2-year-old girl with premature thelarche

Endorama
February 5, 2015
Carmen Mironovici, M.D.
Chief complaint

- Premature thelarche first noted at 21 months of age
- Patient referred to Endocrinology Clinic for evaluation
Soon after birth, she developed “milk lumps” which persisted, stable in size, during her first year of life, then regressed

January 2014 (21 mo.): “rapid” breast enlargement

May 2014 (25 mo.):
- sparse axillary hair
- accelerated linear growth
- apocrine body odor

ROS:
- No vaginal bleeding or discharge; no acne, pubic hair; no change to muscle bulk
- No exposure to tea tree oil, lavender oil, soy products, estrogen products
- No hx of head trauma, CNS infections, brain radiation
Past Medical History

**Birth history**
FT, NSVD, no complications
No hx. of SGA

**Medical history**
Acute otitis media at 6 mo.
Left hypotonia at 9 mo.
Speech delay

* **Allergies** - None

* **Social History** - Lives with both parents
  * No siblings
Family History

* Mother: 5’6”, obese, delayed puberty menarche at 16 yrs.

* Father: 5’9”, obese, delayed puberty started shaving his face at 20 yrs.

* MPH = 65 in

* No hx. of precocious puberty
Constitutional: Negative for fever, diaphoresis, activity change

Endo: premature thelarche, accelerated linear growth

HENT: Negative - no neck swelling

Eyes: Negative for redness.

Respiratory: No wheezing / stridor.

Cardiovascular: Negative for leg swelling.

Gastrointestinal: No diarrhea, constipation; no abdominal distention.

Genitourinary: No hematuria, normal urine volume.

Musculoskeletal: Negative for joint or other swelling.

Skin: No color changes, pallor and rash.

Allergic/Immunologic: Negative

Neurological: Speech delay
Physical Exam

* T 36.4 C   HR 112   RR 23   BP 88/54   Ht 94 cm (82%)   Wt 12.6 kg (26%)   BMI 14.25 kg.m2 (5%)

* Constitutional: WN, WD. No distress.
* HEENT: No dysmorphic facial features
* Eyes: Conjunctivae and EOM are normal. Pupils are equal, round, and reactive to light.
* Mouth/Throat: Mucous membranes are moist. Clear oropharynx.
* Cardiovascular: Normal rate, regular rhythm, S1 normal and S2 normal. +2 Pulses. No murmur.
* Pulmonary/Chest: CTA b/l. No respiratory distress.
* **Tanner III breast development, symmetrical. R breast bud 2.7 cm, L 2.1 cm. No breast discharge. Sparse axillary hair.**
* Abdominal: Abdomen soft, NT, ND. Normoactive BS. No organomegaly, no masses.
* GU: **Tanner I Female external genitalia/pubic hair. No clitoromegaly. Red vaginal mucosa**
* Musculoskeletal: FROM. Mild Left curvature of the thoracic spine. No edema or signs of injury.
* Skin: Warm. **3 hyperpigmented areas, flat, < 1 cm diam.,** on R arm, R upper thigh and back.
  No acne, no hirsutism, no acanthosis nigricans.
Growth chart

Weight for age

Height for age

MPH: 164.9 cm
Differential Diagnosis?
Etiology of PP in girls

Precocious puberty

Incomplete variants
- Premature thelarche
- Premature adrenarche
- Premature menarche

Complete precocious puberty

Gonadotropin independent
- Estrogenic ovarian cyst
- Estrogenic ovarian tumor
- Estrogenic adrenal tumor
- McCune Albright syndrome
- Primary hypothyroidism

Gonadotropin dependent
- Idiopathic
- Organic
- Brain tumor
  - Hypothalamic hamartoma
  - Glioma
- Congenital anomaly
  - Hydrocephalus
  - Arachnoid cyst
  - Cerebral dysgenesis
- Neurological insult
  - Infection
  - Trauma
  - Surgery
  - Radiation
- Genetic
  - Activating GPR54 mutation

Fugua JS. J Clin Endocrinol Metab. 2013
Evaluation?
Precocious Puberty Workup

- Careful history, PE
- **Laboratory Studies**
  - Basal LH, FSH, Estradiol
  - Consider GnRHa stim
  - Adrenal Androgens
  - TFTs
- **Imaging studies**
  - Bone age
  - Consider MRI brain, pituitary
  - Consider Pelvic US
### Characteristic findings in different forms of PP

