

# Delayed Puberty

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# Delayed Puberty

- Delayed puberty is the failure to begin sexual maturation at an age that is 2.5 SD above the mean age of the onset of puberty w/in a specific population
- Occurs in ~3% of children
- In the U.S. evaluation of delayed puberty is recommended in **girls 13 years** and in **boys 14 years** or older who do not demonstrate signs of sexual maturation
- Diagnosis is also made in the **absence of menarche by age 16** or within 5 years after the onset of puberty

# Delayed Puberty

- Testicular enlargement (diameter 2.5cm or greater) or breast budding is the first normal pubertal event in the majority of children
- *Constitutional delay of growth and puberty* is the most common cause
- Measurement of Gonadotropins (LH/FSH) helps to classify the various diagnoses
  - Elevated gonadotropins = gonadal disease or primary hypogonadism
  - Low or normal gonadotropins = hypothalamic/hypopituitary disease or secondary hypogonadism

# History

- Chronic disease symptoms
- Excessive exercise
- Anorexia/bulimia
- Family members with delayed puberty or infertility
- Birth history (congenital anomalies)
- Previous surgery, chemotherapy, RXT
- Neurologic symptoms (vision, sense of smell)
- Substance abuse
- Medications
- Head trauma

# Physical Exam

- Growth measurements
  - eunuchoid, short stature, obesity, cachexia (body wt <80% ideal weight for height)
- Sexual maturity rating (Tanner stages)
  - Testicular size  $\geq$  2.5cm (boys) or presence of breast buds (girls) indicates initiation of puberty
  - Pubic hair is not necessarily evidence that puberty has begun
  - Evaluate for microphallus (stretched penis length < 4cm)
- Thyroid exam
- Neurologic exam
  - Sense of smell, hearing, visual fields, optic discs
- Cognitive development/ Behavioral abnormality
- Physical stigmata associated with various syndromes (Turner, Klinefelter, Prader-Willi, Kallmann's)

# Tanner Staging

## **Tanner Stages of Development of Secondary Sexual Characteristics**

### **Boys – development of external genitalia**

- Stage 1: Prepubertal
- Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture
- Stage 3: Enlargement of penis (length at first); further growth of testes
- Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker
- Stage 5: Adult genitalia

### **Girls – breast development**

- Stage 1: Prepubertal
- Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
- Stage 3: Further enlargement of breast and areola; no separation of their contour
- Stage 4: Areola and papilla form a secondary mound above level of breast
- Stage 5: Mature stage: projection of papilla only, related to recession of areola

### **Boys and girls – pubic hair**

- Stage 1: Prepubertal (can see velus hair similar to abdominal wall)
- Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
- Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes
- Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
- Stage 5: Adult in type and quantity, with horizontal distribution ("feminine")

# Differential Diagnosis: *Hypogonadotropic Hypogonadism*

- Constitutional Delay of Puberty (most common)
- Congenital deficiency
  - Hereditary hypopituitarism
  - Idiopathic hypogonadotropic hypogonadism (IHH)
  - Kallmann's syndrome
  - Prader-Willi, Laurence-Moon-Biedel syndromes
  - LH and FSH receptor defects
- Acquired deficiency
  - Functional
    - Chronic disease
    - Anorexia nervosa
    - Excessive exercise
    - Hypothyroid, hyperprolactinemia
  - Anatomic
    - Pituitary tumors
    - Craniopharyngioma
  - Head Trauma
  - Drugs (opiates, marijuana)
  - Infiltrative disease

# Differential Diagnosis: *Hypergonadotropic Hypogonadism*

## ■ Congenital

- Gonadal dysgenesis
  - Klinefelter syndrome
  - Turner syndrome
- Androgen resistance (receptor defects)
- Steroidogenic enzyme defects

## ■ Acquired

- Cryptorchidism
- Radiation or chemotherapy
- Trauma/surgery
- Autoimmune or post-infectious (mumps, coxsackie)

# Diagnostic Approach

- Routine Labs: CBC, ESR, TSH, Cortisol
  - To r/o growth-retarding disorders
- Gonadotropin levels (LH/FSH)
  - Normal or low in constitutional delay and other causes of secondary hypogonadism
  - Elevated in primary gonadal failure
  - *Exception*: normal levels do NOT r/o primary hypogonadism if bone age is pre-pubertal

# Diagnostic Approach

## Constitutional Or Secondary Hypogonadism

(normal or low FSH/LH)

- Bone age (left hand and wrist film)
  - Delayed in both constitutional delay and GnRH deficiency
  - If bone age reaches 13yr in girls or 14yrs in boys without evidence of puberty, the patient almost definitely has GnRH deficiency
- Neuroimaging (MRI)
  - Evaluate for tumors of the pituitary or hypothalamus; absent olfactory bulbs and tracts/hypoplastic olfactory gyri (Kallmann syndrome)
- A child with constitutional delay carries a *presumptive* diagnosis and requires follow-up to rule out GnRH deficiency!

