Biopsychological and Cognitive Differences in Children With Premature vs On-Time Adrenarche

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Background: Puberty consists of 2 components: gonadarche and adrenarche. Both components have distinct endocrine changes. Adrenarche has virtually been ignored with respect to examining hormone-behavior relations.

Objectives: To provide descriptive biological and behavioral information on children with premature adrenarche (PA) and to examine differences in biological, psychological, and cognitive variables of children with PA and a healthy comparison group of children with on-time adrenarche.

Design: Descriptive pilot study.

Setting: A consecutive sample of patients was recruited from pediatric endocrine clinics; comparison children were recruited from the community.

Participants: Children aged 6 to 9 years. Mean (±SD) age of children with PA (n = 9) was 7.8 (±1.3) years; of children with on-time adrenarche (n = 20), 8.0 (±1.2) years.

Methods and Measures: Serum and saliva samples were collected for measurement of hormone concentrations. Questionnaires, tests, and interviews were completed by children and parents.

Results: Compared with the on-time group, the PA group had significantly higher concentrations of adrenal androgens, estradiol, thyrotropin, and cortisol. By parent report on the Diagnostic Interview Schedule for Children, 4 children (44%) met diagnostic criteria for psychological disorders (primarily anxiety disorders). The PA group also had more self-reported depression and parent-reported behavior problems and lower scores on various intelligence tests.

Conclusions: Although PA is considered a normal variation of pubertal development that warrants no medical intervention, PA presents with significant psychosocial problems. Children with PA may need psychological evaluation and follow-up. Future studies should confirm these findings with a larger sample and examine the long-term ramifications of this early presenting abnormality.


Editor's Note: This pilot study provides intriguing data about the perhaps not-so-benign nature of premature adrenarche. Stay tuned.

Catherine D. DeAngelis, MD

Hormonal Changes of puberty have long been implicated as a causative factor in mood and behavior changes exhibited during adolescence. During the past decade, several studies have examined relations of physical development and/or hormone-behavior links in various populations of adolescents. Most of these studies have focused primarily on behavior of adolescents and increased gonadal hormone levels of puberty (eg, testosterone, estradiol [E2]) and their concurrent external physical manifestations (eg, breast and genital development).

Also of import are the few studies that have examined behavior problems in children with precocious puberty (PP). Children with PP enter puberty much earlier than the norm, as evidenced by breast development before 8 years of age in girls and genital development before 9 years of age in boys. Children with PP also exhibit the characteristic pubescent endocrine profiles. Although the behavior of these children is understudied, there is some evidence that 6- to 11-year-old girls with PP have more internalizing and externalizing behavior problems. Specifically, these girls show more aggressive behavior and
SUBJECTS AND METHODS

DESIGN AND SUBJECTS

The cross-sectional pilot study enrolled subjects from the population of children seen in pediatric endocrine clinics from Children’s Hospital of Pittsburgh or the Department of Pediatrics of Allegheny General Hospital, both in Pittsburgh, Pa. The study was approved by the Institutional Review Board of cooperating institutions. Parents provided informed consent, and the children provided assent. The sample of children included a group of 6- to 9-year-old boys and girls referred to the clinic to determine whether their early pubic hair growth was benign and due to PA or whether it was abnormal and due to an endocrinopathy. Children met the previously described criteria of onset of pubic hair before 8 years of age in girls and 9½ years of age in boys and onset of pubic hair preceding any breast or genital development. All medical evaluations yielded negative findings; that is, the diagnosis of congenital adrenal hyperplasia or adrenal tumor was ruled out. At the first site, children undergoing their initial endocrine work-up to confirm PA were considered for recruitment. Eight children were eligible during the study, and all but 1 child agreed to participate during the recruitment phase. At the second site, 12 eligible children had already completed their diagnostic work-up, which confirmed PA. Two of the 12 agreed to participate. The consent rate was lower at the second site because these children had already undergone their clinical work-up for PA and thus the necessary venipuncture. Most of the nonconsenting parents of these children did not want their child to have additional venipuncture for research purposes only.

A total of 9 children with PA completed the protocol. The study included 8 girls and 1 boy, not unlike the sex distribution of PA of 10 to 1 reported in the literature.33 Seven children were white, and 2 were African American. Unless otherwise indicated, data are given as mean (±SD). Table 1 describes the chronological age, pubertal stage, and bone age for the PA sample. As anticipated, all children had stage 2 or 3 pubic hair development. For breast development, 4 girls were at stage 1; 3 girls, stage 2; and 1 girl, stage 3. In the 1 boy, both testes were retracted and estimated to be 3 to 4 cm³. Some children had moderately advanced bone age. Mean age of subjects in the PA group was 7.8 (±1.3) years. On average, children with PA were 133.4 (±10.2) cm in height and 35.0 (±14.2) kg in weight. Percentiles for height and weight were 77.8 (±24.1) and 82.1 (±16.4), respectively.

