Delayed Puberty

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TEEN-AGER
(Labeled for convenience)

- Weed Whacked Hair
- Look of Apathy
- Funky Teen-Ager Odor
- Sub-Standard Posture
- Wallet Chain ($200 in Wallet)
- Big-Ass Pants
Objectives

• Review normal puberty
• Definition(s) and Diagnosis of delayed puberty
• Etiologies of delayed puberty
• Treatments
Definition

Absence or incomplete development of secondary sexual characteristics by an age when 95% of children of that sex and culture have initiated sexual maturation (for girls, age 12 in US)
Girls
- Breast budding
- Growth of pubic hair
- Growth spurt
- First period (menarche)
- Growth of underarm hair
- Change in body shape
- Adult breast size

Boys
- Growth of scrotum and testes
- Change in voice
- Lengthening of the penis
- Growth of pubic hair
- Growth spurt
- Change in body shape
- Growth of facial and underarm hair
Serum LH mIU/ml

Time (clock)

Adult
Mid-Late Puberty
Early-Mid Puberty
Prepuberty

2200 0400 1000 1600 2200

Sleep

Source: Semin Reprod Med © 2003 Thieme Medical Publishers
Physical Examination

• Height, weight, arm span (serial heights best)

• Secondary sex characteristics (Tanner Staging)

• Arm span > height by 5 cm suggests delayed epiphyseal closure (hypogonadism)
The Tanner Stages of Adolescent Development

Diagram A. Stages of breast development

Diagram B. Female pubic hair development

Diagram C. Development of testes and penis
Stature-for-age percentiles:
Girls, 2 to 19 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Estrogen and Growth Plate Resorption (Epiphyseal Closure)

- Estrogen critical for closure in both men and women
- Precocious puberty therefore associated with early closure and short stature
- Biological examples: aromatase deficiency/estrogen receptor defects - growth persists into adulthood
MY Approach to Delayed Puberty

• You are going to get this question so be prepared

• Watchful waiting is almost always a good answer

• TWO GROUPS (by AGE 13)
  • Estrogen exposed (+ breast development)
  • Estrogen naive (- breast development) OR
  • High Serum FSH (Primary hypogonadism)
  • Low/normal FSH (Secondary hypogonadism)
Estrogen exposed by age 13

- Have some (any) evidence of breast development on physical examination
- No laboratory/radiographic evaluation necessary - just reassurance
- Wait for menses
- If no menses by age 16…
Breast development + No menses by age 16

- Physical examination - including ultrasound

- If on examination - either inspection or radiologic - there is no uterus, and a blind ending vagina - Draw a Serum Testosterone

- Androgen insensitivity - normal male level T

- Mullerian agenesis - normal female level T
Androgen Insensitivity

- Karyotype (46 XY)
- Androgen Receptor Defect (>400 mutations known)
- X linked recessive
- Counseling regarding gender
- Sterile
- Need gonadectomy
- Need HRT
Mullerian Agenesis (MRKH)  
(1/4500 newborn females)

- Ovaries are present
- No uterus on sonogram
- Female level T
- 46 XX
- Inheritance multifactorial (may be an autosomal dominant form)
- Think RENAL - absent, pelvic
- NO GONADAL SURGERY NEEDED
- Gestational Carrier for pregnancy
Common Problem for MRKH and AI Patients:
Reconstruction of functional vagina

- Surgical creation of neovagina
- Usually use a graft
- Call Dr Delmore
Creation of Neovagina uUsing Dilators

- Vaginal dilators
- Progressive dilatation
- 2-3 x per day to point of discomfort
- Call Dr Tjaden
Don’t Create a Vagina Until The Patient Plans to Use It!!!
Delayed Puberty
No (nada, none) Breast Development by Age 13

- FACT - the ovary is not making estrogen
- QUESTION: CAN the ovary make estrogen?
- ANSWER: Check a serum FSH
Delayed Puberty
No Breast Development by Age 13
HIGH FSH

• FACT - the ovary is not making estrogen

• QUESTION: CAN the ovary make estrogen?

