

## Late-Onset Adrenal Steroid 3B-Hydroxysteroid Dehydrogenase Deficiency: (I) A Cause of Hirsutism in Pubertal and Postpubertal Women

The physical signs and symptoms, as well as abnormalities in glucocorticoid and mineralocorticoid hormonal levels, have been well documented in the "classical" forms of congenital virilizing adrenal hyperplasia. Within the past decade it has become increasingly clear that genetic defects of an adrenal steroidogenic enzyme such as 21-hydroxylase or 11- $\beta$  hydroxylase can be manifested during *peripubertal* life and that the steroidogenic enzyme defect may be one of the causes of androgen excess in *peripubertal* and *postpubertal* women. In 21-hydroxylase deficiency, the mild enzyme defect manifested at puberty results from an allelic mutation at the 21-hydroxylase locus.

A mild defect in 3B-hydroxysteroid dehydrogenase (3B-HSD) in adult women with hirsutism has also been found and may not be recognized until later in life, when symptoms of excessive androgen production occur. Thus, it is possible that allelism at the 3B-HSD locus occurs and is responsible for a classical severe form that presents at birth, and for a milder nonclassical form that presents later in life and causes *peripubertal-onset* hirsutism.

The present study was conducted on 30 normally menstruating women (controls) and 116 postmenarchal women with either long-standing or slowly progressive excessive hair growth. None had ambiguous genitalia at birth by history. All had an adrenocorticotrophic hormone (ACTH) stimulation test, and blood samples were analyzed for glucocorticoids, mineralocorticoids, sex steroids, and their precursors. Partial 3B-HSD deficiency was suspected in hirsute women in whom the  $\Delta^5$  precursors and the ratios of  $\Delta^5$  steroids to their reduced products all increased after ACTH stimulation to more than 2 SD above the mean for normal women.

Sixteen of the 116 hirsute women were classified as having nonclassical (partial) adrenal 21-hydroxylase deficiency based upon very low  $\Delta^5$ -17 hydroxypregnenolone ( $\Delta^5$ -17P) to 17-hydroxyprogesterone (17-OHP) levels following ACTH administration. An additional 17 hirsute women, including three sisters, met all criteria for partial adrenal 3B-HSD deficiency—the  $\Delta^5$ -17P and dehydroepiandrosterone (DHEA) levels and the ratio of  $\Delta^5$ -17P:17-OHP were all significantly elevated following ACTH when compared with normal women. These women were classified as having partial adrenal 3B-HSD deficiency.

Eighty-three of the 116 hirsute women had no apparent adrenal steroidogenic defect. Many had classical or other types of polycystic ovarian disease.

Women with partial 3B-HSD deficiency had an exaggerated diurnal variation in  $\Delta^5$ -17P, with the major peak at 8 AM higher than in any of the normal women. These high levels of

the  $\Delta^5$  steroids were readily suppressed with glucocorticoid therapy in those with 3B-HSD deficiency.

In retrospect, of the 17 hirsute women with partial 3B-HSD deficiency, seven had final heights at least two to five inches below their parents' height. Five had pubarche between ages 5 and 8.5 years and six between 10.5 and 12 years. None had thelarche before pubarche. Reliable data could not be obtained from the other six women. The onset of hirsutism or acne in all 17 occurred between 12 and 20 years of age. Baseline urinary 17-ketosteroid excretion was elevated in the majority, but was suppressed by dexamethasone therapy.

Pang S, Lerner AJ, Stoner E, et al: *JCE&M* 1985;60:428-439.

**Editor's comment**—*These data, along with those from several other laboratories, indicate that partial 3B-HSD deficiency is a common (approximately 12%) cause in this referral population of hirsute women. The most valuable hormonal tests in differentiating patients with 3B-HSD deficiency from normal women and from patients with variant 21-hydroxylase deficiency or hirsutism without an adrenal steroidogenic defect, are the ratio of  $\Delta^5$ : $\Delta^4$  steroids and the high level of precursor  $\Delta^5$  steroids after ACTH stimulation. ACTH stimulation and dexamethasone suppression, plus the characteristic adrenal circadian rhythm of the steroids, indicate an adrenal source of the elevated  $\Delta^5$  steroids due to partial 3B-HSD deficiency. Hirsutism in these women may result from the *peripubertal* conversion of  $\Delta^5$  steroids to  $\Delta^4$  steroids in situ at the target organ—for example, the hair follicle. The 83 women without defect in steroidogenesis probably represent a spectrum of ovarian disorders (many had cystic ovarian changes) that together represent the largest cause of *peripubertal* hirsutism.*

*Since adrenal steroid biosynthetic disorders are readily treated, they should be considered during an evaluation by physicians who see female adolescents with severe acne and hirsutism.*

9- to 17-year-old controls. The mean GH levels in TS decreased between childhood and adolescence from  $4.6 \pm 0.7$  ng/ml to approximately 2.5 ng/ml. The difference in the secretion of GH by the girls with TS in the two age ranges is not statistically significant. The observed difference in the mean GH secretory rates, therefore, is primarily related to an increase in GH secretion in normal female adolescents and is not surprising.

The discrepancy of the somatomedin-C determinations during adolescence is also probably related to the absence of sex hormones in the TS patients. The authors found a mean level of approximately 0.85 U/ml for the 11 TS patients who were 11 years of age and older. If estrogen were administered to girls in this age group, the somatomedin-C levels would very likely increase and approach those seen in normal female adolescents.

That bone age is delayed in TS patients is also not surprising, since sex hormones contribute to skeletal maturation after the age of about 9 years. Patients with TS do not have sex steroids present, and, therefore, the clinical observation of delayed skeletal maturation discussed by the authors is expected.