The pattern of gonadotropin and estradiol secretion in exaggerated thelarche

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Purpose: To assess the dynamics of the pituitary-ovarian axis in exaggerated thelarche, defined as premature thelarche associated with signs of systemic estrogen effects (advanced bone age and/or growth acceleration) without progression to complete puberty. Subjects and methods: Seven girls (age <2.5 years) with exaggerated thelarche, 6 girls with inactive pituitary-ovarian axis (premature thelarche) and 21 girls with activated axis (central precocious puberty) had serum FSH, LH and E2 measured serially before and 1 to 24 h after gonadotropin-releasing hormone agonist (GnRHa) administration (leuprolide, 20 µg/kg sc), used as a test of combined pituitary-ovarian stimulation. Results: Although girls in the exaggerated thelarche and adenarche group had similar [mean (SEM)] baseline FSH [3.2 (0.9)] vs 1.4 (0.3) IU/l], LH [0.36 (0.1) vs 0.27 (0.02) IU/l] and E2 [20 (1.2) vs 21 (2) pmol/l] concentrations, and similar peak post-GnRHa LH concentrations [5.5 (1.1) vs 2.4 (0.5) IU/l], girls with exaggerated thelarche achieved higher peak FSH [41 (9) vs 14 (3) IU/l, p<0.01] and E2 [243 (40) vs 37 (6) pmol/l, p<0.001] concentrations after GnRHa. In comparison to patients with exaggerated thelarche, girls with precocious puberty had higher (p<0.01–0.001) baseline LH [3.6 (0.8) IU/l], baseline E2 [69 (11) pmol/l], GnRHa-stimulated peak LH [68 (17) IU/l] and peak E2 [648 (58) pmol/l] concentrations, but similar FSH parameters. Conclusions: Girls with exaggerated thelarche exhibit substantial E2 secretory potential that can be demonstrated by GnRHa stimulation, is predominantly FSH-driven, and probably accounts for the manifestations of estrogen effect seen in these girls.

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The clinical features of premature thelarche, including non-progressive breast development and absence of systemic estrogen effects on growth and bone maturation (1, 2), differentiate this entity from central precocious puberty (3). In response to GnRH stimulation, FSH predominates over LH in girls with premature thelarche, while LH predominates over FSH in girls with precocious puberty (4).

During the last few years, we have encountered a new variant of precocious sexual maturation, whose characteristics are intermediate between those of premature thelarche and those of central precocious puberty, as described by Stanhope and Brook (5). The aim of this study was to assess the pituitary-ovarian interactions and determine the estradiol secretory potential in this condition (hereofore referred to as “exaggerated thelarche”). To this end, we assessed the FSH, LH and estradiol response to the acute administration of a single dose of GnRH agonist, used as a biological probe of the pituitary-ovarian axis (6, 7), in seven girls with exaggerated thelarche. For comparison, we studied a group of girls of prepubertal age with inactive hypothalamic-pituitary-ovarian axis and a group of girls with central precocious puberty and activated axis.

Subjects and methods
Seven young girls (age <2.5 years) referred to the Pediatric Endocrinology Division between 1988 and 1991 for premature breast development had a combination of features that we considered atypical for simple premature thelarche. These features included: (a) in 5 of 7 subjects, a substantial amount of breast tissue (uncompressed diameter > 5 cm, compressed diameter > 3 cm), with moderately firm, glandular-like consistency rather than the soft, smooth consistency generally observed in idiopathic premature thelarche; (b) in every subject, either an advanced bone age at the time of the initial evaluation or a relative increase of the bone age to chronological age ratio (BA/CA) upon re-evaluation 6–12 months later; (c) in 2 of 7 subjects, accelerated growth [height velocity > 2 sd scores (SDS) for age]; (d) in 4 of 7 subjects, enlarged ovaries (ovarian volume > 2 SDS for age); (e) stage II pubic hair in one subject. These
patients differed, however, from girls with central precocious puberty, as they showed no progression or regression of breast development, decrease in growth velocity and no increase of the ΔBA/ΔCA ratio after 12–24 months of observation. The ovarian volume remained above normal in two patients at 12–24 months.