The on-time adrenarche group (n = 21) was recruited from the community using advertisements in newspapers, notices on bulletin boards, and word of mouth. Data from 1 African American boy were not used, because results of his physical examination indicated stage 2 pubic hair. He was referred to the pediatric endocrine clinic to rule out an endocrinopathy. Thus, our sample of 20 children with on-time adrenarche included 8 girls and 12 boys. Fourteen were white and 6 were African American. The mean age of the children with on-time adrenarche was 8.0 (±1.2) years. Age differences between the PA and on-time adrenarche groups were not significant (t₁₀ = −0.41; P = .68). All children with on-time adrenarche were at stage 1 breast or genital and pubic hair development. Boys had a mean testicular volume within the prepubertal range (2.3 ± 0.3 cm³). There were significant gender differences for height and weight in the on-time adrenarche group (t₁₁ = 2.9; P = .01). On average, compared with girls, boys were taller (132.1 ± 6.6 vs 123.0 ± 7.5 cm) and heavier (29.9 ± 3.3 vs 25.2 ± 4.2 kg). In the subsample of girls, on average, those with PA were taller (133.7 ± 11.0 vs 123.0 ± 7.5 cm; t₁₁ = 2.24; P = .04) and heavier (36.1 ± 15.0 vs 25.2 ± 4.2 kg; t₁₁ = 1.98; P = .07) than the girls with on-time adrenarche. Children were from low- to middle-class families as designated by Hollingshead socioeconomic status (SES) scores³⁶ of 38.6 (±14.7) and 44.3 (±20.4) in the PA and on-time adrenarche groups, respectively. There were no group differences in social class (t₁₂ = −0.75; P = .46).

PROCEDURES

For site 1, once the pediatric endocrinologist confirmed the diagnosis of PA, clinic nurses obtained parental permission to be contacted by telephone by 1 of us (L.D.D.). The parents then received an explanation of the study by the investigator. For site 2, a recruitment letter was sent out by the collaborating pediatric endocrinologist (D.R.). The consent form was mailed to families who expressed further interest. A return telephone call was placed to answer questions and to schedule the visit, if so desired.

In preparation for the visit, children provided 1 saliva sample at home (Tₐ) at approximately noon on the day of testing. Children underwent evaluation in the General Clinical Research Center of the local children’s hospital on an outpatient basis, where 3 additional saliva samples and 3 blood samples were obtained. The visit began at approximately 1:30 PM, when the first clinic saliva sample was obtained (T₁). The intravenous catheter was then placed, and the first blood sample was drawn (T₂). Parallel saliva samples were obtained, and serum samples were collected from the same catheter, 20 minutes (T₃) and 40 minutes (T₄) later. After serum and saliva sampling was completed, the child was provided with a snack and a short break. A physical examination was then conducted by a nurse practitioner or nurse practitioner student trained in the procedures. The examination included characterization of secondary sexual characteristics using the criteria of breast and pubic hair development for girls and genital and pubic hair development for boys.³⁷,³⁸ Testicular volume was obtained using an orchidometer. Psychological and cognitive testing followed for the child. Parents completed a medical and psychosocial history pertaining to the child, family demographic information, and various psychological and behavioral measures on their child.

BIOLGICAL MEASURES

Adrenal Androgens

Serum samples were assayed for DHEA, DHEAS, and Δ⁴-A. All assays were run in duplicate. The DHEAS and Δ⁴-A were stored at −70°C, and the assays were run in a batch. The DHEA samples were run in the clinical research laboratory as the children enrolled in the study.
Levels of DHEA were determined using radioimmunoassay (RIA) with tritiated DHEA and charcoal separation. Kits were purchased from Wien Laboratories, Inc (Succasunna, NJ). The sensitivity of the assay is 1.39 nmol/L. Intra-assay coefficients of variation (CV) were 3.6%, 2.8%, and 3.2% at low, medium, and high concentrations, respectively. Interassay CV were 12.4%, 7.8%, and 11.1% at low, medium, and high concentrations, respectively.

Levels of DHEAS were determined using RIA (Diagnostic Products, Los Angeles, Calif). Level of detection for the assay was at 0.02 µmol/L. The intra-assay CV ranged from 0.03% to 4.8%, with a mean of 1.58%. Interassay CV ranged from 8.7% at 0.01 µmol/L to 7.7% at 0.35 µmol/L.

Levels of D4-A were determined using RIA (Coat-A-Count, Los Angeles). The minimal detectable dose of this assay was 1.4 nmol/L, and the laboratory has observed an interassay CV of 8.8% and intra-assay CV of 3.0%.

**Estrogen**

Levels of E2 were measured using an ultrasensitive recombinant cell bioassay that can measure extremely low concentrations. Samples were centrifuged, stored in polypropylene tubes at −70°C, and assayed in 2 batches. The sensitivity of the assay is 0.07 pmol/L (0.02 pg/mL). Interassay and intra-assay CV were 13% and 15%, respectively, at concentrations of 0.00734 nmol/L (0.002 ng/mL). All samples were run in duplicate.

**Thyroid Measures**

Levels of thyrotropin (TSH) and free thyroxine (T4) were measured with the Wallac Delfia System (Wallac, Inc, Gaithersburg, Md) using a time-resolved fluorimunoassay. The reportable range for TSH was 30.0 to 324,000 µIU/L. The T4 reportable range was 0.2 to 6.0 ng/dL. Interassay CV for TSH ranged from 6.67% at low concentrations to 4.9% at high concentrations. For T4, the interassay CV ranged from 7.8% at low concentrations to 7.6% at high concentrations.

The method of determination for TSH and T4 was changed at the point of entry of our last 2 subjects. We used a commercially available automated clinical immunoassay analyzer with magnetic separation assays (Technicon Immuno-1 System Methodology, Bayer Diagnostics, Tarrytown, NY). The TSH assay is a heterogeneous sandwich magnetic separation assay with an analytical range of 0.00003 to 0.015 µIU/L and for T4, a heterogeneous competitive magnetic separation assay with an analytical range of 0.0013 nmol/L (0.1 ng/dL) to approximately 99.7 pmol/L (7.75 ng/dL). Interassay CV for TSH ranged from 7.9% at low concentrations to 2.6% at high concentrations. For T4, CV ranged from 7.1% at low concentrations to 3.9% at high concentrations. Samples of TSH and T4 were run in the clinical research laboratory as the children enrolled in the study.

