The McMaster at night Pediatric Curriculum

Objectives

Medical Expert

Review of physiology of puberty

Definition of delayed puberty

Understand differential diagnoses between males and females
Background
Background

Gonadotropin Releasing Hormone (GnRH)

- Released by hypothalamus
- Pulsatile secretion
- Stimulates release of FSH and LH
- Inhibited by testosterone, estrogen, progesterone
- In utero activity then quiescent by 6 months postnatally
Background

**Follicle Stimulating Hormone (FSH)**

- Stimulates ovarian follicular development
- Gametogenesis in the testes
- Inhibited by inhibin (made in sertoli cells of testes)
Background

**Luteinizing Hormone (LH)**

- Stimulates testosterone secretion (leydig cells)

- Luteinization of ovary – corpus luteum, ovulation

- Inhibited by androgens, estrogens
Background

**Adrenal cortex**

- Androgen production: progesterone, DHEA
- Stimulate conversion into testosterone
- Testosterone converts to estradiol
- Leads to adrenarche
  - Pubic hair, axillary hair, body odour, voice changes, acne
- Not related to HPG axis
Background

Prepubertal Development:
• Up to 8-9 years old
• GnRH secretion stops by 6 months postnatally
• GnRH secretion dormant until peripubertal stage
Background

Peripubertal Development:
• 1-3 years before clinically evident puberty
• GnRH pulsatility increases in frequency
• Low serum LH levels during sleep
• LH levels found during daytime once enter puberty
Background

**Pubertal Development – Females**

- 8-12 years old on average
- Stage 1: Thelarche
- Stage 2: Pubarche 6-12 months later
- Stage 3: Increased growth velocity
- Stage 4: Menarche (~12.5 years old)
Background

Pubertal Development – Males
• 9-14 years old

Stage 1: Testicular enlargement, thinning scrotum
  – Testes >4ml or 2.5cm

Stage 2: Pubarche

Stage 3: Penile growth, scrotum pigmentation

Stage 4: Increased growth velocity
Background

Delayed Puberty Definitions:

Female:
- No breast development by 13 years of age
- Absence of menarche by 16 years or within 5 years of pubertal onset

Male:
- Failure of maturation by 14 years of age
The Case

13.5 year old boy, previously healthy, complains of short stature and delayed sexual development. 5\textsuperscript{th} percentile for height, 10\textsuperscript{th} percentile for weight. Mom’s height is 160cm and dad’s is 172cm. Dad’s growth spurt was in college. Mom had menarche at 14 years of age.

Systemic exam is normal. Both testes are 3cc in volume and tanner stage 1 for pubic hair.
History

What would you ask?
History

HPI
• Time course of pubertal development
• Males: Gynecomastia, testicular/penile enlargement
• Females: Thelarche, leukorrhea, menarche
• Both: pubarche, growth spurts, adrenarche

PMHx
• Malignancy, radiation, chemo, surgeries
• Chronic illness
• CNS – seizures, intellectual disability
History

ROS

• Headache, visual changes, vomiting
• Sense of smell (anosmia)
• Temperature intolerance, weight, skin/hair changes, bowel movements
• Abdo mass, pain, energy levels, skin pigmentation
• Watery, fatty, loose stools
• Weight and nutritional status
History

Fam Hx:
• Maternal/paternal pubertal development
• Parental heights
• Females with infertility, hirsutism, irregular menses
• CAH, ambiguous genitalia

Medications
Allergies
Pregnancy History
Birth History
Physical Exam

What would you look for?
Physical Exam

- Growth parameters
  - Height, weight, head circumference
- Dysmorphic features
- H+N
  - Goiter, webbed neck, apthous ulcers
- Cardioresp
  - Murmur, shield chest, wide spaced nipples
- Abdo
  - Striae, skin changes, inguinal masses
- Neuro
  - Cranial nerves, reflexes, spine
- Tanner staging
Physical Exam
Physical Exam

Mid-Parental Height (MPH):

Female:
\[ \frac{[(\text{Paternal Height} - 13\text{cm}) + \text{Maternal Height}]}{2} \]

Male:
\[ \frac{[\text{Paternal Height} + (\text{Maternal Height} + 13\text{cm})]}{2} \]

Child’s height can be within +/- 5cm of calculated MPH
Workup

What would you order?
Workup

- R/o chronic illness
- LH and FSH
- Testosterone
- +/- Estradiol
- TSH, FT4
- IGF-1
- Prolactin
- GnRH stimulation test
- Chormosomal Analysis
- Imaging: CT/MRI head, Bone age, Pelvic U/S
**Differential Diagnosis**

<table>
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<td>Constitutional Delay</td>
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<tr>
<td>Isolated Gonadotropin Deficiency (IGD)</td>
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<td>Kallman Syndrome (IGD with anosmia)</td>
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<td>Functional Gonadotropin Deficiency (chronic illness, exercise, malnutrition, anorexia)</td>
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<td>Pituitary hormone deficiency (congenital panhypopituitarism, acquired panhypopituitarism i.e. CNS lesions)</td>
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<td>Genetic Syndromes (Prader-Wili)</td>
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## Differential Diagnosis

### Hypergonadotropic Hypogonadism (high FSH/LH)

<table>
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<tr>
<th>Males</th>
<th>Females</th>
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<tr>
<td>Primary Gonadal Failure</td>
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<td>Klinefelter’s Syndrome</td>
<td>Turner’s Syndrome</td>
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<td>Previous radiation</td>
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<td>Post-operative cryptochochordism</td>
<td>Autoimmune Ovarian Failure (T1DM, Addison’s, Hypothyroidism)</td>
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<td>Vanishing testes syndrome</td>
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<td>Previous mumps/orchitis</td>
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<td>Previous torsion</td>
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Constitutional Delay

- More common in boys
- Healthy
- Can also have short stature but normal growth velocity
- Bone age delayed > 2 years from chronological age
- Family history of “late bloomers”
- For boys:
  - linear growth then relative fall off the growth curve as others have their growth spurt
- For girls:
  - functional gonadotropin deficiency more common
Management

• Guided by underlying cause

• Can use short courses of testosterone or estrogen to induce puberty

• Lifelong hormone replacement may be required in some cases

• Referral to endocrine

• Ongoing follow up required to ensure progress through puberty
Test Your Knowledge

15 year old boy presents with delayed puberty and on exam has small testes and is Tanner Stage V of pubic hair.

a) Turner Syndrome  
b) Kallman Syndrome  
c) Klinefelter Syndrome  
d) Constitutional delay
The Answer

• Klinefelter’s
Klinefelter Syndrome

- 47XXY or XY/XXY
- 1/500-1/1000
- Penile enlargement at usual age
- Testes small <3cm, <6mL
- Seminiferous tubule dysgenesis from extra X
- Tall, learning/behaviour difficulties
- Infertility
Klinefelter Syndrome

- Frontal baldness absent
- Tendency to grow fewer chest hairs
- Breast development
- Female-type pubic hair pattern
- Small testicular size
- Poor beard growth
- Narrow shoulders
- Wide hips
- Long legs
Summary

• Differentiate between HPG axis and adrenarche

• Hypergonadotropic hypogonadism = gonads not responding so high FSH/LH

• Hypogonadotropic hypogonadism = gonads not stimulated so low FSH/LH

• Constitutional delay most common reason for delayed puberty in boys and functional gonadotropin deficiency in girls