For comparison, we studied two groups of girls with prepubertal and pubertal hypothalamic–pituitary–gonadal axis, respectively. The first group (inactive or prepubertal axis) consisted of five girls with premature adrenarche and one girl with isolated vaginal bleeding subsequently found to be secondary to trauma, none of whom showed evidence of breast development during a follow-up period of at least six months. The second group (activated or pubertal hypothalamic–pituitary–gonadal axis) consisted of 21 girls with central precocious puberty. This was defined as progressive breast development starting before age 8 years, associated with bone age advancement and/or pubic hair development, and with evidence of pubertal LH secretion [peak LH value > 10 IU/l following GnRH agonist stimulation (see below)]. Because of ethical and practical limitations, we were unable to test a prepubertal group of the same age as the girls with exaggerated thelarche. For the sake of simplification, the two comparison groups will be referred to as “adrenarche” and “puberty” in this paper. Finally, we measured baseline, but not GnRH-stimulated, hormone concentrations in a group of six girls with idiopathic, typical premature thelarche.

All subjects had normal T4, TSH and prolactin concentrations. Serum DHEA-sulfate concentrations were low in girls with exaggerated thelarche [0.5 (0.14) μmol/l] and were appropriate for age or clinical condition (adrenarche) in the other groups. A computerized tomography (CT) scan with contrast or magnetic resonance imaging (MRI) of the brain and pituitary gland was normal in all index patients, except for the equivocal finding of asymmetrical pineal enhancement by gadoxilin on MRI in patient A (Table 2). Three of 21 girls with central precocious puberty had MRI findings consistent with a hypothalamic hamartoma. All subjects were studied with written parental consent, under a protocol previously approved by the Institutional Review Board of St Louis University.

### Methods

Length (in children less than 3 years of age) and height were measured with a horizontal or vertical stadiometer, respectively. Height velocity (HV) and HV SDS were calculated from the data of Tanner et al. (8). Pubertal staging was performed according to Tanner (9). The ovarian volume was measured by sonographic technique, and related to normative data for age (10). The bone age was read by a single observer [LRG] according to the Tanner–Whitehouse-2 radio–ulna–short bone (TW2 RUS) method, which best reflects the maturation of the sex-hormone dependent areas (11).

The GnRH agonist (GnRHa) stimulation test was used as a combined test of pituitary–ovarian function in the three groups of subjects. The rationale for this procedure is that GnRHa induces FSH and LH release, which in turn stimulates ovarian E2 secretion in girls with activated hypothalamic–pituitary–ovarian axis (6, 7). After a baseline blood sample was obtained, the GnRHa leuprolide acetate ([D-Leu6, des-Gly-NH210]. Pro-ethylamide')-GnRH; LuponTM, TAP Pharmaceuticals, Abbott Park, IL) was injected subcutaneously at the dose of 20 μg/kg between 06.00 and 09.00, and blood samples were collected serially for up to 24 h after the injection, for measurement of serum FSH, LH and E2 concentrations. The dose of leuprolide was chosen after preliminary comparison studies with a traditional GnRH test (unpublished data) and with a stimulation test employing a different GnRHa (7) indicated this amount of drug to induce a robust and prolonged gonadotropin and E2 stimulation.

Nocturnal serum gonadotropin measurements were carried out in 3 of 7 index patients, in 4 of 6 patients with prepubertal hypothalamic–pituitary–gonadal axis and in 9 of 21 patients with pubertal axis, by collecting blood samples every 30 min from 22.00 to 06.00 via an indwelling intravenous line. Mean and peak nocturnal serum LH concentrations, as well as mean FSH concentrations, were used for statistical analysis.

Serum LH concentrations were measured by a previously described sensitive immunoradiometric assay (IRMA), with a midrange intra- and interassay coefficient of variation (CV) of < 5%, and a limit of detection of 0.25 IU/l (1st LH IRP 68/40 units) (12). Serum FSH concentrations were also measured by IRMA (FSH MALA Clone. Serono/Ciba Corning, Medfield, MA), with intra- and interassay cvs of 5.4 and 8.2%, respectively, and a limit of detection of 0.5 IU/l (2nd IRP 78/549 units). Serum E2 levels were measured by a sensitive RIA in extracted (Hexane:Ethylacetate 3:1) serum samples with reagents purchased from ICN Diagnostics (Costa Mesa, CA). The detection limit was 18 pmol/l, the intra- and interassay cvs were 7.5 and 16%, respectively. The percent recovery of E2 in the RIA was consistently 87–95%. The normal range for prepubertal girls 2–8 years of age was < 0.5 IU/l for LH, < 0.5–5 IU/l for FSH, and < 30 pmol/l for E2.

