

A Rare Cause Of Virilization Of Females; Congenital Adrenal Hyperplasia Due To 3- Beta Hydroxysteroid Dehydrogenase Enzyme Deficiency

Nadir Bir Virilizasyon Nedeni; 3-Beta Hidroksisteroid Dehidrogenaz Enzim Eksikliğine Bağlı Konjenital Adrenal Hiperplazi

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31

ÖZET:

Amaç: Steroid hormonların yapımında gerekli olan enzimlerin kısmi veya tam eksiklikleri infant döneminde veya sonrasında hafif dereceden ağır derecelere kadar geniş bir semptomlar spektrumuna neden olabilmektedir. Bu yazımızda oldukça nadir görülen, kadınlarda virilizasyon ve labial füzyon gibi semptomlara neden olabilen 3 beta hidroksi steroid dehidrogenaz enzim eksikliği tespit ettiğimiz bir olguyu sunmak istedik

Anahtar kelimeler: 3 beta hidroksi steroid dehidrogenaz enzimi, virilizasyon, labial füzyon

SUMMARY:

Objective: Partial or complete absence of enzymes which are necessary in the production of steroid hormones can cause a wide spectrum of symptoms during or after the infant from mild to severe degrees. We here present a 27-year old woman with labial fusion and virilization due to 3 β -Hydroxysteroid dehydrogenase enzyme deficiency, a rare type of congenital adrenal hyperplasia

Key words: 3 β -Hydroxysteroid dehydrogenase enzyme, virilization, labial fusion

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INTRODUCTION

Steroid hormones produced by adrenal cortex have an important role in physiological events like development, growth, osmoregulation and reproduction. Congenital adrenal hyperplasia (CAH), an autosomal recessive disorder, refers to the deficiency or absence of enzyme activity functioning on the biochemical steps of production of steroid hormones from cholesterol. Deficiency of 3 β -Hydroxysteroid dehydrogenase (one of the enzymes in the production of steroid hormones) is an uncommon form of congenital adrenal hyperplasia, caused by a mutation in the gene for one of the key enzymes in this synthesis (1,2).

The clinical presentation of 3 β -Hydroxysteroid dehydrogenase deficient congenital adrenal hyperplasia (3 β HSD CAH) shows a wide spectrum from mild to severe forms. The very uncommon severe form (complete loss of enzymatic activity) manifests itself in infancy as salt wasting due to the loss of mineralocorticoids synthesis. In milder forms (incomplete loss of 3 β HSD function), virilization of female infants is the most seen symptom (3).

Here we report a woman with hirsutism and labial fusion, diagnosed as congenital adrenal hyperplasia due to 3 β -Hydroxysteroid dehydrogenase enzyme deficiency.

MATERIALS AND METHOD

A 27 year-old female (height 159cm and weight 61kg) applied to our clinic with hirsutism. She had experienced menarche when she was 14 years old. Since then, she had regular menstrual bleedings without any disorder. Both the ovaries and the uterus were normal at the transabdominal ultrasonographic evaluation (she had no previous sexual intercourse). At the physical examination the fused labium majors were seen with a distinct hirsutism. Increase of the number of hair follicles at the axillaries, pubic and the umbilical areas was remarkable. Breast development was consistent with her age.

At the first laboratory investigation the DHEA-S, testosterone levels were remarkable high (DHEA-S:1184 mg/dL, Total testosterone:1,44ng/ml). So, the possibility of CAH was investigated, too. The second step laboratory investigations revealed high levels of Renin:4.5ng/ml/

saat, 17 α -hydroxypregnenolone :3.2ng/ml, with normal FSH(Follicle-Stimulating Hormone):6,1mIU/ml, LH(Luteinizing Hormone):7,9 mIU/mL, Prolactin:13,7 mIU/mL and 17 α -hydroxyprogesterone:1.1ng/ml.

Consultation with an endocrinologist led to the diagnosis of partial 3 α -Hydroxysteroid dehydrogenase deficient congenital adrenal hyperplasia. After the diagnosis, the labial correction was performed (Figure 1). Since the cortisol levels were normal, no replacement was arranged but she was advised to start oral contraceptives with an anti-androgenic treatment (ciproterone acetate).

