

Puberty

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Learning Objectives

- Understand physiology of puberty
- Causes and management approach to Precocious puberty
- Identify and investigate children with delayed puberty

Physiology of puberty

- What is puberty?
- It is the transitional period of development during which an individual mature from childhood to physical, psychosocial, sexual & reproductive maturity

NORMAL PUBERTAL DEVELOPMENT

- Major characteristics of puberty
 - 1-Maturation of the primary sexual characteristics
Hypothalamic Pituitary Ovarian Axis
 - 2-Development of secondary sexual characteristics
 - Sexual hair
 - Breasts
 - Genitalia
 - 3-Dramatic growth spurt
 - 4-Psycological changes ⇒ mental & emotional maturity
 - 5-Fertility

Endocrine Regulation of Puberty & Reproduction

- Hypothalamus releases LHRH (GnRH)
- Anterior pituitary secretes:
 - LH .
 - FSH.
- Secreted in pulsatile fashion to prevent desensitization and down regulation of receptors.
- Primary effects of LH and FSH on gonads:
 - Stimulation of spermatogenesis and oogenesis.
 - Stimulation of gonadal hormone secretion.
 - Maintenance of gonadal structure.

Mechanism of Puberty

- GnRH stimulates pituitary gonadotropins (LH & FSH)
- During childhood pubertal Gn secretion is initially low due to downregulation
- Negative feedback of hypothalamic-pituitary-gonadal axis
- As puberty progresses, episodic release of LH
 - Increased amplitude & frequency
 - Progressive secretion extends over the 24 hr period
- Mechanism of why puberty occurs is unknown(theories?)

NORMAL PUBERTAL DEVELOPMENT

- THE AGE OF ONSET OF PUBERTY

- Females ----8-13

- Males -----9-14

- Lawson Wilkins Pediatric Endocrine Society recommended 7 for white girls/ 6 for black

- AVERAGE AGE of ONSET:

1. GIRLS 10 to 11 years (range 8 to 13 years)

2. BOYS 11 to 12 years (range 9 to 14 years)

NORMAL PUBERTAL DEVELOPMENT

- THE TIME FROM ONSET TO COMPLETION OF PUBERTY?

Average	4.2 Y
Range	1.5-6 Y

Factors That Affect Puberty

- Genetics
- Race/Ethnicity
- Previous nutrition
- Subcutaneous fat
- Birth weight
- Obesity
 - Increased leptin and estrogen production
 - Insulin stimulation of ovaries & uterus

NORMAL PUBERTAL DEVELOPMENT

INITIAL SIGNS OF PUBERTY:

1. GIRLS – Breast Development

2. BOYS – Testicular Enlargement

- **Volume $> 3.0 \text{ cm}^3$**
- **Length $> 2.5 \text{ cm}$**

NORMAL FEMALE PUBERTAL DEVELOPMENT

- THE USUAL SEQUENCE OF SOMATIC CHANGES OF PUBERTY

1-Onset of growth spurt (9.6)

2-Beast development (mean 10.6 Y)

3-Pubic & axillary hair (11.2)

4-Maximal growth velocity (12)

- 5-Menarche (12.7)

Tanner's Staging of Puberty in Girls

STAGE	BREAST DEVELOPMENT (B)	PUBIC HAIR (PH)
1	Prepubertal; no breast tissue	None
2	Areolar enlargement with breast bud	A few darker hairs along labia
3	Enlargement of breast and areola as single mound	Curly pigmented hairs across pubes
4	Projection of areola above breast as double mound	Small adult configuration
5	Mature adult breast with single contour	Adult pubic hair distribution

Tanner's Staging of Puberty in Boys

STAGE	GENITAL MATURITY (G)	PUBIC HAIR (PH)
1	Prepubertal; testes 2 ml	None
2	Enlargement of the testes ≥ 4 ml; reddening of the scrotum	A few darker hairs at the basis of the penis
3	Lengthening of the penis; further enlargement of testes to 6-10 ml	Curly pigmented hairs across pubes
4	Broadening of the glands penis; growth of testis to 10-15 ml	Small adult configuration
5	Genitalia adult in size and shape; testes 15-25 ml	Adult pubic hair distribution

GROWTH SPURT

- Peak Height Velocity
 - 8.1 cm/year (before puberty 3-6 cm/y)
 - by the time PHV is achieved \Rightarrow 90% of adult height has been achieved
 - the average \uparrow in height from the onset of growth spurt to cessation of growth 25 cm
 - girls who start the growth spurt early will have a shorter adult height

Assessment of Puberty

History

- Parents
 - onset of puberty in parents
 - Menarche (more reliable in mothers as they remember onset)
 - Male growth spurt (as most fathers recall their pubertal progression more vaguely)
 - » Age of first shaving regularly
 - Parental heights (identify midparental height)
- **prenatal and perinatal (exposure to exogenous sex steroids in intrauterine period; birth weight, length, mechanism of delivery, perinatal pathology - resuscitation,...)**
- **concomitant illnesses, postnatal exposure to sex steroids**
- **time of first sign of puberty**
- Body changes? (important to ask about EACH)
 - Thelarche (galactorrhea)
 - Adrenarche/pubarche (body odor, axillary & pubic hair, acne)
 - Menarche
 - Gonadarche

History cont'd...