### Statistical analysis

Analysis of variance (ANOVA), followed by post-hoc Scheffe’s test, was used to determine the differences between the groups. Because of unequal variance, hormonal concentrations were log-transformed before statistical analysis (13). All data (including clinical and hormonal data) are given as mean (±SEM), unless otherwise specified. Values below the limit of sensitivity were attributed a value equal to the limit of sensitivity of the respective assay, for statistical purposes. The Statview and SuperANOVA statistical software programs for the
Table 1. Clinical characteristics and bone age data.

<table>
<thead>
<tr>
<th></th>
<th>Premature adrenarche</th>
<th>Typical prem. thelarche</th>
<th>Exaggerated thelarche</th>
<th>Precocious puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.5 (0.6)</td>
<td>1.8 (0.3)</td>
<td>1.6 (0.2)b</td>
<td>7.4 (0.4)</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>8.6 (0.6)</td>
<td>1.9 (0.2)</td>
<td>2.5 (0.3)b</td>
<td>10.9 (0.4)</td>
</tr>
<tr>
<td>Height SDSa</td>
<td>+1.9 (0.5)</td>
<td>−0.2 (0.5)</td>
<td>+0.7 (0.3)</td>
<td>+1.7 (0.3)</td>
</tr>
<tr>
<td>Height velocity SDSa</td>
<td>+0.6 (0.5)</td>
<td>+0.1 (0.6)</td>
<td>+0.8 (0.4)c</td>
<td>+3.2 (0.3)</td>
</tr>
<tr>
<td>Tanner stage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>2.7 (0.2)</td>
<td>2.9 (0.1)</td>
<td>3.1 (0.2)</td>
</tr>
<tr>
<td>Pubic hair</td>
<td>1.9 (0.2)</td>
<td>1</td>
<td>1.1 (0.4)</td>
<td>2.3 (0.2)</td>
</tr>
</tbody>
</table>

Values are mean (SEM).
a Standard deviation score. b p<0.001 vs premature adrenarche and precocious puberty. c p<0.01 vs precocious puberty.

Table 2. Individual clinical and radiological characteristics of girls with exaggerated thelarche.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Tanner stage breast (B) and pubic hair (PH)</th>
<th>Height SDS</th>
<th>Height velocity SDS</th>
<th>Bone age advance</th>
<th>Outcome After 12 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.6</td>
<td>B3 PH1</td>
<td>+1.1</td>
<td>−0.3</td>
<td>1</td>
<td>&gt;97</td>
</tr>
<tr>
<td>B</td>
<td>1.4</td>
<td>B3 PH1</td>
<td>−1.3</td>
<td>+0.8</td>
<td>0.3</td>
<td>&gt;75</td>
</tr>
<tr>
<td>C</td>
<td>1.6</td>
<td>B3 PH1</td>
<td>−0.4</td>
<td>+0.6</td>
<td>1.1</td>
<td>&gt;97</td>
</tr>
<tr>
<td>D</td>
<td>0.75</td>
<td>B3 PH1</td>
<td>+0.2</td>
<td>+0.5</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>1.1</td>
<td>B3 PH1</td>
<td>+1</td>
<td>+2.4</td>
<td>0.5</td>
<td>97</td>
</tr>
<tr>
<td>F</td>
<td>2.3</td>
<td>B3 PH1</td>
<td>+1.2</td>
<td>+2.3</td>
<td>1</td>
<td>97</td>
</tr>
<tr>
<td>G</td>
<td>2.2</td>
<td>B2 PH2</td>
<td>+3</td>
<td>+0.5</td>
<td>1.8</td>
<td>&gt;97</td>
</tr>
</tbody>
</table>

* Standard deviation score. a According to Tanner et al. (11). b Relative advancement of bone age versus chronological age after 6–12 months of observation. c Each (+) indicates the number of sds above the average for age (10).

Table 3. Comparison of mean (SEM) baseline/nocturnal serum concentrations of FSH, LH and estradiol.