## Primary Gonadal Failure (elevated FSH/LH)

- Chromosome analysis to confirm Turner or Klinefelter syndromes
- Evaluation for testicular feminization syndromes (androgen insensitivity) or steroidogenic defects

# Constitutional Delay of Puberty

- Most common diagnosis
- Normal pre-pubertal growth nadir is protracted and pulsatile GnRH secretion is slow to develop
- Boys present more often than girls b/c short stature and sexual immaturity cause more psychosocial effects in males
- Family history is often positive for siblings or parents with delayed puberty
- Laboratory evaluation reveals pre-pubertal testosterone levels and low or normal gonadotropins
- Bone age is delayed
- Sexual maturity is not affected by the timing of pubertal onset, but final adult height may be less than predicted

# Characteristics of Constitutional Delay of Puberty

## ■ Before puberty

- Puberty delayed but begins before 16yr in girls and 18yr in boys
- Puberty begins before bone age 13 in girls or 14 in boys
- Height is often < 5<sup>th</sup> percentile; but growth rate is normal for skeletal age
- Onset of adrenarche is delayed
- Laboratory tests resemble hypogonadotropism
- Family history + for delayed puberty

## ■ After Puberty

- Pubertal hormonal and physical stages advance at normal temp
- Genetic height potential is often achieved

**Differentiating constitutional delay from idiopathic Hypogonadotropic hypogonadism (GnRH deficiency) is often difficult! There is no single test to distinguish between the two**

# Constitutional Delay in Puberty: *Treatment*

- Reassurance and anticipatory guidance
- Exogenous steroid course may be used in boys with overwhelming psychosocial stress associated w/ delayed puberty
  - Low dose IM testosterone given monthly increases pubic hair by 1-2 stages and growth rate by 75%
  - Low doses have not shown to have adverse effects on height potential
  - 6 month course is recommended followed by reassessment; spontaneous puberty should progress over the next 6 months
  - A second course may be helpful in extreme delay

# Idiopathic Hypogonadotropic Hypogonadism

- IHH refers to congenital isolated **GnRH deficiency** and is the functional absence of GnRH secretion from hypothalamic neurons
- Suspected if microphallus is seen at birth and confirmed by findings of incomplete (or failure of) puberty, decreased testosterone, decreased or normal LH Most cases are sporadic and occur primarily in males
- If signs of GnRH deficiency occur *after* puberty, consider tumors of the H-P axis

# Kallmann's Syndrome

- Association of hypogonadotropic hypogonadism and anosmia (or hyposmia)
- Incidence- 1:7500 males and 1:50,000 females
- Inheritance is usually X-linked
- Involves mutation of the KAL1 gene which encodes for proteins involved in neuronal cell adhesion
- Inability of GnRH-secreting neurons to migrate from the olfactory placode to the brain and occupy the olfactory bulb and hypothalamus (leads to anosmia and hypogonadism)

# Kallmann's Syndrome: *Clinical Features*

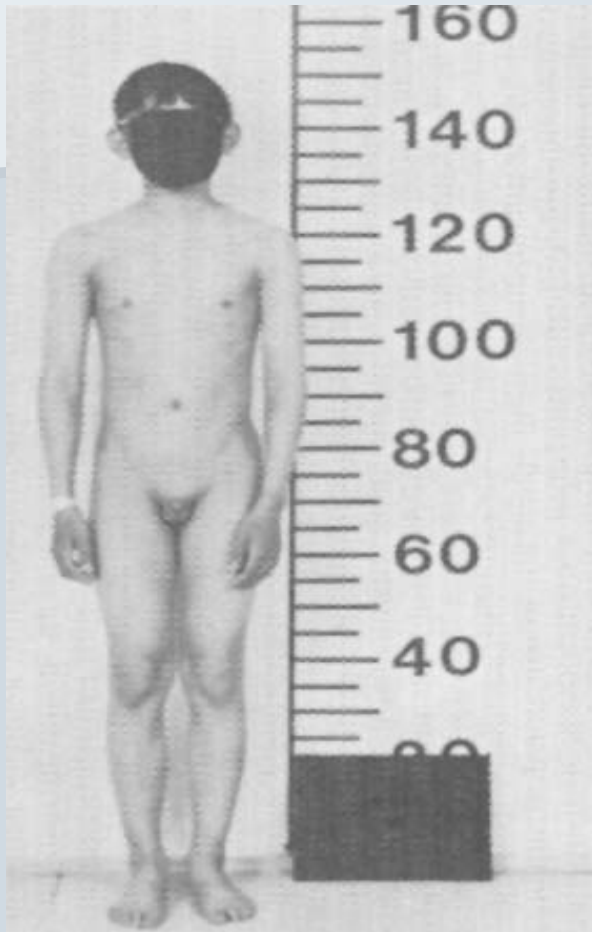
- Delayed puberty
  - Pre-pubertal testicular size (<2.5cm or <4mL)
  - Absence in voice change
- Normal Adrenarche
  - Pubic hair is usually present b/c adrenarche is normal
- Eunuchoid body habitus
  - Arm span exceeds height by 2cm or more. This reflects the delayed closure of the epiphyses of long bones caused by hypogonadism
- Normal stature and growth in childhood
- Congenital anomalies:
  - anosmia, red-green color blindness, midline facial abnormalities (cleft palate), unilateral renal agenesis (40%), neurosensory hearing loss, cryptorchidism, pes cavus
- Birth history of microphallus and/or cryptorchidism common

