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PUBARCHE AS WELL AS THELARCHE MAY BE A MARKER FOR THE ONSET OF PUBERTY

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Abstract

STUDY OBJECTIVE—To define anthropometric and hormonal differences in a group of black and white girls who began puberty with breast development alone (“thelarche” pathway) compared to those who began with pubic hair development alone (“pubarche” pathway), and test the hypothesis that pubarche may represent true pubertal development.

DESIGN—Longitudinal cohort seen annually for ten years.

SETTING—Recruited through elementary schools in Cincinnati OH and Richmond CA; through HMO in Washington DC.

PARTICIPANTS—9 years old, either Black or White, in the NHLBI Growth and Health Study.

INTERVENTIONS—None; observational study.

MAIN OUTCOME MEASURES—Initial secondary sexual characteristic at onset of puberty; anthropometric measures; hormone measures.

RESULTS—478 of 1155 girls matured through a defined pathway. Age at onset of secondary sexual characteristics was similar between pathways, although girls in the thelarche pathway had puberty at a somewhat younger age, and black participants entered at a significantly younger age. Height velocity was the same in both pathways, and in the pubertal range. DHEA-S levels at onset

of puberty were significantly greater in girls in the pubarche pathway, but levels of estradiol and testosterone were not different. Age of menarche was different by race (younger in blacks) and pathway (younger in thelarche pathway).

CONCLUSIONS—Given similar age and height velocities at onset of secondary sexual characteristics, these results suggest that pubarche, the development of pubic hair without breast development, may represent true pubertal maturation.

Keywords

Pubertal onset; pubarche; thelarche; female puberty; breast development; pubic hair development in girls

INTRODUCTION

Pubertal maturation consists of two associated processes: adrenarche, the reappearance of adrenal androgen production; and gonadarche, the pubertal reactivation of the hypothalamic-pituitary-gonadal axis. Pubarche is the appearance of pubic hair and is considered a manifestation of adrenarche. Thelarche is the development of breast tissue and is considered generally the representation of gonadarche in girls; many studies, as well as clinicians, utilize the onset of breast development as the onset of puberty in girls.^{1–5} Typically, adrenarche occurs before gonadarche. The earlier onset of adrenarche has led to the belief that adrenal androgens are an important factor in the onset of puberty.⁶ Many have questioned whether the appearance of pubic hair without breast development represents true pubertal maturation, or is merely a manifestation of adrenarche or premature adrenarche.^{7, 8} A recent study examined longitudinally a group of white girls who had asynchronous maturation.⁹ The girls either had initial breast development (thelarche) or pubic hair development (pubarche), but without development of the other manifestation. The two groups had similar age of onset of maturation, but greater adiposity and ponderosity was noted in girls with thelarche, at the onset of, as well as throughout, pubertal maturation.⁹ This current study was designed to define further anthropometric and hormonal differences in a group of black and white girls who began puberty with breast development alone (thelarche pathway) compared to those who began with pubic hair development alone (pubarche pathway). The study hypothesis proposes that pubarche may represent true pubertal development.

MATERIALS AND METHODOLOGY

Participants

A group of girls, age 9 at time of recruitment into the NHLBI Growth and Health Study, were seen annually for 10 years to assess growth and maturation. Details of the parent study have been published previously.¹⁰ Although the parent study recruited both 9 and 10 year old girls, only girls who were 9 years of age at time of recruitment were chosen for inclusion in this study to minimize bias from early maturers among 10 year old girls who might have been misclassified. At the time of recruitment, 41 white participants (6.7%) and 116 black participants (21.4%) were too physically mature to determine the pathway of entry into puberty and excluded from the analyses. Girls were recruited from three metropolitan areas: Cincinnati, Ohio (public and parochial schools to provide a broad racial and socioeconomic representation); Richmond California Unified School District; and Washington DC (through a health maintenance organization and Girl Scout troops). Race was defined as “white” if both the participant and her parents identified themselves as white, or “black” if both the participant and her parents identified themselves as black.

Maturation assessment

Pubertal maturation was assessed utilizing the criteria established by Marshall and Tanner for pubic hair stages,¹¹ and by Garn and Falkner for areolar maturation.¹² This study utilized areolar maturation, which appears to distinguish breast maturation from fat deposition in early puberty better than the traditional Tanner breast staging system; there is high correlation between traditional Tanner breast assessment with the Garn and Falkner system, $r = 0.94$.¹² The discrepancies between the two systems occur occasionally when overweight prepubertal females are overestimated to have Tanner 2 breast stages.¹² Girls were defined to have “thelarche” if they had breast development without pubic hair development, and “pubarche” if they had pubic hair development without breast development.