RESULTS

3 β -Hydroxysteroid dehydrogenase Δ 5-4 isomerases (3 β HSD) are nicotinamide adenine dinucleotide (NAD)+ dependent membrane bound enzymes localized to the endoplasmic reticulum and mitochondria. The enzyme catalyzes dehydrogenation of the 3 β -hydroxyl group and the subsequent isomerization of the Δ 5 olefinic bond to yield a Δ 4 three-ketone structure. and convert pregnenolone into progesterone, 17 α -hydroxypregnenolone into 17 α -hydroxyprogesterone and dehydroepiandrosterone into androstenedione (3,4).

DISCUSSION

Depending on the deficiency of the enzyme, time of onset, and duration of exposure, the presence of excessive androgens in 3 β HSD CAH patients, is manifested by different symptoms. A history of ambiguous genitalia with circulatory collapse, low serum sodium, high serum potassium levels should suggest the deficiency. In older patients with mild defect in the enzyme activity (late-onset or nonclassic variant) premature pubic hair development in young children or irregular menstrual cycles and hirsutism in postpubertal adolescent females seems to be the other symptoms (4,5).

Affected female newborns may be normal or have varying degrees of clitoromegaly and labial fusion. In older children, including acne, premature pubarche, and advanced linear and skeletal growth may be seen. Adolescent or older women may present only with hirsutism and mild clitoromegaly. The degree of deformities is related to the timing in prenatal development of the onset of androgen effect. Because there is no anomalous secretion of anti-mullerian hormone in fe-

males with 3β HSD CAH, the internal genital system develops normally. But the external genitalia can be altered by the disease. After the tenth week, after the vagina and urethra have separated, the excess androgen may cause only clitoral hypertrophy. High androgen levels earlier than the twelfth week of fetal age may cause progressive fusion of the labia, formation of a urogenital sinus and hypospadias(4-6).

Since, the symptoms are variable and the diagnosis is very difficult to be assessed. especially the patients with mild deficiencies of 3β HSD present imperceptible signs which may delay the diagnosis. Frequently seen symptoms like hirsutism with labial fusion should always make the practitioner suspect of a late-onset CAH (6).

Here in the case, the patient is presented only with the fusion of the labial folds and hirsutism without any menstrual abnormalities and clitoromegaly.

CONCLUSION

The diagnosis is usually confirmed by the high levels of 17-hydroxypregnenolone compared with that of 17-hydroxyprogesterone, and also an increase of DHA and DHAS, as well as the renin. But nowadays an elevated ratio of $\Delta 5/\Delta 4$ steroids is considered to be the best biological parameter for the diagnosis of 3β HSD deficiency. However, it is well recognized that plasma levels of 17-hydroxyprogesterone and androstenedione and other $\Delta 4$ -steroids are frequently elevated in 3β HSD-deficient patients due to the peripheral type I 3β HSD activity which explains why certain patients were initially misdiagnosed as suffering from 21-hydroxylase deficiency. Due to these conflicts, many authors believe that 3β HSD deficiency may be more frequently seen than 21-hydroxylase deficiency(7,8).

Molecular diagnosis of the disease seems to be more reliable than the biological examination. To date, a total of 37 mutations (including five frameshift, four nonsense, one in-frame deletion, one splicing, and 26 missense mutations) have been identified in the HSD3B2 gene in cases suffering from classical 3β HSD deficiency(3,9).

It should be kept in mind that a history and a focused physical examination are very essential for the evaluation of androgen excess in the clinic. Determination of clinical manifestations both serves to diagnose hyp-

randrogenism and is helpful for the differential diagnosis of androgen excess disorders even before hormonal and biochemical workup. Onset and progression of hirsutism and the other features of androgen excess including fusion of the labia, or signs of virilization such as clitoromegaly, should be determined. Especially in patients suspected as CAH the biological findings may not be enough and molecular genetic consultation must be done for the actual diagnosis.

Figure 1: External genitalia 1 month after the labial correction.



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