Hormonal Findings in African-American and Caribbean Hispanic Girls With Premature Adrenarche: Implications for Polycystic Ovarian Syndrome

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ABSTRACT. Background. Premature adrenarche refers to the early maturation of the adrenal zona reticularis such that the resultant modest hyperandrogenism causes the early appearance of pubic hair before the age of 8 years in girls and 9 years in boys. The precise etiology of premature adrenarche is not known. However, recent studies indicate that certain girls with premature adrenarche are at risk of developing functional ovarian hyperandrogenism, polycystic ovarian syndrome, and hyperinsulinism. Caribbean Hispanic women in general are at increased risk of developing polycystic ovarian syndrome, and African-Americans are at increased risk of developing the complications of hyperinsulinism. Previously, girls with premature adrenarche were reported to have androgens in the range found in normal children in the early stages of puberty. We noted that many of our African-American and Caribbean Hispanic patients with premature adrenarche had androgens that were much higher than what has been reported previously.

Objective. The retrospective study was performed to characterize the adrenocorticotropin-stimulated androgen response in an African-American and Caribbean Hispanic population of girls with premature adrenarche.

Methodology. The androgen response to adrenocorticotropin stimulation in 72 African-American and Caribbean Hispanic girls with premature adrenarche was compared with those reported for normal girls in early puberty (Tanner stages II and III). The mean age was 6.8 ± 0.8 years, bone age was 8 ± 1.5 years, pubic hair was Tanner stages II and III, and body mass index was 18.6 ± 4.

Results. Of the girls, 28% were found to have elevated stimulated 17OHPregnenolone (17OHPreg) levels that were >2 SD units above the mean for normal early pubertal children. The stimulated ratio of 17OHPreg/17OHPregosterone also was elevated in 18% of the girls and showed a modest correlation with body mass index.

Conclusion. In contrast to previous studies of girls of mixed ethnic backgrounds with premature adrenarche, 28% of the 72 African-American and Caribbean Hispanic girls with premature adrenarche had adrenocorticotropic-in-stimulated 17OHPreg levels that were significantly higher than those seen in early pubertal girls. Because 17OHPreg hyperresponsiveness has been described previously in women with hirsutism or polycystic ovarian syndrome, the similar finding in many African-American and Caribbean Hispanic girls with premature adrenarche suggests that the two conditions may share a common mechanism for their hyperandrogenism. Therefore, the hyperandrogenism in certain African-American and Caribbean Hispanic girls with premature adrenarche may not be benign and may be the first presentation of polycystic ovarian syndrome.

ABBREVIATIONS. 17OHPreg, 17OHPregnenolone; ACTH, adrenocorticotropin; 17OHPreg, 17OHProgestosterone; DHEA, dehydroepiandrosterone; Δ4A5, Δ4 androstenedione; BMI, body mass index.

Premature adrenarche refers to the appearance of pubic hair before age 8 years in girls and 9 years in boys.1 Axillary hair, apocrine odor, and acne may or may not be present. Early appearance of sexual hair growth may herald early puberty or may be the first sign of clinically significant hyperandrogenism derived from a virilizing tumor or an enzymatic defect of steroidogenesis.2 Most girls being evaluated for premature adrenarche do not have greatly elevated steroid levels. Instead, adrenocorticotropin (ACTH) testing more commonly reveals moderately elevated androgen levels, similar to those found in the early pubertal stages.3,4 Children who present with premature pubic hair and modestly elevated androgens have been designated as having benign premature adrenarche. This condition has been attributed to the early maturation of the zona reticularis of the adrenal gland, such that adrenal androgens rise to levels normally seen in early puberty.5,6 In benign premature adrenarche, growth and development, as well as the initiation and progression of puberty, are said to be normal or slightly advanced.7 However, although long-term studies of ovarian function are not available, recent data indicate that some girls with premature adrenarche may not have a benign outcome. Certain girls with premature adrenarche have been reported to develop functional ovarian hyperandrogenism.8 Furthermore, insulin resistance in children and adolescents who had premature adrenarche has been found by us9 and others.10 Although most girls with premature adrenarche reportedly have modestly elevated an-
dripped, we noted that many of our African-American and Caribbean Hispanic patients had levels of 17OHPPregnenolone (17OHPPreg) higher than those reported previously for children of mixed ethnic background. Hyperresponsiveness of 17OHPPreg has been described in women with hirsutism or polycystic ovarian syndrome.11,12 This similar finding in many African-American and Caribbean Hispanic girls with premature adrenarche suggests that the two conditions may be linked. Therefore, the hyperandrogenism in certain African-American and Caribbean Hispanic girls with premature adrenarche may not be benign and may be the first presentation of polycystic ovarian syndrome. Furthermore, Caribbean Hispanic women are known to have an increased risk of developing polycystic ovarian syndrome.13 Thus, the purpose of this study was to characterize the adrenal androgen response to ACTH testing in prepubertal African-American and Caribbean Hispanic girls with premature adrenarche, a population at increased risk for polycystic ovarian syndrome.

