous Genitalia: Surgery with Dexamethasone Resulting in Live New-born Normal Child

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Abstract

Hirsutism is normally found with raised androgens along with excessive hair in the female giving a male like pattern and rarely in anovulation a female may present with virilization extreme in just simple PCOS. But here we present a girl who presented with late onset congenital hyperplasia who presented at puberty with development of ambiguous genitalia giving the impression of a fall causing it but investigations revealed a normal karyotype & raised 17 hydroxy progesterone with marked stimulation with ACTH and examination under anaesthesia revealing a normal female like pattern after which her external genitalia were refashioned and she conceived after getting married on dexamethasone giving birth to an apparently normal daughter.

Keywords: Hirsutism; Virilization; Anaesthesia

Introduction

Hirsutism is defined as the terminal hair on the body of a female patient which is distributed in a male like pattern. It affects roughly 5-10% of women [1-4]. A Number of factors determine that cosmetically disturbing hirsutism will ensue.

1-Hydroxylase defect

These Patients presenting with late onset adrenal hyperplasia due to a 21-hydroxylase deficiency, respond to ACTH stimulation in a modest fashion, between the classical adrenal hyperplasia-homozygotes response and the mild heterozygote response.

A 21-Hydroxylase deficiency is the commonest autosomal recessive disorder, which surpasses cystic fibrosis as well as sickle cell. Variable clinical presentations can be seen and it may appear and disappear over time. Therefore, the diagnosis needs laboratory evaluation.

Genetic diagnosis for known mutations like Cyp21 gene is not discussed here. The 3 reasons that why it should be diagnosed are: i) Therapy which is accurate should be used, as it may be long term. ii) Pregnant women with these conditions need genetic counselling, along with assessment of asymptomatic offspring. But for that the father's carrier status is important for estimating the risk to the fetus. Though the risk for having a child with CAH is very low, the couple must get paternal testing for homo/heterozygosity. If father is positive, prenatal diagnosis and treatment is reasonably required. Iii) These Patients might be having a cortisol deficiency, theoretically when they experience severe stress; however this has not been a clinical problem.

Other enzymatic defects

3-β hydroxyl steroid

Dehydrogenase (type1) deficiency can present in both ovary and adrenal. Thus significant androgen production is not seen, but enzymatic activity remains intact in peripheral tissues. Hence hirsutism, present in this deficiency is due to a target tissue conversion of the increased secretion of precursors [5]. Unlike 21-hydroxylase deficiency, no genetic markers are currently available. Thus for diagnosis, an ACTH stimulation test and demonstration of altered conversion of 17-hydroxy pregnenolone to 17-hydroxy P (17 OHP) ratio is required. Though increased 17 OHP response to ACTH stimulation is common in women with hyperandrogenism, response is consistent with adrenal hyperactivity and not an enzymatic deficiency [6,7]. Molecular studies fail to find mutations in the genes for the 3β-hydroxy steroid dehydrogenase in patients appearing to have mild-moderate deficiency in 3β-hydroxy steroid dehydrogenase [8-10]. The deficiency present is so subtle, that accurate diagnosis is not essential. Usual therapeutic approach to hirsutism will be effective.

11β-hydroxylase deficiency is very rare and gets diagnosed at a younger age. It is not worthwhile to measure the 11-deoxy cortisol response to ACTH stimulation in adult hirsute women, which is just an effort to detect a very rare deficiency [11].

17-Hydroxy progesterone (17 OHP)

1-5% of women presenting with hirsutism show a biochemical response which is consistent with the less severe form of the adrenal hyperplasia namely 21-Hydroxylase variety [12-16]. Thus the relative frequency of NCAH requires the routine screening of 17 OHP screening of women who complain of hirsutism. Routine use of ACTH stimulation test is not warranted [12,17] fCYP21 mutations, are

heterozygous it does not increase the risk, of clinically significant hirsutism [18].

To make 17 OHP testing cost effective, a decision of ACTH stimulation test can be based on clinically significant hirsutism [11].

If there is a strong family history of androgen excess, it suggests the presence of an inherited disorder. Hirsutism due to an adrenal enzyme defect is more severe, beginning at a young age, mainly at puberty. Short stature and very high levels of androgens signify a more severe problem. Finally it is worth considering that with normal baseline steroid levels, even if a woman has subtle enzyme defects, the management of the problem does not require its discovery.