**Cortisol**

Serum and saliva cortisol levels were determined using RIA (Coat-A-Count). Sensitivity is 0.8 nmol/L. Intra-assay and interassay CV average less than 5% and 10%, respectively. Samples were stored at −70°C. All assays were run in duplicate.

**PSYCHOLOGICAL AND COGNITIVE MEASURES**

The Diagnostic Interview Schedule for Children (DISC-2.3P) is a highly structured clinical interview, designed to be administered by a trained lay interviewer. Questions involve broad inquiries about the presence of a behavior; specific questions about duration, intensity, frequency, and impairment; and questions assessing age at onset, degree of impairment with current episode, context in which current symptoms may have occurred or been exacerbated, and need for or receipt of any treatment interventions. In general, the DISC-2.3P items parallel the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised requirements for diagnosis. The interview was administered by 1 of us (L.D.D. or S.F.H.) or by graduate students trained in the interview. Parents were the reporters for the DISC-2.3P interview. Children in our sample were younger than the suggested age to be interviewed with this instrument.

The Child Behavior Checklist (CBCL) is a self-administered, parent-reported measure designed to record in a standardized format the behavioral problems and competencies of children aged 4 to 16 years. The CBCL contains 118 behavior problem items and 20 social competence items. The following subscales can be determined: 4 social competency scales (Activity, Social, School, Competence); 8 behavioral problem scales (Withdrawal, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent, and Aggressive); and 3 composite scales (Internalizing, Externalizing, and Total Problems). For each subscale, T scores (mean, 50 ±10) based on age- and sex-related norms can be obtained. This instrument is widely used and has very good reported reliability and validity.

Children’s Depression Inventory is a 27-item, self-rated, symptom-oriented scale that has been designed to require only minimal reading ability. Symptoms addressed include disturbed mood, hedonic capacity, vegetative functions, self-evaluation, and interpersonal behaviors. Each item offers 3 choices for response, with higher scores indicating increasing severity. The Children’s Depression Inventory has undergone lengthy psychometric examination. Reported α coefficients for internal consistency reliability ranged from .71 to .89, depending on the nature of the test sample. For this sample, α = .71.

State Trait Anxiety Inventory for Children consists of two 20-item self-report inventories that measure trait and state anxiety. For I inventory, subjects rate on a scale of 1 to 3 (1 indicates hardly ever; 3, often) how self-descriptive each statement is in general (trait). For the other inventory, subjects describe, again on a scale of 1 to 3, how they feel at the moment (state). In this sample, α coefficients were .77 and .87 for state and trait anxiety, respectively.

Weschler Intelligence Scale for Children–Revised (WISC-III) is a standardized intelligence test for children and adolescents. The summary scores have a mean of 100 ±15). Subtests have a mean of 10 (±3) and include Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Coding. The internal consistency reliability coefficients for the subscales range from .70 for Object Assembly to .86 for Vocabulary; coefficients for summary scores are .94 for state and .95 for trait.
Verbal Scale IQ, .90 for Performance Scale IQ, and .96 for Full Scale IQ.12 The WISC-III was administered by 1 of us (L.D.D.).

STATISTICAL METHODS

Distributions were examined for normality using the interquartile range, as described by Tukey.26 Departure from normality (eg, an outlier) was defined as scores greater than an interquartile range of 3 from the 25th or the 75th quartiles. Cortisol, 

E, and Δ4-A were not normally distributed and therefore were logarithmically transformed. The T scores of the CBCL were used as computed. Due to the inequality in sex distribution for the PA group, we were unable to conduct a 2-factor (group and sex) analysis of variance. Thus, the first step was to examine sex differences in our dependent variables within the on-time adrenarche group. If sex differences were not significant, we then combined boys and girls in the analysis. In addition, the scores from the 1 boy with PA were examined against the descriptive statistics of the girls with PA. The boy was not an outlier based on our criteria, except for the Delinquency subscale on the CBCL. Therefore, his data were included in the analyses. Level of significance was set at P<.10 for this exploratory pilot study. Actual P values are reported to assist the reader in the interpretation of results.

<table>
<thead>
<tr>
<th>Patient No./</th>
<th>Breast or</th>
<th>Pubic Hair</th>
<th>Bone Age, SD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/Age, y</td>
<td>Genital Stage</td>
<td>Stage</td>
<td>Age, y*</td>
</tr>
<tr>
<td>1/F/8.4</td>
<td>2</td>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td>2/F/7.9</td>
<td>1</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>3/F/8.6</td>
<td>3</td>
<td>3</td>
<td>10.5</td>
</tr>
<tr>
<td>4/F/6.3</td>
<td>1</td>
<td>2</td>
<td>7.8 at 6.2</td>
</tr>
<tr>
<td>5/F/6.3</td>
<td>1</td>
<td>2</td>
<td>7.8 at 5.8</td>
</tr>
<tr>
<td>6/F/7.9</td>
<td>2</td>
<td>2</td>
<td>11.0 at 7.8</td>
</tr>
<tr>
<td>7/F/6.1</td>
<td>2</td>
<td>3</td>
<td>7.8 at 6.0</td>
</tr>
<tr>
<td>8/M/8.5</td>
<td>1</td>
<td>2</td>
<td>9.5</td>
</tr>
<tr>
<td>9/F/8.9</td>
<td>1</td>
<td>2</td>
<td>7.0 at 8.1</td>
</tr>
</tbody>
</table>

* On some occasions, bone age was obtained before psychological testing. Thus, the age obtained is reported if it differed by 1 month or more.

depressive symptoms, and they are more socially withdrawn compared with peers matched by age, sex, social class, and race.15 In an adolescent sample of girls with a history of PP, 7 of the 16 girls (mean age, 17.5 years) had psychiatric diagnoses, and parents reported greater behavior problems compared with control subjects.13,14 Thus, in these studies, hormone levels have been implicated in behavior, but there also may be a socioenvironmental component to behavior.