METHODS

We reviewed the charts of all girls between the ages of 5 and 8 years who were referred to the pediatric endocrine clinics at Montefiore Medical Center and the Bronx Municipal Hospital Center for early appearance of pubic hair or premature adrenarche. All children seen in our clinic for the evaluation of premature adrenarche underwent ACTH testing. We analyzed the hormonal data of the ACTH stimulation tests performed on 74 girls with premature adrenarche. They all were either of Caribbean Hispanic (n = 41) or African-American (n = 33) ethnic background. A standard ACTH-stimulation test was performed by administering 250 μg of ACTH (Cosyntropin) at −9 AM. Serum was drawn at 0 and 60 minutes and assayed for 17OHPreg, 17OHPregsterone (17OHPreg), dehydroepiandrosterone (DHEA), and Δ4 androstenedione (Δ4AS). Two of these patients had hormone levels that met the standard criteria for 21 hydroxylase deficiency and 11 hydroxylase deficiency.14,15 We analyzed the data of the remaining 72 children. Their mean age was 6.8 ± 0.8 years, bone age was 8 ± 1.5 years, pubic hair was Tanner stages II and III, and body mass index (BMI) was 18.6 ± 4. The hormonal results were compared with the normative data previously published for normal healthy girls in the early Tanner stages II and III pubertal stages.16 We opted to use control normative data from a non-Caucasian but Hispanic population rather than the standard Caucasian normative data, thus eliminating errors that could be attributed to differences in ethnic backgrounds.

All data have been expressed as mean ± 1 SD. Statistical analysis between hormones and ratios was performed using the Student’s t test. A P value of <.05 was considered to be statistically significant. The correlation coefficient between groups was done using Pearson’s bivariate analysis.

RESULTS

The ACTH-stimulated levels of 17OHPreg, 17OHPreg, DHEA, and Δ4AS in our patients are compared with the normal levels of these hormones seen in girls in Tanner stages II and III (Fig 1). The mean values ± 1 SD in our patients (and controls) were 17OHPreg, 766.6 ± 366 ng/dL (558.5 ± 170.9); 17OHPreg, 213.8 ± 117 ng/dL (199.8 ± 10); DHEA, 449 ± 195 ng/dL (360.2 ± 25); and Δ4AS, 80 ± 28 ng/dL (112 ± 53.7). Although the vast majority of the Hispanic and African-American girls with premature adrenarche had stimulated levels of 17OHPreg consistent with what has been reported previously in girls with benign premature adrenarche, nearly one third of our prepubertal patients had marked hyperandrogenism, with levels of 17OHPreg >2 SD units above the mean for normal Tanner stages II and III pubertal girls (Fig 1). Stimulated DHEA and 17OHPreg levels were comparable with those for the controls. The mean Δ4AS level in the children with premature adrenarche was lower (P = .003) than that for early pubertal girls.

