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Case Report

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Dichotomy of Androgen Levels in a case of Polycystic Ovarian Syndrome Caused by a 17 Hydroxy Steroid Dehydrogenase Type 5 Deficiency

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ABSTRACT

In the investigation of hirsutism, if the etiology involves an increase in androgens, the source may be either the ovaries e.g., from polycystic ovaries (most common cause), or the adrenals e.g., congenital adrenal hyperplasia of the adult-onset type (21 hydroxylase or 11-beta hydroxylase deficiency) or, less commonly, Cushing's disease. The latter is the least common pathological entity of those mentioned above with increased androgens. If there is also an increase in serum cortisol, this could suggest Cushing's disease. Dehydroepiandrosterone sulfate (DHEA-S) is only made by the adrenal glands. However, polycystic ovaries can be associated with a mild increase in DHEA-S because the elevated serum levels of DHEA reaching the adrenals can be sulfated. Very high DHEA-S, however, suggests an adrenal source. A case of acne without hirsutism is presented where the patient had very high DHEA-S and also increased serum cortisol. However, the absence of phenotypic features of Cushing's syndrome, along with cortisol suppression by the overnight dexamethasone suppression test, low adrenocorticotrophin (ACTH) levels, and negative magnetic resonance imaging of the pituitary excluded Cushing's disease. The very surprising aspect of this case was despite very high serum DHEA-S levels; the serum testosterone was low normal. The best educated guess as to the cause of this dichotomy of serum androgen levels was polycystic ovaries (suggested by high anti-mullerian hormone levels), with the further increase in DHEA-S related to high levels caused by stress of college, but with a deficiency of the 17-beta hydroxysteroid dehydrogenase type 5 (17HSD5) enzyme preventing adequate conversion of androstenedione in the ovaries and adrenal glands to testosterone. This is the first case report of a 17HSD5 deficiency in a female or male.

Introduction

There are 5 major androgens found in the blood of post-pubertal females including dehydroepiandrosterone sulfate (DHEA-S), DHEA, androstenedione (A), testosterone (T), and dihydrotestosterone (DHT). Though the serum concentration of DHEA-S, DHEA, and A are much higher than T and DHT, the latter 2 have much greater androgenic phenotypic effects. Thus, the main function of DHEA-S, DHEA, and A are basically to act as steppingstones to the production of T and DHT. Thus, some consider them as pro-androgens.

Androgens in the female are synthesized in both the ovaries and adrenal glands. The 17hydroxylase enzyme and the 17.20 lyase enzyme are involved in the conversion of pregnenedione, which has 21 carbons, to 17-OH pregnenolone, which is converted to DHEA (19 carbons). Pregnenolone is also converted to progesterone (P) by the 3 beta hydroxysteroid dehydrogenase enzyme, which is then converted by the 17-hydroxylase enzyme to 17-hydroxy progesterone (17-OHP). The 17-OHP is converted to A by the 17, 20 lyase enzyme. More A is also synthesized by conversion of DHEA to A by the enzyme 3 beta hydroxysteroid dehydrogenase (17-B-HSD3).

The A is converted to T by the 17 beta hydroxysteroid dehydrogenase enzyme-type 5 (17BHSD-5) in both the ovaries and adrenal (type 3 in the testes). The ovaries do not secrete DHEAS, but some of the ovarian DHEA is converted to DHEAS by the adrenal glands. The androgen pathway is seen in Figure 1.

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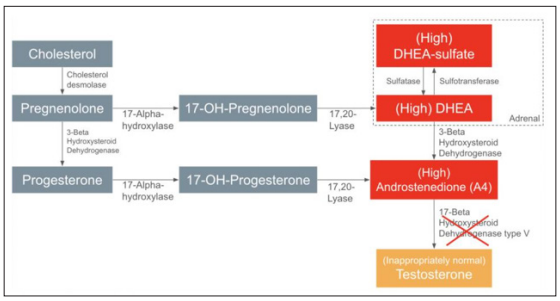

Figure 1: The Androgen Pathway in the ovaries and adrenal glands Indicating the Proposed Enzyme Deficiency to Explain High DHEA with Normal Testosterone

The most potent androgen (but with the least serum concentration level) is DHT which is converted from T by the enzyme 5 alpha-reductase. The ovarian stroma and the zona reticularis of the adrenal cortex are responsible for 25% each for the daily T production, with the remaining 50% from conversion from circulating A.

17-B-HSD3 deficiency has been documented in some XY males presenting with ambiguous genitalia [1-3]. Ambiguous genitalia is related to the insufficient production of T and thus insufficient DHT from the testes because of failure to convert A to T. This condition is rare, and it is usually an autosomal recessive disorder. In most cases the male and female parents each contribute the 17-B-HSD3 mutation (though there have been some compound heterozygous mutations found) [4].

If a female was homozygous for the 17-B-HSD5 mutation there would be normal genitalia because no phenotypic anomaly would occur since in the absence of a critical increased level of DHT made from conversion of T to DHT, the external genitalia will remain female. To date there does not appear to be any reported cases of 17-beta-HSD5 deficiency in females. A male with this 17-beta-HSD5 deficiency in his adrenal would probably have normal external genitalia because the testes would most likely produce sufficient T and DHT to produce normal male genitalia. As mentioned, it is 17BHSG-3, not type 5, that converts A to T in the testes.