Anthropometric assessment

Height was determined at each visit with the same model portable stadiometer for two measures, with a third measurement if the first two were more than 0.5 cm apart. The methods for anthropometric measurements have been described previously.¹⁰ Height velocity was determined by calculating differences between annual visits, and correcting to 12 months (visit windows were ± 3 months). Body mass index (BMI) was calculated from weight (kg) divided by height (M) squared. Percent of body fat was calculated from the triceps and subscapular skin folds using the formulae of Slaughter, et al.¹³

Hormone assessment

Hormone measures were assessed as an ancillary study only on girls at the Cincinnati study site. Serum levels of dehydroepiandrosterone sulfate (DHEA-S), estradiol (E2), and testosterone (T) were measured by radioimmunoassay (RIA) as described previously.¹⁴ Serum DHEA-S levels were measured with double antibody RIA; assay sensitivity was 15 ng/mL, and intra-assay and inter-assay coefficients of variation were 5.2% and 10.5%. Serum E2 was measured by double-antibody RIA; assay sensitivity was 5 pg/mL, and intra-assay and inter-assay variabilities were 8.3% and 13.0%. Serum T was measured by double antibody RIA; assay sensitivity was 2 ng/dL and intra-assay and inter-assay variabilities were 5.0% and 9.3%, respectively. Estradiol levels < 11 pg/mL were considered pre-pubertal values.¹⁵

Statistical analyses

The outcome measures for the anthropometric analyses included height velocity, age at onset of puberty, and age of menarche. The chronologic age at the last visit prior to the onset and age at the visit of the onset were used to establish the time intervals for the pubertal event. For those participants who had experienced onset before the study, the age of onset was treated as left-censored data (that is, that age was considered an estimation of the maximal age of transition). Because of the censored nature of the age at onset of puberty, survival regression analysis was used to compare the “thelarche” and “pubarche” subjects on their age of onset; the model also included race and race by pathway interaction. The height velocity and hormone measures (which included T, E2, and DHEA-S) obtained at onset of puberty were determined by time of onset of puberty (defined by earliest sign of puberty, either pubic hair or breast development). All hormone concentrations were log-transformed.

Participants with an established pathway were compared to those participants without an established pathway on baseline age, age of onset of puberty, age of menarche, baseline BMI, and height velocity at onset of puberty, using two-way analysis of variance (ANOVA), adjusted for race. Participants who had hormone measures were compared with participants without hormone measures at onset of puberty, using two-way ANOVA adjusted for race. The baseline variables that were identified as significantly different between the groups in

these ANOVA were included in further analysis on the comparisons on outcome variables between the pathways. Regression analyses were used to compare percent body fat at onset of puberty as well as one year earlier; pathway, race, and an interaction between pathway and race were included in the analyses. All analyses were carried out in SAS 9, and statistical significance level was set at 2-sided p value of 0.05.

RESULTS

At baseline, there were 1155 girls who were age 9. The majority of girls (58.6%), of whom 55.7% were white and 61.9% were black, had simultaneous breast and pubic hair development noted by the examiners between the annual visits, as described above. Baseline age, BMI, and height velocity were similar in those with a defined pathway, as contrasted to those with simultaneous development. However, age at onset of puberty was different, with a mean onset of puberty of 9.65 years in girls entering puberty via thelarche or pubarche, and 10.16 years in girls entering puberty with simultaneous breast and pubic hair development ($p < .0008$). Among the subjects who had a defined developmental pathway, 67.3% (183/272) of white participants as contrasted to 48.5% (100/206) of black participants had thelarche (Chi-square $p < 0.0001$). Age at onset of puberty was marginally younger in the thelarche compared to the pubarche pathway among black participants ($p = 0.025$), and black participants matured at a significantly younger age ($p < .0001$) (Table 1). Height velocity at the time of onset of puberty, by race and pathway, were not significantly different: 6.82 cm/yr for thelarche and 7.07 cm/yr for pubarche, among the white participants, and 6.95 cm/yr and 6.88 cm/yr among black participants, respectively.

There were results from hormone samples available at the onset of puberty for 88 participants in the thelarche pathway and 47 in the pubarche pathway. There were significant differences in levels of DHEA-S, with girls in the pubarche pathway having higher mean levels (Table 2, $p = 0.004$). Mean testosterone (T) and estradiol (E2) levels were not different between the pathways (Table 2) ($p = 0.37$, $p = 0.46$, respectively). Although 32–59% of E2 values were in the prepubertal range at the time of thelarche or pubarche, the relative proportion of values that were prepubertal from either pathway were not different (chi square, $p = 0.24$ –.65). Of note, among those with simultaneous development (i.e., those who did not have a defined pathway), E2 levels were greater than in either thelarche or pubarche pathways ($p < .0005$). DHEA-S levels in those with simultaneous development were greater than those in the thelarche pathway ($p = .002$), and no different from those in the pubarche pathway ($p = .95$). Although included in the subsequent analyses, those participants without specimens for hormone analysis were slightly but significantly younger at recruitment (9.49 contrasted to 9.63 years, $p < .0001$), had slightly but significantly younger age of menarche (12.27 contrasted to 12.46, $p < .01$), and lower body fat (20.0% contrasted to 21.4%, $p < .01$).