More important, most of the aforementioned studies have focused on pubertal changes in adolescents; ie, those in the second decade of life. In the case of the PP group, however, these studies include children younger than adolescents but with physiological changes characteristic of adolescents in puberty. The entire endocrine system is altered during puberty. Whereas staging of puberty is defined by gonadarche (breast and pubic hair development), adrenarche and gonadarche are components of puberty that reflect progressional development of the breast, external genitalia, and sexual hair. Adrenarche (awakening of the adrenal glands) occurs from ages 6 to 9 years. In boys and girls in adrenarche, the adrenal androgen levels begin to rise,15 while the gonadal axis continues to be quiescent. Such early hormonal increases in the adrenal axis are generally not accompanied by any external physical changes. Although the mechanism of adrenarche is controversial, recent evidence16 suggests corticotropin may play a significant role in regulation of adrenarche. The second component of puberty is called gonadarche and is the time the gonadotropin-releasing hormone pulse generator is reactivated17,18 and maturation of the gonads occurs. Gonadarche begins at approximately age 9 or 10 years in girls and shortly thereafter in boys. Maturation of the gonadal axis is accompanied by breast and genital development. Adrenarche and gonadarche are thought to be independent events controlled by different mechanisms.19

To date, the early part of puberty, ie, adrenarche, has been virtually ignored with respect to examining hormone-behavior relations. These early hormonal changes of adrenarche may provide activating influences for behavioral development. Furthermore, biological transitions (eg, puberty) have been proposed as a potential time of risk for vulnerable individuals.8,20,21 Thus, adrenarche is 1 component of a biological transition yet to be carefully examined in conjunction with behavior.

The rationale for studying hormone-behavior links, in particular, adrenal androgens, is supported by studies of animal models,22,23 including humans. Recently, 3 programs of research have focused on adolescents and the adrenal androgens and how those hormones may relate to behavior.1,3-5,8-10 Adrenal androgens such as dehydro-3-epiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenedione (Δ4-A) are weaker androgens and therefore thought to be less likely to influence behavior. Concentrations of these adrenal androgens also continue to increase across gonadarche until approximately 20 years of age. Hormones other than adrenal androgens also have been implicated in mood and behavior. For example, estrogen was found to be related to mood in adolescent girls24 and in adult women with premenstrual mood disorders25 or those in perimenopause or menopause,26,27 whereas in depression, the thyroid axis28,29 and the hypothalamic-pituitary-adrenal axis30,31 have been reported to be dysfunctional and may influence mood. Thus, because of the potential relationship of hormones to behavior, we included hormones from the adrenal, gonadal, and thyroid axes in our study.

In light of recent literature on hormone-behavior relations in adolescents, we sought to extend the research into an understudied area, that is, to children in adrenarche, when adrenal androgen levels are rising. To capitalize on the endocrine changes unique to adrenarche, we included not only a group of healthy children with

Table 1. Pubertal Stage and Bone Age in Children With Premature Adrenarche

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on-time adrenarche but a group of same-aged children with premature adrenarche (PA). Premature adrenarche is defined by evidence of pubic hair in girls younger than 8 years and boys younger than 9½ years.31-33 Premature adrenarche results from early activation of adrenal androgen synthesis. In PA, the concentration of adrenal androgens is higher than in age-matched control children. This concentration may be equivalent to the later part of adrenarche as defined by Korth-Schutz.34 Adrenal androgen synthesis is part of adrenarche as defined by Korth-Schutz.34 Adrenal androgens characterize the transition to adulthood.32-34

Adrenal Androgens

Serum concentrations were significantly higher in the PA group compared with the on-time adrenarche group for DHEA, DHEAS, and Δ4-A.

RESULTS

BIOLOGICAL PROFILE

Descriptive statistics and statistical test results for the hormone concentrations by group appear in Table 2. There were no significant sex differences in the on-time adrenarche group for any of the hormone measures.

Adrenal Androgens

Serum concentrations were significantly higher in the PA group compared with the on-time adrenarche group for DHEA, DHEAS, and Δ4-A.

Table 2. Hormone Concentration Differences Between Children With Premature and On-Time Adrenarche