# Kallmann's Syndrome: *Diagnosis & Treatment*

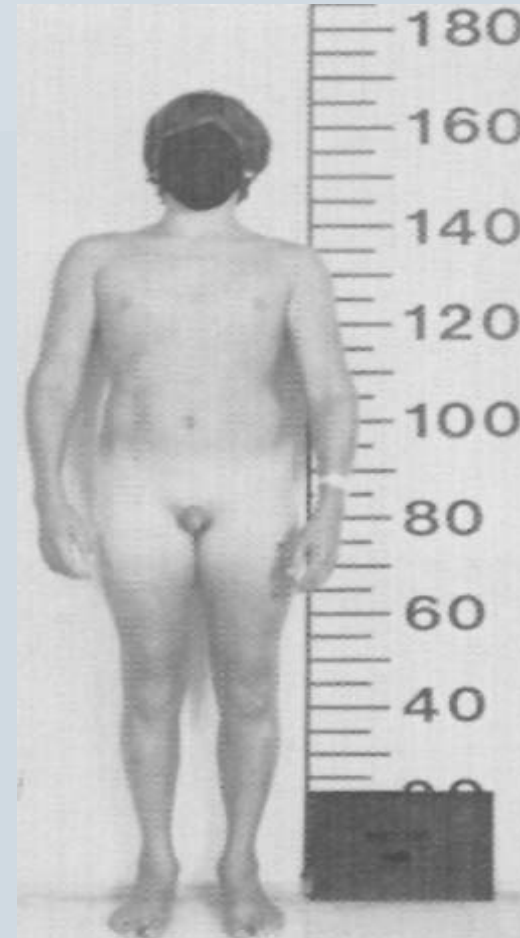
- Diagnosis:
  - Laboratory evidence of hypogonadotropic hypogonadism (low to nl LH/FSH, low testosterone)
  - MRI with aplasia or hypoplasia of olfactory bulbs and/or sulci
- Treatment:
  - Oral testosterone to induce virilization
  - Intranasal GnRH or IM hCG treatment needed to stimulate endogenous sex steroid production and even reproductive capability
- Life-long therapy is needed

# Constitutional Delay Vs. GnRH Deficiency

- A definitive diagnosis is usually not made before the patient is 18yrs (or bone age >14yrs with no pubertal development)
- No single test can reliably distinguish between these two disorders
- Family history of GnRH deficiency, anosmia, and/or congenital anomalies suggest GnRH deficiency
- Adrenarche and the normal growth spurt are attenuated in constitutional delay; whereas adrenarche proceeds unaffected in GnRH def.



Constitutional Delay  
of Puberty



Kallmann's  
Syndrome

# Klinefelter Syndrome

- Most common congenital abnormality causing primary hypogonadism (1:500-1000 live male births)
- 47,XXY is most common genotype
  - The greater # of X chromosomes, the greater the phenotypic consequences
- Testes may grow normally until the time of puberty when dysgenesis ensues
- Gonadal manifestations include small, firm testes, decreased sperm count and testosterone, **increased FSH/LH**, infertility, increased leg and arm length, gynecomastia
- Extra-gonadal manifestations include abnormal behavior, long bone abnormality and predisposition to pulmonary disease, cancers, DM
  - All of these manifestations are independent of testosterone deficiency
- Diagnosis is made via karyotype of peripheral leukocytes
- Diagnosis is often delayed until young adulthood (commonly presents with infertility)

# Prague



# Prague (Charles Bridge)



# Oktoberfest 2005 Munich, Germany



You think they look innocent now.....

# Oktoberfest 2005

even kids enjoy the festivities....



# Oktoberfest 2005