Age of menarche was different by race as well as pathway. Among white participants, girls who matured in the thelarche pathway had menarche at 12.68 years, compared to those in the pubarche pathway who were 13.06 years old. Among black participants, the ages of menarche were 12.04 and 12.42 in thelarche and pubarche, respectively. Although race ($p < .0001$) and pathway ($p < .0002$) were both significant, the interaction term was not significant.

The proportion of body fat was significantly different between pathways (Table 3). Girls in the thelarche pathway had significantly greater percent body fat at onset of puberty, as well as one year prior to onset of puberty (both $p < .0001$); race was not significant ($p = .56$ and .27, respectively); the interaction term between path and race was not significant one year prior to puberty, but was at onset of puberty, $p = .012$.

DISCUSSION

This study examined a group of girls longitudinally from ages 9 until 18 who had a defined pubertal pathway beginning with either thelarche or pubarche at the time of development of secondary sexual characteristics. Girls who had breast development as the initial stage of puberty (thelarche), as well as those who had pubic hair as the initial stage of puberty (pubarche), had similar ages of pubertal onset. Parent, as well as others, has noted that the earliest manifestation of puberty in girls is acceleration of growth velocity.¹⁶ We found a similar height velocity of approximately 7 cm per year at the time of development in both the pubarche and thelarche pathways, values which are more consistent with early pubertal, rather than prepubertal growth.¹⁷

In the cohort who had hormone levels evaluated, testosterone and estradiol levels were similar between the girls who had a defined pathway, and the proportion of girls in the defined pathways who had serum concentrations below the pubertal range was no different. DHEAS values, however, were clearly different between the groups, with girls in the pubarche pathway having significantly greater levels, with girls in the thelarche pathway having values similar to girls with simultaneous breast and pubic hair development.

Although some authors have used the terms “adrenarche” and “pubarche” interchangeably, adrenarche refers to the (re)activation of the adrenal zona reticularis for production of androgens, and pubarche refers to the clinical appearance of pubic hair. Indeed, in Turner’s syndrome, there appears to be dissociation between adrenarche and pubarche.¹⁸ Similarly, the terms “gonadarche” and “thelarche” have been used interchangeably, although gonadarche refers to the pubertal reactivation of the hypothalamic-pituitary-gonadal axis and thelarche refers to the appearance of breast tissue.

Typically, adrenarche occurs earlier than gonadarche. Some authors believe that adrenal androgens may be one of the factors necessary for the reactivation of the hypothalamic-pituitary-gonadal axis.⁶ Of interest, the majority of authors consider thelarche as the marker of the onset of puberty in girls^{1–5} and that appearance of pubic hair does not represent the true onset of puberty.¹⁹ The data presented in this manuscript suggest that pubarche actually may represent the onset of true puberty in a substantial proportion of girls. This conclusion is based on the observations that height velocity data and age at development of secondary sexual characteristics are similar. Girls in the thelarche pathway, indeed, are marginally younger than those in the pubarche pathway, among black participants. Although several older papers note the majority (72–85%) of girls had evidence of breast development before pubic hair,^{11, 20, 21} Largo noted pubic hair occurred in most girls (75%) prior to development of breast tissue.²² A more recent study, utilizing cross-sectional data from NHANES III²³ reported results similar to those presented here. In that cross-sectional study utilizing data from NHANES III, the majority of girls (65.2%) had concordant maturation of breast and pubic hair development, compared to 58.6% in the current study. Of girls who were discordant, non-Hispanic white girls were more likely to have breast development prior to pubic hair (19.7% v 14.2%), and non-Hispanic black girls were slightly more likely to have breast development first (18.5% v 17.2%).²³ Similar to an earlier study of the same population reported here,⁹ girls from the NHANES study with the thelarche pathway had greater weight and ponderosity. Prior to gonadarche (as well as in the postmenopausal period), much of the circulating estrogen is believed to be derived from the peripheral conversion within the adipocyte of adrenal androgens into estrogens.²⁴ The greater body fat for girls with initial breast development noted by both studies^{9, 23} suggests greater estrogen to androgen activity which could be mediated through increased aromatase activity derived by the greater volume of adipocytes.^{25, 26} Greater levels of DHEA-S noted in pubarche girls is consistent with this premise, since these girls would have lower

aromatase activity and require greater adrenal androgen levels for comparable estrogen levels.

