

PRECOCIOUS and DELAYED PUBERTY

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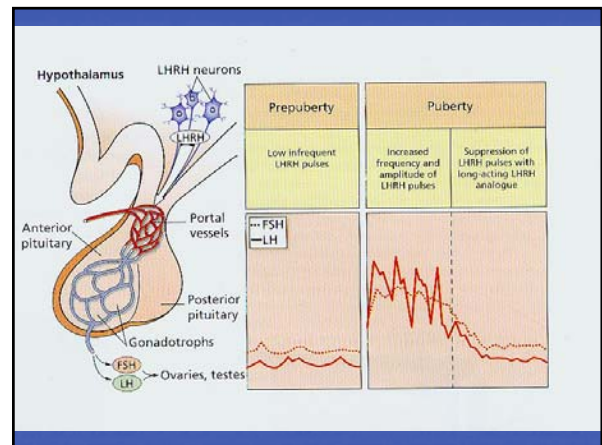
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Onset of Normal Puberty

- BOYS: Age 11.5 (range 9-14) yrs
- GIRLS: Age 10.5 (range 8-13) yrs
- Ethnic variation: Earlier Breast, Pubic hair development in African-American > hispanic > caucasian girls (data somewhat controversial)
- Apparent earlier onset of puberty in any race in the last 40 years – yet age of menarche has decreased only a few months

Peak Height Velocity (“Growth Spurt”)

- BOYS: 1.5-2.5 years after onset of puberty (≅ age 13-14 yrs)
- GIRLS: 0.5-1.5 years after onset of puberty (≅ age 11-12 yrs)



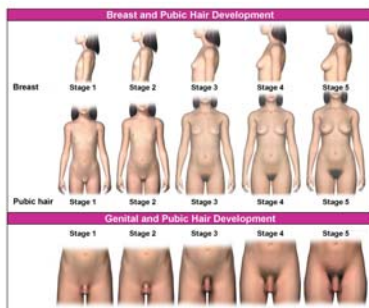
Mechanisms of Growth During Puberty

- Sex hormones stimulate growth hormone (GH) production
- GH → IGF-1 → Bone Growth
- Sex hormones (estrogens mainly) directly stimulate bone growth and maturation

Menarche

- Average age 12.5-12.75 years (range 10.8-14.6 years)
- Late event in female puberty
- Little residual bone growth left after menarche in most girls (exception: precocious puberty)

Tanner Stages of Pubertal Development



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Premature Sexual Development

- One or more secondary sexual characteristics by:
 - Age 9 in boys
 - Age 8 (range 7-5-8.5) in Girls
- Age limits are somewhat arbitrary and may need to be reassessed periodically

Precocious Sexual Development

- *Incomplete Forms*
 - Premature Thelarche - common
 - Premature Pubarche - common
 - Premature Menarche – very rare

Hormones and Sexual Characteristics

- Estrogens → Breast Development
 - Low levels, insensitive routine assays- use ultrasensitive estradiol measurement (LC/MS/MS)
- Androgens → Sexual Hair, Phallic enlargement, Clitoromegaly
 - DHEAS, major adrenal androgen
 - Testosterone – use ultrasensitive assays (LC/MS/MS)

Premature Thelarche

- Very common
- Age usually 1-2.5 years
- Unilateral or bilateral
- Fluctuation in size common
- Non progressive
- No estrogen effects on bones/growth

Atypical (Exaggerated) Thelarche

- Age range 1-3 years
- Breast tissue may be larger and firmer than in typical forms
- Growth acceleration
- Initially somewhat progressive, than spontaneously regressive

Evaluation of Premature Thelarche

- Clinical Follow-up
- Bone age in selected cases
- No Lab work
- Cases of exaggerated/atypical thelarche may require complete w/u with Leuprolide stimulation test, pelvic sonogram

Premature Pubarche

- Isolated pubic (axillary) hair development
- Most common in girls
- Age variable (usually 5-8 yrs)
- Normal or above normal weight
- Other signs of mild androgen excess (acne, body odor)