The case presented here, we believe, is the first reported case of a 17-beta-HSD5 deficiency in a female especially one who presents with very high DHEA-S levels. We do not believe that cases of 17-beta-HSD5 mutations in the adrenals of a male have been reported yet either.

Case Report

A 21-year-old female was seeking a 4th opinion concerning her very high serum DHEA-S levels. She had been treated with isotretinoin at age 15 for severe acne with only limited success. At that time, because her serum T was normal at 18 ng.dL (nl<40ng/dL), free-T at normal 3.4 pg/nL (nl=0.5-3.9 pg/nL), 17-OHP 19 ng/dL (nl=<185 ng/dL), but mildly elevated DHEA-S level of 421 mcq/DL (nl=37-307 mcq/dL), the dermatologist chose isotretinoin to treat her acne since she did not think that the acne was on an androgen basis. Related to weight gain, oligomenorrhea, fatigue, premenstrual syndrome, and persistent acne without hirsutism, she was evaluated by an endocrinologist at age 21 after first being evaluated by her family physician. Her 8:00AM serum cortisol level was 19.45 ug/dL (nl=5.27-22.5ug/dL). A repeat serum cortisol 3 months and 4 months later were elevated to 31.9 and 28.6 ug/dL. The serum DHEA levels were increased to 973.0 and 937 ug/dL ((nl=110-431.7 ug/dL) drawn at the same time as the serum cortisol levels.

She consulted our reproductive endocrine group, and we performed a rapid dexamethasone (1mg) suppression test, and her 8:00am serum cortisol level suppressed to <1 ug/dL. Furthermore, the computed tomography (CT) scan of the adrenal glands and pituitary magnetic resonance imaging (MRI) showed no evidence of a pituitary or adrenal tumor. A repeat of the 8am cortisol level was 19.9 mcg/mL and the 2pm serum cortisol level was 5.7 mcg/dL. The DHEA-S level was still high, however, at 817 ug/dL. The serum androstenedione was top normal at 212 ng/dL (nl-51-213ng/dL) and the serum T was only 12ng/dL (nl 2-45 ng/dL). The serum anti-mullerian hormone (AMH) level was 9.64 ng/mL which is top normal even for a young adult. The plasma ACTH level was 9 pg/mL (nl= 6-50 pg/mL) which was obtained at 8am. Her height was 5'2, her weight was 137.2, and her blood pressure was 96/62.

Discussion

DHEA-S is strictly made by the adrenal cortex. However, there has been documented a subgroup of patients with polycystic ovarian syndrome (PCOS) who present with excessive adrenal androgens [5-8]. It is generally considered that if the serum DHEA is over 700mcg/dL an adrenal tumor needs to be excluded [8]. The results of the dexamethasone suppression test, low serum ACTH, negative pituitary and adrenal imaging studies suggested that Cushing's disease (where ACTH is elevated) was unlikely and this was supported with the finding that the plasma ACTH level was low normal. Furthermore, Cushing's syndrome related to an adrenal adenoma is unlikely since adenomas generally involve only the zona fasciculata and glomerulosa and spare the zona reticularis. In fact, because of negative feedback of cortisol to the pituitary, ACTH is usually suppressed, so DHEA is typically low with adrenal adenomas. It is not unusual for adrenal carcinomas to make DHEA-S, but they are typically large and thus generally visualized on CT scan. Also, similar to adenomas, the cortisol will usually not suppress following the rapid dexamethasone suppression test. An androgen secreting adrenal tumor is possible and could be so small that it is not detected following adrenal imaging studies [9-11]. Androgen secreting ovarian tumors, which may be too small to detect, should have increased T secretion [12].

Thus, we favor her clinical and hormonal presentation to be related to polycystic ovarian syndrome (consistent with her serum AMH levels) magnified by college psychological stress creating a pseudo-Cushing's syndrome presentation with high serum cortisol levels and very elevated DHEA-S levels. The low normal levels of T, and thus absence of hirsutism, was most likely related to a 17B-HSD5 enzyme deficiency. Perhaps the high levels could also be influenced by the inability of the A being converted to T, so some of the A was shifted back to DHEA-S. The 17-beta-HSD5 mutation would probably be present in both the ovaries and adrenal.

Depending on the type of the less common defect of an adrenal enzyme deficiency coupled with the more common polycystic ovarian syndrome, one may see the opposite findings than what was seen in the present case. For example, a case was reported of a 17,20-lyase deficiency of the adrenal gland which would prevent the conversion of 21 carbon progesterone and other 21 carbon derivatives to androgens. This would lead to increased serum progesterone and 17OHP even in the follicular phase, and this was present in that previous case reported. However, the increased level of serum T that was found was produced by the ovaries related to her PCOS. This suggested that the 17,20 lyase deficiency was only present in the adrenals but not her ovaries [13].

There are no genetic studies available as yet to detect a gene mutation for 17-BHSD5. A thorough search of the literature failed to find another case report of a 17-HSD5 deficiency in a male or female. In a male the enzyme that converts A to T is 17HSD type 3 and phenotypically can present with ambiguous genitalia. Though this seems to be the first case report of a 17-betaHSD5 deficiency in a female or male it possibly is not as rare as it seems because not only females may not show phenotypical abnormalities but neither would males because in males the majority of T production comes from the testes. In the testes it is the 17-betaHSD3 enzyme that is needed to convert A to T. Thus, this case is more of academic interest rather than clinically useful

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