Early Adiposity Rebound and Premature Adrenarche

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Objectives To examine differences in the growth pattern and the age at adiposity rebound (AR) between children with premature adrenarche (PA) and their healthy peers (controls).

Study design In this cross-sectional study of 82 prepubertal children with PA and 63 controls, the main outcome measures were height and body mass index SDS progression, from birth to presentation at the clinic, baseline biochemical and hormonal evaluation, bone age determination, and age at AR.

Results Children with PA were significantly taller and more adipose than controls from the first years of life. 33% of children with PA presented the growth pattern of constitutional advancement of growth (ie, early growth acceleration) vs 19% of controls ($P = .045$). Children with PA had an earlier AR compared with controls; mean age at AR in girls with PA was 3.73 (1.03) years vs 4.93 (1.36) years for control girls ($P = .001$) and in boys with PA was 3.45 (0.73) vs 5.10 (1.50) years in control boys ($P = .048$). Both obese and nonobese girls with PA were taller and had earlier age at AR compared with nonobese controls.

Conclusions Early AR and constitutional advancement of growth may be triggering factors for adrenal androgen production and PA. *(J Pediatr 2017;186:72-7).*

The term adrenarche refers to the maturation of the *zona reticularis* of the adrenal cortex, and it is marked by an increase in serum dehydroepiandrosterone and dehydroepiandrosterone sulfate (DHEAS) levels, occurring at approximately 5-8 years of age (biochemical adrenarche). It defines the onset of juvenility, a life history stage associated with programming/predictive adaptive responses of body composition to the environment.[1]

The adrenal androgen rise before puberty is responsible for pubarche, which is the appearance of pubic hair, apocrine odor, and acne (clinical adrenarche) after the age of 8 years in girls and 9 years in boys. Here, we define premature adrenarche (PA), as part of premature juvenility,[2] as pubarche before age 8 or 9 years for girls and boys, respectively. Idiopathic PA is multifactorial including genetic predisposition and history of intrauterine growth retardation, whereas adipose tissue excess seems to be involved as well.[3] Although PA may occur in nonobese children, there is a significant association between PA and obesity.[4,5]

The growth of children with PA has been studied extensively. Children with PA have an above average body height, somewhat advanced bone age (BA), accerelated linear growth,[6-8] and changes in body composition, such as an increase in percentage total body fat.[9] Pubertal timing may be normal or slightly advanced, and final height is usually normal.[10] However, the growth pattern from birth until diagnosis and the role of adiposity has not been well documented.

Recently, it was reported that girls with PA present accelerated growth starting in early childhood.[11,12] We have suggested that girls with PA may present with early adiposity rebound (AR).[12] Indeed, German et al[13] found that AR could be detected in approximately one-half of children and that children with AR had earlier and faster puberty than those with no evident AR.

The aim of this study was to examine the growth pattern, from birth until diagnosis, and the age at AR of children with PA. Moreover, we examined differences in the growth pattern and age at AR, and the role of adiposity in PA.

Methods

The study group was composed of 82 unrelated children (66 girls, 16 boys) of Greek origin with PA, who were consecutively examined in our pediatric endocrinology clinic from September 2011 to December 2014. None of the children with PA had signs of virilization other than those associated with PA (ie, pubic and/or axillary hair, acne, apocrine odor, or any chronic disease). We also studied 63

AR	Adiposity rebound	HSDS	Height SDS
BA	Bone age	IGF	Insulin-like growth factor
BMI	Body mass index	PA	Premature adrenarche
BMISDS	Body mass index SDS	TH	Target height
CAG	Constitutional advancement of growth	THSDS	Target height SDS
DHEAS	Dehydroepiandrosterone sulfate	17OHP	17*OH*-progesterone

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The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.03.058

(48 girls, 15 boys) age-matched normal children with no secondary sex characteristics that served as controls. Control children presented to our outpatient clinic mainly for thyroid evaluation (usually mild elevation of thyroid-stimulating hormone levels) that, with the appropriate laboratory investigation, proved to be normal.

In each patient and control subject, height and weight were measured at presentation, whereas data on body height and weight at birth and at every age recorded until diagnosis were taken from their personal health records. Growth measurements (mostly once every 6 months or once a year) registered in the health records were usually taken by the child's pediatrician. Target height (TH) was calculated by measuring the height of both parents.