<table>
<thead>
<tr>
<th></th>
<th>Height velocity</th>
<th>Bone Age</th>
<th>Sex steroids serum conc.</th>
<th>Response to GnRHa stim.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central PP</strong></td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Predominant LH</td>
</tr>
<tr>
<td><strong>Peripheral PP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>McCune-Albright</strong></td>
<td></td>
<td></td>
<td></td>
<td>Prepubertal/Suppressed LH</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>Prepubertal/Suppressed LH</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Prepubertal LH</td>
</tr>
<tr>
<td><strong>Normal variants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Premature thelarche</strong></td>
<td>N</td>
<td>N</td>
<td>Slight increase E2</td>
<td>Prepubertal LH</td>
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<tr>
<td><strong>Premature adrenarche</strong></td>
<td>N- ↑</td>
<td>N- ↑</td>
<td>DHEA-S appr. for Tanner stg</td>
<td>Prepubertal LH</td>
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</tbody>
</table>

## Initial Labs (drawn at 9:30 a.m.)

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>Units</th>
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<tbody>
<tr>
<td>LH</td>
<td>&lt; 0.2 mIU/L</td>
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<tr>
<td>FSH</td>
<td>&lt; 2.7 mIU/L</td>
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<tr>
<td>Estradiol</td>
<td>4-12 pg/mL</td>
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<tr>
<td>17-OH progesterone</td>
<td>&lt; 100 ng/dL</td>
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<tr>
<td>Androstenedione</td>
<td>&lt; 51 ng/dL</td>
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<tr>
<td>DHEAS</td>
<td>&lt; 45 ug/dL</td>
<td>&lt;15</td>
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</table>
Bone Age = 3 yr 3mo at CA of 2 yr 3mo
(1 SD for age=5.2 mo)
Assessment and Plan?
Second visit (after 3 mo.)

- **Active breast enlargement:**
  Tanner III breast development, symmetrical.
  Compressed breast tissue: R 3.0 cm, L 2.3 cm

- Stable axillary hair

- Tanner I external genitalia/pubic hair
  No menarche

- **Accelerated growth velocity:** 3.5 cm in 3 mo.
### Lupron Stim test

<table>
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<tr>
<th>time (min)</th>
<th>-10</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
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<tbody>
<tr>
<td>LH</td>
<td>&lt; 1</td>
<td>1</td>
<td>4.1</td>
<td>3.7</td>
<td>3.5</td>
<td>3.3</td>
<td>2.5</td>
<td></td>
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<tr>
<td>FSH</td>
<td>2.1</td>
<td>2.0</td>
<td>19.8</td>
<td>23.1</td>
<td>28.2</td>
<td>30.7</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120</td>
</tr>
</tbody>
</table>

**MRI Brain and Pituitary gland, WWO contrast: Unremarkable**
Central Precocious Puberty, based on:

* Early onset and progression of pubertal development

* Acceleration of growth rate and skeletal maturation

* Laboratory evidence of pubertal gonadotropin secretion
Management

- Started on Lupron-1 mo
- Will follow up in one month to assess tolerability
- Transition to Lupron-3 mo
- Closely monitor growth and pubertal status
Clinical Questions

* What controls the timing of puberty onset?
* When should CNS pathology be investigated in CPP in girls?
Neurobiology of puberty

* Pubertal onset is determined by the interplay between strong genetic determinants and a large number of regulators (endogenous and environmental), starting at very early developmental stages

Tena-Sempere M. Current topics in Developmental Biology, 2013
Clinical Questions

* What controls the timing of puberty onset?

* When should CNS pathology be investigated in CPP in girls?
Diagnosis Tree to predict CNS abnormalities in girls with CPP

Fig. 2. Diagnosis tree constructed with the pilot population to predict low or high risk of CNS abnormalities for girls with CPP. *Idiopathic CPP; †CPP revealing CNS abnormalities; ‡E2 was unknown for 9 girls (5%) with idiopathic CPP.
Female CPP is a common pediatric endocrine problem.

The genetic factors influencing pubertal onset are being actively elucidated with kisspeptin, NKB and Dyn identified as key players.

Majority of cases are idiopathic, but CNS imaging is indicated for young age and more biologically advanced puberty with high E2, LH and FSH.

Conclusions
References

* Nathan BM, Palmert MR. Regulation and disorders of Pubertal timing. Endocrinol Metal Clin N Am 34(2005) 617-641
* Ng SM, Kumar Y, Cody D, Smith CS. Cranial MRI scans are indicated in all girls with central precocious puberty. Arch Dis Child 2003; 88: 414-418