• IT CANNOT

• ANSWER: Primary Hypogonadism

  • Gonadal dysgenesis - needs karyotype

  • Rarely FSH or LH receptor defects on granulosa/theca cells)
Delayed Puberty
No Breast Development by Age 13
LOW/LOW NORMAL FSH

- FACT - the ovary is not making estrogen
- QUESTION: CAN the ovary make estrogen?
  - IT CAN (presumably)
- ANSWER: Secondary Hypogonadism
  - Hypothalamic dysfunction
  - Hypopituitarism
  - Hypothyroidism
  - Hyperprolactinemia
  - Constitutional delay
Hypothalamic Dysfunction

- Functional
  - Nutritional disorders
    - Eating disorders
    - Female athlete triad
    - Chronic disease (Crohn’s)
  - Liver disease
- Anatomic
  - Craniopharyngioma, hamartoma
  - Kallman’s syndrome
  - Congenital GnRH deficiency
Laboratory Evaluation

- CBC
- ESR
- CMP
- FSH/LH
- TSH, T4 (if TSH is low because of hypothalamic or pituitary dysfunction)
- Prolactin
- Adrenal androgens (as warranted)
- Karyotype (or CGH) as warranted (Kleinfelter Syndrome in boys, Turner Syndrome in girls)
Radiographic Studies

- Bone Age (left hand and wrist) - relates chronologic age to skeletal maturation, potential for further growth, preliminary prediction of adult height
- Pelvic ultrasound
- Head MRI
TABLE 2 - Comparison of the chronological ages and the ages (years) according to the methods of Greulich, Pyle (1959), Elklif, Ringertz (1967), and Nolla (1960) – HIV* and control groups – Female sex – 1999.

<table>
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*Significantly different. Source: School of Dentistry, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre – RS.
Delayed Puberty - Age 13

Breast development?

yes no

Watchful waiting FSH?

High Low

Gonadal dysgenesis MRI

Karyotype

Rarely FSH/LH receptor defect
Craniopharyngioma

- Complex cystic mass
- Sellar/supracellar location
- Displaces or occupies third ventricle
- May present with visual and/or endocrinopathies
- Surgery/cyst aspiration/radiation
What can you expect from your evaluation?

- Constitutional delay - 30%
- Delayed but spontaneous pubertal development - 19%
  - GH deficiency, poor nutrition, or heterozygous mutations in genes associated with congenital GnRH deficiency
- Hypogonadotrophic hypogonadism - 12%
  - Often but not always permanent
- Hypergonadotrophic hypogonadism - 13%
- Unclassified - 3%
Treatments

• Target underlying disorder if identified

• Treat hypothyroidism, hyperprolactinemia, surgery for tumors

• However in most patients the distinction between congenital GnRH deficiency and Constitutional Delay remains uncertain

• Serial observations
Treatment Choices

- “Watchful Waiting vs

- Administration of gonadal steroids

  - Short term steroids may be appropriate if psychosocial concerns outweigh reassurance and education

  - Should restrict steroid therapy to boys older than 14 and girls older than 12
Short-term therapeutic goals of steroid therapy

- Attainment of age-appropriate secondary sex characteristics
- Induction of growth spurt without inducing premature epiphyseal closure (monitor bone age every six months)
- Potential induction of a “reversal” of their GnRH deficiency, whether congenital or functional
Long-term goals of steroid therapy

- Maintain normal adult serum levels of sex steroids
- Induce fertility when desired (if possible)
Estrogen therapy

- Premarin 0.3 mg daily, or even lower doses initially, increasing over two years (0.25 mg micronized estradiol, transdermal estradiol 14 mcg/day)

- NO PROGESTERONE until
  
  - substantial breast development that is not confined to the areolae and full contour breast growth has plateaued

  - Or breakthrough bleeding occurs

  - Traditional HRT (200 mg oral micronized progesterone days 1-12 of calendar month)

- After secondary sex characteristics are established, HRT can be discontinued for 1-3 month intervals to assess for ovulation

- Persistence of hypogonadism past 18 years of age = congenital GnRH deficiency
Growth Hormone Therapy

- Without documented GH deficiency, controversial
- Serum GH and IGF-1 are usually low in patients with constitutional delay of puberty, and increase in response to estrogen therapy
- Patients with congenital GnRH deficiency are not usually GH deficient and usually don’t benefit from additional GH (estrogen will evoke normal GH secretion)
Summary

• Definition - absence or incomplete development of secondary sexual characteristics by an age when 95% of children of that sex and culture have initiated sexual maturation (for girls, age 12 in US)

• Categorize patients by primary (high FSH) or secondary (low FSH) hypogonadism

• No single test reliably differentiates between constitutional delay and GnRH deficiency - focused history, physical exam - serial measurements
Summary

- History - no pubertal development vs stalled pubertal development; evidence of chronic disease (IBD), other congenital anomalies, FH of pubertal development, and sense of smell (Kallman’s Syndrome)

- PE: Tanners stages of development, height, weight, arm span

- Bone age at initial evaluation - chronological age and skeletal maturation; MRI when indicated

- Labs: FSH/LH, Prolactin, TSH and T4, CBC, ESR, CMP; Adrenal androgens and Karyotype as indicated
Summary

- Therapy - target specific disorder if identified
- Constitutional delay vs GnRH deficiency - difficult to distinguish
- GnRH stimulation test is not very sensitive in distinguishing these disorders and is rarely done
happy first period!