Premature Pubarche: Differential Diagnosis

- Premature adrenarche (90-95%)
- Congenital adrenal hyperplasia, non-classical (2-5%)
- Adrenal or ovarian tumor (<1%)

in addition:

- 1st sign of puberty in ? 5-10 % of children

Premature Pubarche

- Premature adrenarche
→ *slowly progressive*
- Congenital adrenal hyperplasia
→ *more progressive*
- Adrenal or ovarian/testicular tumor
→ *rapidly progressive*

Evaluation of Premature Pubarche Stepwise workup

- Observation
- Bone Age - reliable reading necessary
- Simple blood tests to exclude CAH/tumors
 - DHEAS, Testosterone, (androstenedione)
 - 17-hydroxyprogesterone (early AM preferred)
- Follow up at puberty- Risk of PCOS

Precocious Puberty

- Usually more than a single sexual characteristic
- Clear progression
- Signs of systemic effects of sex hormones (growth spurt, bone maturation, genital maturation)

Sexual Precocity

Baseline LH, FSH, Estradiol and/or

**FSH, LH Response
to GnRH or Leuprolide
Stimulation**

CENTRAL
(Gonadotropin- Dependent)

PERIPHERAL
(Gonadotropin-Independent)

Peripheral Precocious Puberty

- Autonomous (gonadotropin-independent) secretion of sex hormones by:
 - Adrenals (Hyperplasia, Tumors)
 - Gonads (Tumors, Ovarian cysts, genetic abnormalities of endocrine signalling)

McCune-Albright Syndrome

- Recurrent ovarian cysts with intermittent estrogen secretion
- Café-au-lait skin lesions
- Polyostotic fibrous dysplasia
- Constitutional activation of the G-stimulatory protein → FSH, LH -like effect on the ovaries

Congenital Adrenal Hyperplasia

- Genetic enzyme defect of cortisol synthesis leads to increased androgen production
- Simple virilizing type presents at 2-6 years of age in boys
- Bone age often greatly advanced at the time of diagnosis

Tumors Causing Sexual Precocity

- Rapid progression of virilization of feminization
- Adrenals: Adenoma / Carcinoma
- Testes: Leydig cell tumors
- Ovaries: Sex-chord stromal tumors (Feminizing), arrhenoblasoma (Virilizing)

hCG-Mediated Precocious Puberty

Hepatoblastomas; Embryomas (associated with Klinefelter's) & other tumors
SECRETING

Human Chorionic Gonadotropin = LH effect
→ Stimulation of Leydig Cells →
→ Testosterone (Boys)
(No known effect in girls)

Central Precocious Puberty

- Most common type of complete sexual precocity
- Normal pubertal process, except for early timing of onset
- Girls>Boys 10:1
- Idiopathic in >90% of Girls
- CNS lesion in 20-50% of Boys

What triggers the onset of precocious puberty ?

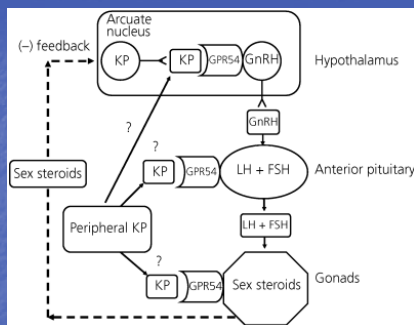
Idiopathic central precocious puberty - - -
 ? Mechanism similar to normal puberty
 - - - *yet Unknown* - - -

Kisspeptins (Product of the Kiss-1 gene)

- Peptides expressed in: Placenta
Hypothalamus, other tissues
- Initially described as anti-tumor
compounds (metastin = kisspeptin 1-54)