17 OHP needs to be measured early in the morning, to avoid later deviation due to the diurnal pattern of ACTH secretion. The baseline 17 OHP levels should be <200 ng/dl [11,12,19]. >200 ng/dL and <800 ng/dl needs ACTH testing. Levels >800 ng/dL are virtually diagnostic of 21-hydroxylase deficiency. DHAS levels are usually normal. Hallmark of NCAH are increased levels of 17 OHP, with a dramatic increase after ACTH stimulation [20]. Still an increased baseline level of 17OHP is often not impressive (e.g. overlapping) with those found in women with PCOS due to anovulation and a simple ACTH stimulation must be utilized.

ACTH stimulation test

Intravenous synthetic ACTH (Cortrosyn) is given in a dose of 250 µg. 17OHP is measured at 0 h and after 1 h at 8 AM at any time of the menstrual cycle. The 1 h value should be plotted to predict the genotype, whether homozygote or heterozygote forms of the 21-hydroxylase deficiency [21]. Dexamethasone preparation at night before is unnecessary [22]. 21-hydroxylase deficiency in case of heterozygote carriers is reflected by ACTH stimulated levels of 17 OHP up to 1000 ng/dl, patient having late onset deficiency have levels >1200 ng/dl.

For diagnosing 3β hydroxy steroid deficiency in the ACTH stimulation test, one measures 17 OHP and 17-hydroxy pregnenolone ratio. An abnormal 17 hydroxy pregnenolone/17 OHP ratio is usually >6 [23]. In this deficiency there is markedly raised DHAS, although serum T is just normal or mildly increased.

To diagnose 11β hydroxylase deficiency de-oxy cortisol will be increased, which is normal in 21-hydroxylase defects. We report a case of late onset congenital hyperplasia who presented with ambiguous genitalia and got treated with surgery, dexamethasone and got married and gave birth to a live normal female child.

Case Report

A 15 year old unmarried girl presented with complaints of a fall following which she had abnormally hypertrophied external genitalia, she attributed or labial hypertrophy to some fall, which were normal apparently earlier. Cycles were slightly irregular lasting 3-4 days/30-40-60 days.

On examination her BP WAS 110/70 mm Hg, height was 154', weight was 55 kg and BMI-23.1 kg/m².

Breasts were normal, inner stage IV, no galactorrhea was observed, hair distribution was practically normal.

On local examination there was a huge phallus like area in the labial region. On deeply exploring one found a hymen with a vagina?

Per abdominal ultrasonography revealed a normal sized uterus, measuring 40 × 36 × 24 mmm, both ovaries were slightly polycystic measuring 3.5 × 2.5 × 1.5 cm and other 3 × 2 × 1 cm. SFSH/LH were 5.6/10 miu/L respectively, S. Testosterone 0.6 ng/ml (0.2-0.8), 17 OH Progesterone was 800 ng/dl and further a confirmatory ACTH stimulation test confirmed 21 hydroxylase deficiency with a level of 1200 after 250 µg ACTH, S Karyotyping was normal 46 XX.

DHEAS was normal, T3, T4 TSH was normal. Initial diagnosis was difficult with a differential diagnosis of elephantiasis with the kind of labial hypertrophy and gradually examination under anaesthesia and preceding with surgery and investigations it got clarified.

A surgery was planned carefully to refashion external genitalia to female like external labia majora being cautious near the clitoromegaly not to cause heavy bleeding. In end gradually a female like external genitalia were refashioned and patient was put on dexamethasone 0.5 mg has daily. Gradually she got married and managed to conceive on dexamethasone only spontaneously and ultimately proceeded to term and delivered a live born healthy female girl weighing 3 kg with no problems in her external genitalia.

Discussion

Here we present a case of Late onset congenital adrenal hyperplasia at puberty with disturbed 17-hydroxy progesterone and further a positive response to ACTH stimulation. Karyotyping was normal along with normal ovaries. Therefore under GA after examination under anaesthesia, a refashioning of external genitalia was done and ending in a female outline after trimming the excessive labium majus. The Patient was counselled regarding testing husband for hetero/homozygosity which they refused, but she conceived spontaneously on dexamethasone and apparently the female child was normal.

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