This study did not examine separately those girls with premature adrenarche or premature thelarche, since the youngest girls were age 9 at recruitment into the study, an age which is greater than the accepted definition for either diagnosis. Premature adrenarche is the precocious appearance of pubic hair, which, traditionally, is onset of pubic hair prior to age 8,²⁷ but more recently has been recommended to be defined as black girls younger than 5, and white girls younger than 7 years of age.^{2, 6, 28} Distinction of premature adrenarche from normal puberty through the pubarche pathway is important for several reasons. Premature adrenarche is considered a risk factor for later development of insulin resistance and polycystic ovarian syndrome, particularly when associated with low birth weight,⁸ as well as for mood disturbances such as anxiety, and more behavior problems.^{7, 29}

There are several potential limitations to this study. Eligibility requirements included ages 9 and 10 at time of recruitment, and a substantial proportion of the 10 year old girls already had entered puberty (33% of white, and 69% of black participants),¹⁰ and were thus excluded from these analyses. Among those 9 years of age at the time of recruitment, however, 41 white participants (6.7%) and 116 black participants (21.4%) were excluded because they were too physically mature to determine the pathway of entry into puberty; this may have led to some bias. Observations conducted at more frequent intervals might have established a thelarche or pubarche pathway for a greater proportion of the participants. Additionally, although more sensitive assays available for hormone analysis might have led to different outcomes for hormone values; more sensitive assays would be unlikely to change the outcomes of higher DHEAS in the pubarche group. Similarly, because all estradiol, and nearly all testosterone levels were above the limit of detection, there should be no differences in testosterone or estradiol levels because of low assay sensitivity. Indeed, with use of more sensitive hormone assays, as well as expansion of the definition of puberty to include those with growth velocities in the pubertal range, one might be able to re-classify girls in the 6–12 months prior to the appearance of secondary sexual characteristics as “pubertal” on the basis of sex hormones and growth velocity. Lastly, although one could propose that girls in the thelarche pathway were misidentified as having breast development rather than greater deposition of fat in the chest area, since they had greater percent body fat than those with pubarche, this study utilized areolar maturation, which appears to distinguish breast maturation from fat deposition in early puberty better than the traditional Tanner breast staging system.¹²

In conclusion, these data demonstrate that girls within a race had similar ages of onset of secondary sexual characteristics whether they had thelarche or pubarche first, although girls in the thelarche pathway matured slightly earlier, and had greater proportion of body fat at the time of puberty. As noted by many authors, black participants matured earlier than white. Growth velocities at the time of thelarche and pubarche were in the pubertal range, and similar between pathways. Estradiol and testosterone levels were similar, but DHEAS levels were significantly greater for girls in the pubarche pathway. This study suggests that pubarche, pubic hair development without breast development, may represent true pubertal maturation.

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Table 1

Age at onset of puberty, in years, by race and pathway

Race	Pathway	
	Thelarche	Pubarche
White		
Years (+/- SD)	9.91 (0.07)	9.96 (0.10)
	N = 183	N = 89
Black		
Years (+/- SD)	9.04 (0.12)	9.42 (0.10)
	N = 100	N = 105

Race difference $p < 0.0001$; pathway difference $p = 0.025$; race by pathway interaction $p = 0.055$

Table 2

Mean geometric hormone concentrations with 95% confidence levels (CI), at onset of puberty, by pathway, controlled for race

	Pathway		P value
	Thelarche	Pubarche	
DHEA-S, ng/ml (micromol/L)	614 (1.66)	974 (2.62)	.004
[95% CI]	[500, 756]	[773, 1230]	
Testosterone, ng/dL (micromol/L)	8.11 (.281)	11.7 (.406)	.37
[95% CI]	[5.49, 12.0]	[7.55, 18.1]	
Estradiol, pg/ml (pmol/L)	8.62 (31.5)	7.28 (26.6)	.46
[95% CI]	[6.92, 10.8]	[5.69, 9.32]	

Table 3

Body fat (+/- standard deviation) at onset of puberty, and one year prior to onset of puberty, by race and pathway

Pathway	% Body fat at onset of puberty		% Body fat one year prior to onset	
	White	Black	White	Black
Thelarche	23.0 +/- 8.2	25.4 +/- 10.0	20.2 +/- 7.9	20.2 +/- 8.0
Pubarche	18.3 +/- 5.5	17.0 +/- 6.3	17.2 +/- 5.6	14.8 +/- 4.7

See text for statistical comparisons.