The ratios of 17OHPreg/17OHPreg and DHEA/Δ4AS are compared with the normative data in Fig 2. The mean ratio (± 1 SD) of 17OHPreg/17OHPreg for the premature adrenarche patients was 4.47 ± 3 and for controls 3.3 ± 1.7. Although the mean ratio of 17OHPreg/17OHPreg was not significantly different from that for the controls, 18% of the girls with premature adrenarche had a ratio that was 2 SD units higher than the mean for the control population. The ratio of DHEA/Δ4AS in the premature adrenarche patients (5.58 ± 1.86) was significantly higher than the same ratio for the controls (3 ± 1) (P < .001). The ratio of 17OHPreg/17OHPreg correlated weakly with BMI (r = 0.25; P = .039). BMI did not correlate with absolute levels of 17OHPreg, 17OHPreg, DHEA, Δ4AS, or with the ratio of DHEA/Δ4AS. There was no correlation between the clinical presentation (age, bone age, and amount of pubic hair; ie, Tanner stages II vs III) and the corticotropin-stimulated hormonal levels. There was no difference in hormonal data between the two ethnic groups.

DISCUSSION

Traditionally, benign premature adrenarche was the term used to describe girls who developed pubic hair before the age of 8 years and who had a modest elevation of androgens. Although the onset of pu-
berty in these girls is reported to be normal, there are recent reports that the pubertal outcome may not be normal. In a study by Ibanez and associates,16 16 (45%) of 35 postpubertal girls from Spain and Italy with a history of premature adrenarche had hirsutism, oligomenorrhea, and a hormonal response to a leuprolide acetate challenge test that was consistent with functional ovarian hyperandrogenism or polycystic ovarian syndrome. Hence, in certain girls with premature adrenarche, the outcome may not be benign. Furthermore, our group has reported that 7 of 12 prepubertal African-American and Hispanic girls with premature adrenarche tested had reduced insulin sensitivity and hyperinsulinism.9 Adolescent and adult women with polycystic ovarian syndrome frequently have hyperinsulinism and decreased insulin sensitivity and are at greater risk for developing diabetes at a young age.17

Although girls with premature adrenarche have been described previously as having ACTH-stimulated androgens similar to those seen in early pubertal children, many children in this large group of African-American and Caribbean Hispanic girls with premature adrenarche demonstrated a hyperresponsiveness of the Δ5 steroids to ACTH. Twenty-eight percent had an ACTH-stimulated 17OHPrep response that was >2 SD units above the mean for Tanner stages II and III pubertal children, 18% had a similarly elevated ACTH-stimulated ratio of 17OHPrep/17OHProg, and the entire group had an mean ACTH-stimulated ratio of DHEA/Δ4AS that was significantly higher than that reported in early pubertal girls. Until recently, girls with hyperresponsiveness of Δ5 steroids and with elevated ratios of 17Preg/17OHProg and DHEA/Δ4AS were designated as having the mild form of 3β-hydroxysteroid dehydrogenase (3βHSD) deficiency. In contrast to our findings, this hyperresponsiveness had been reported previously to occur in 3% to 13% of girls of mixed ethnic backgrounds who were being evaluated for premature adrenarche.3,4,18,19

Interestingly, 17OHPrep hyperresponsiveness has been described previously in women with hirsutism or polycystic ovarian syndrome.11,12 Many of these women with elevated ACTH-stimulated 17OHPrep levels also were previously designated as having a deficiency of the 3βHSD enzyme.20–22 Recently, however, despite the hyperresponsiveness of Δ5 steroids (17OHPrep and DHEA) to ACTH, no abnormality in the gene encoding the 3βHSD enzyme has been found in these women and children.23 Only patients with markedly elevated Δ5 steroids of >10 SD units above the normal level were shown to have defects in the 3βHSD gene.24

Hence, the precise etiology of the hyperresponsiveness of Δ5 steroids in certain girls with premature adrenarche and women with polycystic ovarian syndrome is not clear. Although a specific etiology is yet to be identified, the hyperandrogenism in this subset of girls with premature adrenarche nevertheless may persist into adulthood or adulthood and predispose them to hirsutism, acne, menstrual irregularities, polycystic ovarian syndrome, and infertility. More importantly, in consideration of the modest correlation of 17Preg/17OHProg ratio with BMI and the known association between polycystic ovarian syndrome and obesity, these are yet additional reasons to recommend efforts at weight control and an increase in physical activity while these girls are still young and prepubertal.