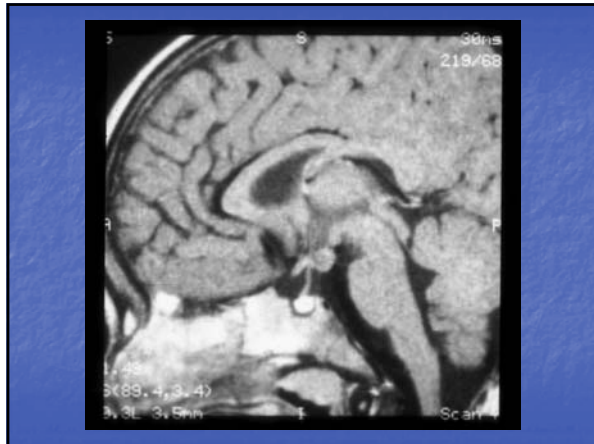
Kisspeptins and Puberty

- Hypothalamic Kisspeptins (arcuate, paraventricular nuclei) → Bind to GPR54 receptor in GnRH secreting cells → Stimulation of GnRH → LH secretion



Murphy, K. G.: Kisspeptins: Regulators of Metastasis and the Hypothalamic-Pituitary-Gonadal Axis. *Journal of Neuroendocrinology* 17 (6), 519-525.





Neurogenic Precocious Puberty

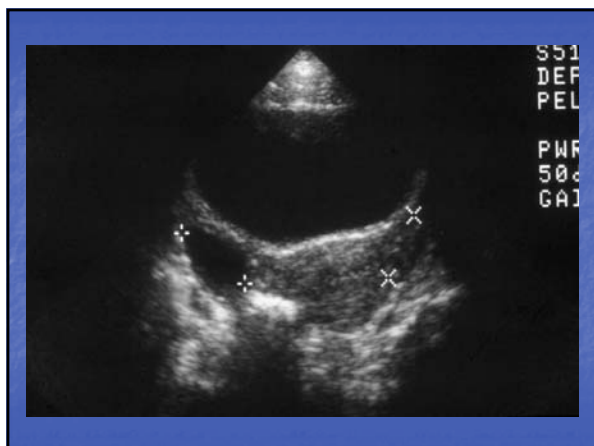
- Hypothalamic hamartoma (+gelastic seizures)
- NF1± Optic glioma
- Myelomeningocele with or w/o Hydrocephalus
- Other CNS Tumors (Ventricles, Pineal, posterior fossa)
- Static encephalopathies

Precocious Puberty after CNS irradiation

- Often associated with GH deficiency
- Despite GH deficiency, the growth rate may be "normal" , (direct sex hormone effect)
- Rapid bone age advancement + GH deficiency → ++short stature
- Treatment include suppression of puberty + GH Rx if there is GH deficiency

The Diagnosis of Precocious Puberty

- History of Progression
- P.E. –Look at the Gonads !
 - ↑ Testicular size in boys
 - Pelvic U/S (↑ ovarian size, uterine stimulation)
- Accurate bone age reading (by an endocrinologist, not a radiologist)



LH assays and puberty

- Current 3rd generation LH assays (ICMA, IFMA) have sensitivity of 0.02-0.05 IU/l
- Automated methods (CHP) approx 0.1 IU/l
- LH < 0.3 IU/l = Prepubertal
- LH 0.3-0.5 IU/l = Early pubertal
- LH > 0.5 IU/l = pubertal
- FSH measurements = useless to detect pubertal activation

Leuprolide Stimulation Test (GnRH-agonist stimulation test)

- Indicated if random LH levels are low
- Leuprolide 20 mcg/Kg SC
- LH, FSH at baseline, +1, +2 (+3) hours
- Girls: E₂ at baseline and +24 hours
- Boys: T at baseline (+24 hr optional)
- Pubertal response:
 - LH > 5 IU/l in either gender
 - E₂ > 50 pg/ml at 24 hr in girls (LH may be low)
 - T > 50 ng/dl at 24 hr in boys

Physical Problems from Sexual Precocity

- Growth spurt
- Rapid bone maturation → Early bone fusion → Short stature
- (F) Premature onset of menses

Psychological Problems from Sexual Precocity

- Embarrassment (tall stature, pubertal development)
- Psychosocial development lags behind physical maturation
- Parental anxiety
- Moodiness
- ? Increased risk of sexual abuse in girls

Practical Approach to Precocious Puberty

- Determine if puberty is central or peripheral
- Rule out malignant tumors or lesions requiring surgery
- Assess the progressiveness of puberty and need for therapy