<table>
<thead>
<tr>
<th></th>
<th>Premature adrenarche</th>
<th>p value*</th>
<th>Exaggerated thelarche</th>
<th>p value*</th>
<th>Precocious puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LH (IU/l)</td>
<td>0.27 (0.02)</td>
<td>NS</td>
<td>0.36 (0.1)</td>
<td>&lt;0.01</td>
<td>3.6 (0.8)</td>
</tr>
<tr>
<td>Baseline FSH (IU/l)</td>
<td>1.4 (0.3)</td>
<td>0.10</td>
<td>3.2 (0.9)</td>
<td>NS</td>
<td>4.2 (0.4)</td>
</tr>
<tr>
<td>Baseline E2 (pmol/l)</td>
<td>21 (2)</td>
<td>NS</td>
<td>20 (1.2)</td>
<td>&lt;0.01</td>
<td>69 (11)</td>
</tr>
<tr>
<td>Mean nocturnal FSH (IU/l)</td>
<td>1.1 (0.2)</td>
<td>&lt;0.05</td>
<td>5.0 (2.6)</td>
<td>NS</td>
<td>4.4 (0.5)</td>
</tr>
<tr>
<td>Mean nocturnal LH (IU/l)</td>
<td>0.26 (0.01)</td>
<td>NS</td>
<td>0.54 (0.14)</td>
<td>&lt;0.05</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Peak nocturnal LH (IU/l)</td>
<td>0.31 (0.06)</td>
<td>NS</td>
<td>1.5 (0.8)</td>
<td>&lt;0.01</td>
<td>10.6 (2.7)</td>
</tr>
</tbody>
</table>

* p values >0.10 are reported as NS (non-significant).

Macintosh computer (Abacus Concepts, Berkeley, CA) were employed for statistical calculations.

Results

Clinical and radiological characteristics (Tables 1 and 2)

Table 1 shows the clinical and bone age characteristics of girls in the exaggerated thelarche group in comparison to the groups of adrenarchal and pubertal girls. Girls with exaggerated thelarche were younger, as expected on the basis of the selection criteria, and their growth velocity was less accelerated than that of patients with precocious puberty. In comparison to the exaggerated thelarche group, the six girls with typical premature thelarche had no acceleration of growth or osseous maturation, although the difference was non-significant. Breast tissue was soft and smooth, and compressed breast diameter was <3 cm in every girl with typical thelarche. Uterine size was normal in each patient.

Table 2 provides individual data for the patients with exaggerated thelarche. Small, bilateral ovarian cysts (1–4 cm, <6 mm in diameter, per ovary) were a consistent feature in patients of this group. This was considered a non-specific finding, as it occurs frequently in premature thelarche (14).

Baseline hormonal values (Table 3)

Serum FSH concentrations in the exaggerated thelarche group were similar to those of the puberty group and slightly, but non-significantly, higher than those of the adrenarche group (p=0.10). Conversely, serum LH
concentrations in the exaggerated thelarche group were equal to those of the adrenarche group, and were lower than those of the puberty group (p<0.01). Serum E₂ concentrations in girls with exaggerated thelarche were similar to those of adrenarchal girls and lower than those of pubertal girls (p<0.01).

In girls with typical premature thelarche, serum hormonal concentrations were similar to those of the adrenarche and exaggerated thelarche groups: LH <0.25 IU/l, FSH 3.3 (0.4) IU/l, E₂ 22 (2.5) pmol/l.

Nocturnal hormonal values (Table 3)

In girls with exaggerated thelarche, mean nocturnal FSH concentrations were higher (p<0.05) than in adrenarchal girls; mean nocturnal (p<0.05) and peak nocturnal (p<0.01) LH concentrations were lower than in pubertal girls. The number of patients who underwent nocturnal sampling was, however, small.

GnRHa-stimulated hormonal values (Figs. 1 and 2)

Following GnRHa stimulation, patients with exaggerated thelarche had a predominant FSH response, a modest LH response and an E₂ response which was intermediate between that of the adrenarche and pubertal groups, respectively (Fig. 1). The peak (post GnRHa) hormonal values in the three groups are compared in Fig. 2. Relative to the adrenarchal group, girls with exaggerated thelarche had higher peak serum concentrations of FSH (0<0.01) and E₂ (p<0.001), but similar peak LH concentrations. In comparison to pubertal girls, patients with exaggerated thelarchehad similar peak serum FSH concentrations, lower peak E₂ (p<0.001) and lower peak LH (0<0.001) concentrations. Thus, girls with exaggerated thelarche exhibited substantial E₂ secretory potential in spite of relatively low LH secretion.