We calculated height SDS (HSDS), body mass index (BMI) SDS (BMISDS), and target height SDS (THSDS) with the use of an auxology calculator (Pharmacia, Stockholm, Sweden) using the British growth data. To examine the child's height in relation to her/his parents' height, we calculated the difference (Δ) between HSDS and THSDS (SDS is also known as z score). Pubertal development was assessed according to the Tanner criteria, and only prepubertal children were included in the study (ie, girls had absence of breast development and boys had testicular volume of ≤3 mL). In children with PA, BA at diagnosis was assessed by the Greulich and Pyle method.[14]

The growth pattern of patients and controls from birth to presentation was analyzed. Age at AR was determined visually after plotting each child's BMI on a BMI chart. The lowest BMI value that was followed by an increase in BMI was considered as the age at adiposity or BMI rebound.[13]

For categorizing a child as obese or nonobese, we adopted the World Health Organization definition of childhood obesity as BMISDS or z score >2 reported to be equivalent to BMI 30 kg/m^2 at 19 years. Thus, according to their BMISDSs, children with PA were categorized as obese (BMISDS ≥2) or nonobese (BMISDS <2).

We also calculated the percentage of PA and control children that presented the growth pattern of constitutional advancement of growth (CAG). CAG, the mirror image of constitutional delay of growth, is characterized by early growth acceleration.[15] Children with CAG are born with an average length but present growth acceleration soon after birth, reaching a zenith percentile in the first 2 to 4 years of life; then the child grows along this centile until the onset of puberty, which is usually early.[16,17] For a child to be considered as presenting the CAG growth pattern, other conditions that lead to early growth acceleration, like genetic tall stature, overfeeding, and history of intrauterine growth restraint have to be excluded. A child was designated as presenting the CAG growth pattern if at the time of diagnosis the ΔHSDS-THSDS was ≥1.5.

The study was approved by the Ethics Committee of "Attikon" University Hospital, and an informed consent was obtained from the parents of the children participating in the study.

Blood samples for baseline biochemistry and adrenal androgens were obtained, after an overnight fast, between 7 and 9 am. Baseline serum glucose, insulin, lipid profile, insulin-like growth factor (IGF)-1, DHEAS, Δ4-androstenedione, and 17*OH*-progesterone (17OHP) were measured. DHEAS was measured by solid phase, competitive, chemiluminescent immunoassay (Diagnostic Products Corporation, Los Angeles, California), with a sensitivity of 30 ng/mL, intra-assay coefficient variation 6.8%-9.5%, inter-assay coefficient of variation 8.1%-15%, and 8%-15% of total variability. Δ4-A was measured by enzyme-linked immunosorbent assay (IBL GmbH, Hamburg, Germany) with theoretical sensitivity of 0.03 ng/mL and coefficient of 4.7%-9.1% for intra-assay and 9.6%-12% for inter-assay variability. 17OHP values were determined by RIA (Bio Source Europe SA, Nivelles, Belgium) with a sensitivity of 0.05 ng/mL and coefficient of 4.3%-8.1% for intra-assay and coefficient of 7.5%-9.5% for inter-assay. Testosterone was measured by Micro particle enzyme Immunoassay (Abbott Laboratories [Diagnostic Divisions] Chicago, Illinois) with a sensitivity of 0.1 ng/mL and a total coefficient of variation of 6%-13.7%. IGF-1 z score was determined by the online calculator tool.[18]

Statistical Analyses

Results are presented as mean (SD) or as frequency (%). The Kolmogorov-Smirnov test was used to assess normality for the distribution of continuous variables. The Student *t* test was used to compare the mean of PA and control participants at the time of diagnosis for the following continuous measures: presentation age, gestational age, birth weight, BMISDS, HSDS, THSDS, age of AR, BA, DHEAS, and IGF-1 SDS. The statistical difference between the mean HSDS and BMISDS at each year of age was calculated from birth onward between the 2 groups. To test whether 2 qualitative variables were related, we used the χ^2 test. The Pearson correlation coefficient was used to assess the linear association between 2 quantitative variables and linear regression was used to assess growth and BMISDS patterns in the 2 groups of interest. To investigate variables that might affect HSDS, we used multiple linear regression adjusting for potential predictors/confounders, such as BMI, indicator for PA, sex, CAG, birth length, etc. To allow for possible nonlinear associations between height and HSDS with age, we used semiparametric regression in R statistical software ([R Foundation for Statistical Computing, Vienna, Austria] with the libraries mgcv and spm). Such an approach allows the estimation of a smooth function of height or HSDS on age, without assuming that this function has a particular functional form, while it is implemented using the penalized splines techniques. Statistical significance was defined as a 2-sided *P* value of <.05. Statistical analysis was performed with SPSS for Windows v 17.0 (SPSS Inc, Chicago, Illinois) and R statistical software.

Results

Characteristics of the children with PA and control children are shown in **Table I**. Only 1 girl of the PA and 1 girl of the control children were small for gestational age. Gestational age, growth measures at birth (body length, weight), and TH were not statistically different between PA and control children.