<table>
<thead>
<tr>
<th>Measure</th>
<th>Groups, Mean ± SD</th>
<th>On-Time Adrenarche</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA, nmol/L</td>
<td>PA</td>
<td>11.41 ± 8.55</td>
<td>2.33 ± 1.35</td>
<td>4.62</td>
<td>25 &lt;.001</td>
</tr>
<tr>
<td></td>
<td>Adrenarche</td>
<td>23.22 ± 13.85</td>
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<td></td>
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<tr>
<td>DHEAS, µmol/L</td>
<td>PA</td>
<td>0.29 ± 0.16</td>
<td>0.09 ± 0.06</td>
<td>4.75</td>
<td>24 &lt;.001</td>
</tr>
<tr>
<td></td>
<td>Adrenarche</td>
<td>0.52 ± 0.34</td>
<td></td>
<td></td>
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<tr>
<td>Δ4-A, nmol/L</td>
<td>PA</td>
<td>4.97 ± 2.71</td>
<td>0.87 ± 0.42</td>
<td>7.27</td>
<td>24 &lt;.001</td>
</tr>
<tr>
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<td>Adrenarche</td>
<td>1.23 ± 0.35</td>
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<td></td>
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</tr>
<tr>
<td>4-A, nmol/L</td>
<td>PA</td>
<td>8.08 ± 14.32</td>
<td>0.66 ± 0.66</td>
<td>4.66</td>
<td>25 &lt;.001</td>
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<tr>
<td></td>
<td>Adrenarche</td>
<td>0.93 ± 0.42</td>
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<td></td>
</tr>
<tr>
<td>E2, pmol/L</td>
<td>PA</td>
<td>2.6 ± 1.4</td>
<td>1.6 ± 0.8</td>
<td>2.36</td>
<td>25 .03</td>
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<tr>
<td></td>
<td>Adrenarche</td>
<td>1.1 ± 0.6</td>
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<tr>
<td>TSH, mU/L</td>
<td>PA</td>
<td>0.01 ± 0.02</td>
<td>0.02 ± 0.002</td>
<td>-1.41</td>
<td>25 ≥.10</td>
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<tr>
<td></td>
<td>Adrenarche</td>
<td>0.01 ± 0.02</td>
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<tr>
<td>Saliva cortisol, nmol/L†</td>
<td>PA</td>
<td>17.65 ± 12.47</td>
<td>5.99 ± 2.01</td>
<td>3.80</td>
<td>23 .03</td>
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<td>Adrenarche</td>
<td>4.17 ± 2.37</td>
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<tr>
<td>Serum cortisol, nmol/L†</td>
<td>PA</td>
<td>16.42 ± 22.70</td>
<td>4.17 ± 2.37</td>
<td>2.71</td>
<td>27 .01</td>
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<tr>
<td></td>
<td>Adrenarche</td>
<td>15.73 ± 17.66</td>
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</tr>
<tr>
<td>cortisol, nmol/L†</td>
<td>PA</td>
<td>15.73 ± 17.66</td>
<td>6.62 ± 6.35</td>
<td>1.93</td>
<td>27 .06</td>
</tr>
<tr>
<td></td>
<td>Adrenarche</td>
<td>10.25 ± 5.19</td>
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<tr>
<td>Free T4, nmol/L</td>
<td>PA</td>
<td>20.54 ± 28.90</td>
<td>6.16 ± 6.59</td>
<td>1.94</td>
<td>27 .06</td>
</tr>
<tr>
<td></td>
<td>Adrenarche</td>
<td>16.42 ± 22.70</td>
<td></td>
<td></td>
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</tbody>
</table>

*PA indicates premature adrenarche; DHEA, dehydro-3-epiandrosterone; DHEAS, DHEA sulfate; Δ4-A, androstenedione; E2, estradiol; TSH, thyrotropin; T4, thyroxine; T0, baseline measurement; T20, 20-minute measurement; and T40, 40-minute measurement.

To normalize the E2 concentration, a logarithm transformation was used. The PA group had significantly higher concentrations of E2 than the on-time adrenarche group.

Thyroid Measures

The PA group had significantly higher concentrations of TSH compared with the on-time adrenarche group. We examined the individual concentrations of the last 2 subjects whose thyroid measures were run using a different method to determine if that may have influenced the results. Concentrations of TSH for these 2 subjects were within 0.5 SD of those of the remaining children with PA. No statistical differences were evident for T4 concentrations.

Cortisol

Compared with the on-time adrenarche group, the PA group had greater concentrations of salivary cortisol for T0, T20, T30, and T40 samples. For serum cortisol, the PA group had greater concentrations compared with the on-time adrenarche group from the T0 sample only.

Table 3. Differences in Anxiety and Depression in Children With Premature and On-Time Adrenarche

<table>
<thead>
<tr>
<th>Measure</th>
<th>Groups, Mean ± SD</th>
<th>On-Time Adrenarche</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>State anxiety (T score)†</td>
<td>PA</td>
<td>46.6 ± 9.2</td>
<td>44.4 ± 7.3</td>
<td>0.68</td>
<td>27 &gt;.10</td>
</tr>
<tr>
<td></td>
<td>Adrenarche</td>
<td>56.2 ± 11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait anxiety (T score)†</td>
<td>PA</td>
<td>56.2 ± 11.6</td>
<td>48.7 ± 12.0</td>
<td>1.59</td>
<td>27 &gt;.10</td>
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<tr>
<td></td>
<td>Adrenarche</td>
<td>56.2 ± 11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PA indicates premature adrenarche. For an explanation of T score, see the “Psychological and Cognitive Measures” subsection in the “Subjects and Methods” section.

†Sex differences were noted in the On-Time group. When the subgroup of girls was analyzed, no differences were noted between girls with PA and on-time adrenarche.

RESULTS

Estradiol

To normalize the E2 concentration, a logarithm transformation was used. The PA group had significantly higher concentrations of E2 than the on-time adrenarche group.

PSYCHOLOGICAL AND COGNITIVE PROFILE

Descriptive statistics for the psychological and cognitive measures appear in Table 3, Table 4, and Table 5. Sex differences in the on-time adrenarche group were noted only in trait anxiety (ie, higher scores for girls).

Diagnostic Interview Schedule for Children

On the parent-reported DISC-2.3P, 4 (44%) of 9 children in the PA group received 1 or more psychiatric diagnoses. Three of those 4 children had a diagnosis of simple phobia, and 1 child had a diagnosis of primary nocturnal enuresis. One of the 3 children with simple phobia had concurrent diagnoses of social phobia, agoraphobia, overanxious disorder, and general anxiety disorder. In the on-time adrenarche group, only 1 child received a very recent diagnosis of secondary enuresis and
simple phobia, both of which seemed to be precipitated by several simultaneous, severe stresses in the family (eg, parent leaving, sibling with terminal illness).