Subtypes of Central Precocious Puberty

- Unsustained or regressive
- Slowly progressive (Girls)
 - Age of onset generally > 7 yrs
 - Bone age parallels height age
- Rapidly progressive
 - Age of onset often < 6 yrs
 - Bone age ↑ disproportionately, with loss of height potential

Central Sexual Precocity Indications for Therapy

- Very young age (< 6 years)
- Rapid progression with loss of height potential:
 - Predicted Ht < 5th percentile
 - Predicted Ht << midparental Ht
- Psychosocial problems within the family

Treatment for Central Precocious Puberty

- Gonadotropin-releasing hormone analogs:
 - Antagonists (No Pediatric Studies, Greater Potential for Allergy/Anaphylaxis, more \$)
 - Agonists ("Superagonists") - FDA approved --> Initial Stimulation --> Downregulation of FSH, LH

Treatment for Central Precocious Puberty

- **Lupron-Depot Ped** (Leuprolide)
 - 7.5/11.25/15 mg via i.m. injection q. 28 days
- **Supprelin LA** (Histrelin) implant 50 mg Q 12 mos
- Synarel (Nafarelin)- intranasal 4 puffs BID
- Lupron (Aqueous)s.c. daily /BID

Under study, not yet FDA-Approved:

- Lupron-Depot injection q. 3 mos

Effects of Treatment for Precocious Puberty

- Menstrual-period 2-3 weeks after initial Rx
- Growth velocity ↓ after 6 mos
- Bone age maturation ↓
- Size of testes (boys) /ovaries (girls) ↓
- Physical signs of puberty may not / may regress slowly - incompletely
- Mood swings – may not improve

Are GnRH analogs safe?

- Menarche occurs 12-18 months after discontinuation in girls
- Sex hormone levels increase to adult values after discontinuation
- Fertility has been documented
- Transient effect on bone density
- Effects on body composition ?

Short stature and Delayed Puberty in a girl



Delayed Sexual Development: a common problem

- Absence of any secondary sexual characteristics by:
 - Age 14 in boys
 - Age 13 in Girls
- Much more common in Boys (M:F > 10:1)
- In Girls with delayed puberty, look for underlying cause

Constitutional Delay of (growth and) Puberty

- Usually lean, very active boys [short]
- Also in some obese boys [normal height]
- Frequently positive Family History
- Substantial growth deceleration; may need to R/O GH deficiency
- May be compounded/worsened by psychostimulant use

Delayed Sexual Development: Differential Diagnosis

- Over 95% are idiopathic: constitutional delay
- Systemic Illness – Celiac disease, sickle cell, etc
- Hypogonadism:
 - Hypergonadotropic: Turner syndrome in girls
 - Hypogonadotropic hypogonadism in boys
 - Hypopituitarism (non organic)
- CNS /Hypothalamic/Pituitary Tumors causing organic hypopituitarism

Screening Tests for evaluation of Delayed Sexual Development

- Bone Age (height prediction)
- Chemistries, CBC, ESR, CRP, celiac screen, FT4 & TSH; IGF-1 usually somewhat low)
- LH, FSH: (pediatric/ ultrasensitive)
- Testosterone (M); Estradiol (F) in early AM by sensitive assays
- Others /pituitary MRI in selected cases

Delayed Sexual Development: The Good News

- It usually takes care of itself
- A short course (4-6 mos) of Testosterone in boys is usually helpful and well received
- Benefits of Testosterone Rx: Growth spurt, virilization, possibly better bone health; no change in adult height
- Even with Rx, boys lag behind their peers
- Psychological problems: very rare

Summary

- Variants of precocious sexual development (telache, pubarche): common and benign
- Central precocious puberty has important (physical > psychological) consequences
- Need to rule out organic/ treatable causes
- Selection of candidates for treatment is crucial in central precocious puberty

Delayed Puberty: Summary

- Common problem in boys in 8-9th grade
- Mild psychological distress attenuated by short-term testosterone therapy in boys
- Estrogen therapy in girls is controversial, as it may adversely affect adult height.
- Organic causes of delayed puberty are rare, but need to be ruled out

The End

Questions ?