Discussion

The pattern of premature sexual maturation observed in the seven index patients described in the present report was atypical for simple premature thelarche, despite the young age of the subjects. The majority of these girls had firmer and somewhat larger breast tissue than we have typically seen in premature thelarche. All patients had evidence of systemic estrogen effect, namely bone age advancement and/or growth acceleration, which are unusual, albeit not unreported, in premature thelarche (15, 16). Four of them also had marked ovarian enlargement, which is rare in premature thelarche (14, 17). However, they showed non-progression or regression of their breast development and other pubertal signs after a follow-up period of at least one year. These girls differ from most of the previously reported girls with transient sexual precocity because of their young age and/or the pattern of gonadotropin response to stimulation (18–21). Rather, they resemble the patients with atypical thelarche and growth acceleration recently described by Stanhope and Brook (5).

In girls with exaggerated thelarche, we evaluated the relationship between gonadotropin and estradiol secretion by means of the gonadotropin-releasing hormone agonist stimulation test. Previous studies in girls with premature sexual development have shown that the robust stimulating effect on the pituitary–ovarian axis achieved by a single injection of GnRHa induces an E₂ rise which is proportional to the degree of endogenous
activation of the axis (6, 7). In response to acute administration of the GnRHa leuprolide, girls with exaggerated thelarche exhibited an FSH predominant gonadotropin response, with serum peak FSH concentrations being substantially higher than those observed in older girls with premature adrenarche and prepubertal hypothalamic–pituitary–ovarian axis. The most important difference in comparison to the adrenarchal group, however, was the ability of girls with exaggerated thelarche to mount a substantial E2 response to GnRHa, in spite of the fact that their LH response to the agonist was modest and non-significantly higher than that observed in the adrenarchal girls. Thus, the index patients exhibited marked estradiol secretory capacity which seemed to be predominantly driven by FSH. Unfortunately, ethical and practical considerations prevented testing with GnRHa of age-matched, normal girls and girls with typical premature thelarche. Several studies employing traditional GnRH testing, however, have shown a greater FSH response in girls with premature thelarche than in normal prepubertal girls (15, 22–24). Thus, the high FSH levels observed in our patients may reproduce, possibly in amplified form, the pattern normally observed in simple premature thelarche.

The capacity of girls with exaggerated thelarche to secrete substantial amounts of estradiol following GnRHa stimulation was in agreement with the clinical findings of substantial breast development and advanced bone maturation in these patients. Even if one considers the supraphysiologic stimulation achieved by GnRHa, peak E2 levels in the index patients were much higher than those achieved in children with prepubertal hypothalamic–pituitary axis and approximated 50% of the values achieved by girls with central precocious puberty. This novel and unexpected finding suggests that ovarian priming by endogenous gonadotropins occurs in girls with exaggerated thelarche and subserves the increased estrogen secretory potential noted in these patients. Despite the limitations of the small number of subjects studied in the adrenarche and exaggerated thelarche groups, our findings seem to indicate that the GnRHa stimulation test may be an important tool to characterize variable patterns of activation of the pituitary–ovarian axis in young girls with sexual development.

In summary, these preliminary data suggest that exaggerated thelarche is related to activation of the hypothalamic–pituitary–ovarian axis causing a predominant increase in FSH secretion which, in turn, primes and stimulates the ovaries to secrete biologically significant amounts of E2. Inasmuch as the axis is active in utero and in the first few months of life (25–27), exaggerated thelarche may stem from delayed inactivation of the axis. The predominance of FSH secretion over LH secretion may account for the self-limited nature of this disorder, as FSH alone is unable to sustain ovarian maturation (28) despite its known simulatory effects on ovarian aromatase in vitro (29, 30).

Finally, the fact that the patients described by Stanhope and Brook (5), our patients with exaggerated thelarche and girls with typical premature thelarche exhibit overlapping clinical features, suggests that similar mechanisms may be operational in these interrelated conditions and account for the variable spectrum of E2 secretion observed in different patients.

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**References**


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