State Trait Anxiety Inventory for Children

There were no significant sex differences in state anxiety in the on-time adrenarche group. However, for trait anxiety in the on-time adrenarche group, girls had higher anxiety. We then ran a group comparison using only girls and found no statistical differences for state or trait anxiety between girls in the PA group and girls in the on-time adrenarche group.

Children's Depression Inventory

The PA group reported higher levels of depression compared with the on-time adrenarche group. No children were above the depression cutoff point for a raw score of 20 as suggested by Kovacs.44

Children's Behavior Checklist

For the group comparisons using t tests, the PA group had significantly higher scores than the on-time adrenarche group for the subscale scores on Withdrawal, Social Problems, Aggressive, and Somatic Complaints, as well as on the broad band scores of Internalizing, Externalizing, and Total Problems. There were no group differences in any of the 4 competence scores.

Weschler Intelligence Scale for Children–III

Using an analysis of covariance model controlling for social class, unexpected group differences were found on the WISC-III. The PA group had significantly lower scores on the subtests of Arithmetic, Information, Vocabulary, and Block Design as well as Verbal Scale and Full Scale IQ, compared with the on-time adrenarche group.

Table 4. Differences in Parent Report of the Child Behavior Checklist T Scores Between Children With Premature and On-Time Adrenarche*

<table>
<thead>
<tr>
<th>Subscale</th>
<th>PA</th>
<th>On-Time Adrenarche</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive</td>
<td>55.1 ± 6.9</td>
<td>51.4 ± 4.0</td>
<td>1.83</td>
<td>.08</td>
</tr>
<tr>
<td>Anxious-depressed</td>
<td>55.4 ± 9.4</td>
<td>52.2 ± 5.1</td>
<td>1.18</td>
<td>.26</td>
</tr>
<tr>
<td>Attention</td>
<td>54.5 ± 5.8</td>
<td>51.4 ± 4.4</td>
<td>1.55</td>
<td>.10</td>
</tr>
<tr>
<td>Delinquent</td>
<td>56.9 ± 10.3</td>
<td>52.0 ± 4.9</td>
<td>1.71</td>
<td>.09</td>
</tr>
<tr>
<td>Thought problem</td>
<td>56.1 ± 7.3</td>
<td>52.3 ± 5.6</td>
<td>1.52</td>
<td>.10</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>56.8 ± 8.5</td>
<td>51.4 ± 3.4</td>
<td>2.42</td>
<td>.02</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>56.9 ± 10.4</td>
<td>51.3 ± 3.9</td>
<td>2.13</td>
<td>.04</td>
</tr>
<tr>
<td>Social problems</td>
<td>54.9 ± 6.2</td>
<td>50.9 ± 2.6</td>
<td>2.50</td>
<td>.02</td>
</tr>
<tr>
<td>Internalizing</td>
<td>52.6 ± 13.5</td>
<td>42.5 ± 9.9</td>
<td>2.20</td>
<td>.04</td>
</tr>
<tr>
<td>Externalizing</td>
<td>54.1 ± 9.7</td>
<td>42.8 ± 9.6</td>
<td>2.83</td>
<td>.01</td>
</tr>
<tr>
<td>Total behavior problems</td>
<td>53.5 ± 11.9</td>
<td>40.3 ± 10.7</td>
<td>2.86</td>
<td>.01</td>
</tr>
<tr>
<td>Activities</td>
<td>44.3 ± 7.9</td>
<td>47.2 ± 6.8</td>
<td>−0.97</td>
<td>.33</td>
</tr>
<tr>
<td>Competence</td>
<td>50.9 ± 24.2</td>
<td>54.8 ± 17.8</td>
<td>−0.48</td>
<td>.63</td>
</tr>
<tr>
<td>Social competence</td>
<td>46.2 ± 7.7</td>
<td>48.5 ± 7.3</td>
<td>−0.78</td>
<td>.44</td>
</tr>
<tr>
<td>School</td>
<td>54.3 ± 18.9</td>
<td>54.2 ± 16.3</td>
<td>0.01</td>
<td>.99</td>
</tr>
</tbody>
</table>

*PA indicates premature adrenarche. For an explanation of T score, see the “Psychological and Cognitive Measures” subsection in the “Subjects and Methods” section. The df is 26 for all comparisons.

Table 5. Differences in the Standard Scores of the Weschler Intelligence Scale for Children–Revised Between Children With Premature and On-Time Adrenarche*

<table>
<thead>
<tr>
<th>Measure</th>
<th>PA</th>
<th>On-Time Adrenarche</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picture completion</td>
<td>9.9 ± 2.4</td>
<td>11.9 ± 4.2</td>
<td>1.1</td>
<td>.26</td>
</tr>
<tr>
<td>Information</td>
<td>10.1 ± 3.0</td>
<td>13.0 ± 3.3</td>
<td>5.3</td>
<td>.03</td>
</tr>
<tr>
<td>Coding</td>
<td>10.3 ± 3.6</td>
<td>12.2 ± 3.1</td>
<td>1.9</td>
<td>.10</td>
</tr>
<tr>
<td>Similarities</td>
<td>10.9 ± 4.9</td>
<td>13.8 ± 3.8</td>
<td>2.6</td>
<td>.10</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>11.0 ± 3.8</td>
<td>10.5 ± 4.2</td>
<td>1.6</td>
<td>.10</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>8.6 ± 4.1</td>
<td>12.4 ± 3.6</td>
<td>5.9</td>
<td>.02</td>
</tr>
<tr>
<td>Block design</td>
<td>9.0 ± 3.8</td>
<td>12.4 ± 5.2</td>
<td>3.5</td>
<td>.07</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>9.9 ± 3.4</td>
<td>12.8 ± 4.0</td>
<td>6.3</td>
<td>.02</td>
</tr>
<tr>
<td>Object assembly</td>
<td>9.0 ± 3.7</td>
<td>10.7 ± 3.3</td>
<td>0.9</td>
<td>.37</td>
</tr>
<tr>
<td>Comprehension</td>
<td>11.1 ± 4.6</td>
<td>10.9 ± 4.1</td>
<td>0.5</td>
<td>.55</td>
</tr>
<tr>
<td>Digit span</td>
<td>11.3 ± 4.2</td>
<td>12.2 ± 2.8</td>
<td>0.2</td>
<td>.64</td>
</tr>
<tr>
<td>Verbal Scale IQ</td>
<td>99.9 ± 21.4</td>
<td>116.2 ± 19.1</td>
<td>4.6</td>
<td>.04</td>
</tr>
<tr>
<td>Performance Scale IQ</td>
<td>99.3 ± 16.6</td>
<td>110.6 ± 20.8</td>
<td>1.5</td>
<td>.10</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>99.3 ± 19.0</td>
<td>114.7 ± 20.7</td>
<td>3.9</td>
<td>.06</td>
</tr>
</tbody>
</table>