The hyperresponsiveness of 17OHPrep to ACTH and decreased insulin sensitivity in certain girls with premature adrenarche and in certain women with polycystic ovarian syndrome suggest that a common mechanism may exist for the two conditions. Barnes and colleagues25 have hypothesized that there is an increase in the activity of the ovarian P450 C17 enzyme in women with polycystic ovarian syndrome resulting in an exaggerated 17OHProg response to LH analogue testing. In 1995, Zhang and colleagues26 proposed a unifying hypothesis for the hyperandrogenism and hyperinsulinemia characteristic of polycystic ovarian syndrome and premature adrenarche. Excess serine phosphorylation of P450 C17 enzyme increases androgen biosynthesis. Additionally, serine phosphorylation of the insulin receptor causes insulin resistance and hyperinsulinism and may provide a common mechanism for the etiology of hyperandrogenism and hyperinsulinism in polycystic ovarian syndrome.12,27 They postulated that this abnormality also may be present in the hyperandrogenism of premature adrenarche and serve as the link to the later development of polycystic ovarian syndrome. The hyperresponsiveness of 17OHPrep and DHEA in our patients is consistent with the role of increased adrenal P450 C17 enzyme activity in the Δ5 steroid pathway.

The presence of hyperandrogenism in African-American and Caribbean Hispanic girls with premature adrenarche may be of significance because Caribbean Hispanic women have an increased incidence of
polycystic ovarian syndrome. A preliminary demographic study showed that Caribbean Hispanic women have twice the prevalence of polycystic ovarian syndrome compared with African-American women who attended an urban reproductive endocrine clinic and compared with the prevalence rate reported in the literature. Additionally, Dunai’s group reported an increased prevalence of insulin resistance in women of Caribbean Hispanic origin and suggested that this alteration in insulin sensitivity increases their chances for polycystic ovarian syndrome. Furthermore, it is well known that African-Americans are at an increased risk of developing complications from hyperinsulinemia resulting from reduced insulin sensitivity, including cardiovascular disease, hypertension, and diabetes.

A recent article suggested that it is common for young girls of African-American origin to develop pubertal changes at an earlier age than their white counterparts. Premature adrenarche is considered to be a benign condition and is probably a normal variant in the vast majority of these children. However, although premature adrenarche is common in African-Americans, in some of these girls, it may be the first presentation of marked hyperandrogenism. We are particularly concerned about the pubertal outcome of those girls who present at this young age with such significant hyperandrogenism. We are currently obtaining follow-up data on these girls, and we hope that long-term studies will elucidate whether those children with an exaggerated androgen response to ACTH and who may be obese are at greater risk of developing polycystic ovarian syndrome.

Whether children with an exaggerated adrenal androgen response are destined to have progression to hyperandrogenic ovarian dysfunction and the same metabolic complications as do adult women with polycystic ovarian syndrome remains to be determined. Studies of the mechanism of hyperandrogenism in young girls with premature adrenarche may help to elucidate the mechanisms or natural history of hyperandrogenism in adults, because these girls have not yet developed the multiple metabolic abnormalities characteristic of adult women with polycystic ovarian syndrome. Once risk factors for polycystic ovarian syndrome are clearly identified, early intervention can be initiated before marked obesity, diabetes, and irreversible ovarian changes occur. If premature adrenarche is indeed found to be a precursor of polycystic ovarian syndrome and is related to obesity, we as health care providers of these children should encourage intervention in the form of weight reduction until other specific preventive measures can be identified.

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