*PA indicates premature adrenarche. Analysis of covariance was performed for each variable, controlling for socioeconomic status based on the Hollingshead score. The F value for main effects is reported. The df is 2, 26 for all comparisons.

COMMENT

PSYCHOLOGICAL AND COGNITIVE DIFFERENCES

Our pilot study provides some of the first descriptive information on the psychological and cognitive profiles of children in adrenarche. In particular, we show group differences on many of these measures in children with PA compared with children in on-time adrenarche. Very early reports showed that children with PA were essentially normal, but some cited studies with an increased incidence of mental retardation.49,50 We found that, compared with peers in on-time adrenarche, children with PA had more psychological abnormalities that met diagnostic criteria, more self-reported depressive symptoms, more behavior problems, and lower cognitive functioning when controlling for SES. However, from an endocrine perspective, children in the PA group represent outliers in the normal distribution of puberty. These children are not considered abnormal from an endocrine perspective, and they are not treated therapeutically for PA. Typically, after their endocrine evaluation, they are followed up 6 months to 1 year later to determine if pubertal advancement has occurred.

With respect to anxiety, children's self-report state or trait anxiety did not show that children with PA had higher scores, although there was a trend for differences. It is particularly concerning, however, that the rate of anxiety disorders was so high in the PA group, as reported by parents on the DISC-2.3P. Anxiety disorders may affect as many as 10% of children and may be one
of the most common psychiatric disorders in this age group. The PA group may be more at risk for current anxiety disorders and future mental health problems as well. Several investigations have reported that the risk for development of major depressive disorder was increased in those with preexisting anxiety disorders. The risk for anxiety disorders may occur before an episode of depression and continue beyond an episode of depression. There were no diagnoses of major depressive disorder in our subjects. The incidence of major depression is thought to be lower in prepubertal age children, and that may contribute to the lack of diagnosis of depression in our sample. Children with PA had higher scores on the Children’s Depression Inventory than children with on-time adrenarche, although the subgroup of girls did not. No children scored above the suggested cutoff point of 20. Whether children with PA and anxiety disorders experience depression at a later point remains an empirical question. Furthermore, across development, children and youth experiencing comorbid psychiatric disorders have more negative outcomes (eg, more severe psychological abnormalities, increased suicidality, or poorer response to treatment) than those without comorbidity.

The role, if any, that higher concentrations of adrenal androgens may play in the psychological abnormalities in children with PA is unknown. Adrenal androgens are weak androgens, compared with testosterone. However, adrenal androgens are precursors of the more potent estrogens and testosterone, and they are considered neurosteroids. These more potent gonadal steroids have been shown to influence the brain. In particular, hormones of ovarian origin can influence neurotransmitters implicated in anxiety. More recently, Reddy and Kulkarni have illustrated that DHEAS prompted an anxiogenic response in a stress paradigm in a mouse model.

Children in the PA group also had significantly more behavior problems as reported by their parents on the CBCL. Scores were in the clinical range in 3 children in the PA group, including the subscales of Somatic Complaints, Withdrawal, Anxious/Depressed, Delinquent, and Total Problems. Two children in the on-time adrenarche group scored in the clinical range (≥2.5 SD) on Thought Problems, Anxious/Depressed, or Total Problems. These behavior problems exhibited by the PA group include internalizing and externalizing behaviors not unlike those reported for children with precocious puberty. One should keep in mind that PP represents a pathological diagnosis with increased gonadal steroid levels and external changes of puberty (eg, breast, genital), where medical intervention is indicated. Alternatively, PA represents a variant of normal puberty with increasing adrenal androgen levels that require no treatment.

Similarities in behavior of these children with PA can be seen in the study by Hayward et al., showing that internalizing symptoms were more likely to develop in young adolescent girls with earlier maturation, and girls with the onset of internalizing symptoms were earlier developers (average, 5 months) compared with girls without internalizing symptoms. However, earlier maturation in their study refers to gonadarche and not adrenarche, and the assessment was performed using self-ratings rather than physical examinations. In our study, whether the endocrine profile of children with PA is causing or contributing to their behavior cannot be determined. In particular, the direction of effects cannot be identified. However, studies of mood and behaviors in adolescents and the relation to adrenal androgen levels have provided the groundwork for testing such hypotheses. Our pilot study supports the need for further empirical investigations in this younger group.

Our reported group differences favoring the on-time adrenarche group on a number of the subtests and Full Scale IQ of the WISC-III were unexpected. However, group means show an average IQ. In our analyses, we adjusted for SES based on reports in the literature that IQ tests may be biased toward a higher SES. Brooks-Gunn et al. also reported that economic and social differences contributed a high percentage of the variance in IQ, thus eliminating racial differences in IQ of 5-year-old children. In our study, children with PA scored significantly lower on Arithmetic, Information, Vocabulary, and Block Design subscales as well as the summary scores for Verbal Scale and Full Scale IQ. Conflicting evidence exists regarding the role that pubertal maturation may play in cognition. Noss et al. hypothesized that spatial abilities would be less in girls with PA. Results indicate that IQ scores were within the reported average range. The older group of girls (n = 6) with past PA scored lower on performance IQ and the spatial task of the Primary Mental Abilities compared with the younger girls (n = 7) with present PA. No differences were noted on Verbal Fluency. Our study sample had active PA and thus cannot be directly compared with the subjects studied by Noss et al.

Most of the literature on cognitive abilities discusses sex differences. Since our sample had a restricted sex distribution, we were limited in making parallel interpretations. In addition, we are limited because we do not have a full cognitive battery that examines verbal and spatial abilities. We did consider the notion that cognitive differences may have been influenced by behavioral differences in these children. That is, from a more normative perspective, more behavioral problems could influence attention to cognitive tasks and in turn decrease performance. In the on-time adrenarche group, this was the case. Numerous subtests of the WISC-III were negatively correlated with behavior problems. However, in the PA group, CBCL behavior problem scores were not related to scores on the WISC-III. Thus, the lower scores on the WISC-III for the PA group may truly represent a central problem.

**BIOLOGICAL DIFFERENCES**

As anticipated, children in the PA group had higher concentrations of adrenal androgens compared with the on-time adrenarche group. The elevation of cortisol levels in the PA group compared with the on-time adrenarche group is of interest. The higher concentration of gluco-
corticoid precursors that define PA may fuel the production of cortisol, which is the end product. We did not measure corticotropin levels to see if there was a difference in endogenous stimulation between both groups. Alternatively, the increased concentrations of cortisol in the PA group may be related to the underlying anxiety disorders in that the PA group may respond to a greater degree in potentially stressful situations. In addition, chronic stress and hence chronic activation of corticotropin-releasing hormone could trigger PA. History of sexual abuse may be associated with hypothalamic pituitary adrenal axis dysfunction, and we cannot rule out this factor as being influential in our study. Increased hypothalamic pituitary adrenal activity also has been associated with low birth weight, but our sample of PA children did not have lower birth weight than the comparison group.

We also found differences in concentrations of E2. All but 1 girl had prepubertal concentrations of E2. The higher concentration of E2 in the PA group is intriguing given the fact that only recently has technology permitted us to measure concentrations of this hormone in prepubertal children. More important, these concentrations are below the level thought to influence target tissues such as the breast, and presumably below the level thought to influence the brain and, hence, behavior or cognition. Unlike Klein et al, we did not find sex differences in concentrations of E2 in these prepubertal children with on-time adrenarche. This could be due to our limited sample size.

The difference in TSH levels is somewhat puzzling and was not accompanied by a difference in free T4 levels. Concentrations of both these hormones were within the normal clinical range and thus, the differences may hold no significance; particularly since free T4, the biologically active hormone, showed no group differences. Alternatively, the subtle elevation of TSH levels for the PA group may reflect alterations in the circadian rhythm of secretion of TSH, which surges at night and peaks in the early morning. It is unlikely that patients with PA have adrenal insufficiency, which is known to elevate TSH levels. Whereas glucocorticoids are known to have effects on TSH secretion, there are no data on whether the elevated precursors of glucocorticoids can have the same effect. The relation of these hormone differences to psychological and cognitive factors remains to be tested.

**LIMITATIONS**

Our exploratory pilot study is limited by the small sample size and the restricted sex distribution. Multiple statistical tests were conducted with a liberal P value. However, this is the first study to examine hormones in conjunction with psychological and cognitive changes in PA and comparison groups. More important, the cause (hormonal) and effect (behavior) cannot be determined from this study design. Numerous other social and environmental cues may contribute to these group differences in behavior and cognition along with other potential biological factors. Alternatively, behaviors may be altering the hormonal milieu.

**CLINICAL IMPLICATIONS**

Our pilot study has clinical implications and provides important information for future studies. Future studies should confirm these findings with a larger sample and examine the long-term ramifications of this early presenting psychological abnormality. However, even without definitive information on the link between PA and psychosocial problems, mental health professionals should be aware of the importance of a physical examination for children exhibiting behavior problems and psychological abnormalities. Although Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnostic criteria for mood disorders generally are not met when there is an underlying physiological problem (eg, an endocrine disorder), mental health professionals may be less likely to consider a physiological problem in children who are presumed to be healthy. In turn, they may be less likely to refer for a medical evaluation. Alternatively, those in primary care practices and pediatric endocrine clinics should be aware that behavior disturbances may be an important issue for children with PA as well as their families. Parents should be asked about their child’s moods, behavior, and performance in school. Children should be questioned as well. Appropriate referrals for evaluation of behavior problems and mood disturbances may be warranted. Given what is reported in the literature about negative outcomes of early puberty, such referrals may be important. Already there is recent concern that children with PA may have long-term sequelae suggestive of exaggerated ovarian and androgen synthesis, an increased incidence of functional ovarian hyperandrogenism with hirsutism and oligomenorrhea, and an increased occurrence of polycystic ovary and insulin resistance. Concern within the medical arena regarding the long-term sequelae of patients with PA should be joined by vigilance in the psychological-cognitive arena as well.

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