- Important to include:
 - Past medical history (history of brain tumor, radiation, chemotherapy, known genetic disorder, chronic disease affecting growth)
 - Eating habits
 - Any evidence of disordered eating
 - Activity level
 - Is exercise excessive or is this an athlete with a high level of training
 - Growth history
 - Previous growth chart can be extremely helpful

History

- Review of Systems
 - CNS: visual changes/visual field abnormalities, headaches, anosmia
 - Cardiac: congenital anomaly
 - Respiratory: asthma
 - Renal:
 - GI: diarrhea, blood in stools

Physical Examination

- Examination of Growth
 - Height
 - Weight
 - Head circumference
 - Upper to lower segment ratios
- Pubertal Assessment (Tanner staging)
 - Axillary hair
 - Pubic hair & staging
 - Breast development & staging
 - Genital development & staging
- **skin, hair, thyroid**
- Neurological assessment

Diagnostic evaluation

Laboratory

- gonadotropins (FSH, LH) basal and peak after LHRH stimulation (prepubertal LH/FSH<1)
- estradiol
- testosterone (basal value and value after LH stimulation)
- adrenal androgens (17-OHP, A-dion,...) and ACTH

Skeletal maturity (bone age)

Pelvic sonography (ovarian and uterine size)

CT or MRI of adrenals, CNS

Vaginoscopy and vaginal cytology

Genetic – karyotype, DNA analysis

Variants of normal development

Premature thelarché (isolated breast enlargement)

- exclude the start of precocious puberty!

Premature adrenarché (pubic and axillary hairs)

- exclude simple virilising form of CAH!

Premature menarché

- exclude vaginal bleeding due to trauma of vagine or rare ovarian cyst!

Bone age is not accelerated!

FSH and LH levels after LH-RH are normal

Gonadal and adrenal steroid levels are normal

Pelvic and adrenal ultrasonography is normal

Reassurance & f/u

Definition of Precocious Puberty

- ONSET OF PUBERTY BEFORE
 - Females ----8 years
 - Males -----9 years
 - Lawson Wilkins Pediatric Endocrine Society recommended 7 for white girls/ 6 for black
- The prevalence
 - is estimated to be between one in 5,000 to 10,000 children annually in the United States.

Classification

Central (true), gonadotropin-dependent

Early stimulation of hypothalamic-pituitary-gonadal axis.

Peripheral, GnRH independent (precocious pseudopuberty)

The source of sex steroid may be endogenous or exogenous, gonadal or extragonadal, independent of gonadotropins stimulation.

True precocious puberty

(central, GnRH dependent)

Idiopathic, constitutional sporadic or familial (common)

CNS abnormalities

- **Congenital (hydrocephalus, arachnoid cysts, ...)**
- **Acquired pathology (posttraumatic, infections, radiation,..)**
- **Tumors (LH secreting pituitary microadenoma, glioma – may be associated with neurofibromatosis, hamartoma,..)**
- **Reversible forms - space occupying or pressure-associated lesion (abscess, hydrocephalus,...)**
- **Empty sella syndrome**

**Adopted children or children emigrating from
developping
countries**

- **Improved nutrition, environmental stability and psychosocial support**

True precocious puberty

(central, gonadotropin-dependent)

Always isosexual!

Bone age is accelerated

**FSH and LH elevation after LH-RH is diagnostic test
($\text{LH/FSH} > 2$)**

$\downarrow \text{LH} \Rightarrow \text{LH/FSH ratio} < 1 \Rightarrow \text{Prepubertal}$

$\uparrow \text{LH} \Rightarrow \text{LH/FSH ratio} > 1 \Rightarrow \text{Pubertal}$

MRI of CNS is necessary to exclude the neoplasia

Treatment of true precocious puberty

- **Purpose of treatment**
 - To prevent psychosocial distress
 - To improve final height outcome
- Treat the underlying cause
- GnRH analogue
 - Lupron depot ped, leuprolide acetate
 - Desensitizes the pituitary
 - Blocks LH and FSH secretion
 - Prevents continued sexual development for the duration of the treatment

Precocious pseudopuberty in girls (gonadotropin-independent)

McCune - Albright syndrome

Ovarian cysts

Isolated follicular cysts with E2 production. Self-limiting with spontaneous regression.

Ovarian tumors

Acceleration of bone age

FSH and LH are low after LH-RH stimulation

Estrogens are elevated

Precocious pseudopuberty in boys

(gonadotropin-independent)

Congenital adrenal hyperplasia (CAH)

Undiagnosed or inadequately treated simple virilising form of CAH caused by 21-hydroxylase deficiency.

Neonatal screening?

Testotoxicosis

Activating mutation of LH receptor. AD inherited.

Tumors

- Gonadal (testosterone-secreting Leydig cell tumor)
- Adrenal (adenoma, carcinoma)

Exogenous androgens (anabolic steroids – iatrogenic, doping)

McCune Albright Syndrome

Acceleration of bone age

FSH and LH are low after LH-RH stimulation

Testicular or adrenal steroids are elevated

Precocious puberty-treatment

Gonadotropin-dependent PP

- **Idiopathic**
 - GnRH (LH-RH) analog (triptorelin) to block LH-RH receptor in gonadotroph of pituitary gland
- **Organic – tumor or cysts**
 - Surgery

Gonadotropin independent (pseudopuberty)

- testicular, ovarian or adrenal tumors –surgery
- CAH – substitution of corticosteroids
- autonomous steroid secretion-estrogens receptor antagonists (tamoxifen), steroid synthesis inhibitors (ketoconazole), aromatase inhibitors (testolactone)

Delayed puberty - definition

Initial physical changes of puberty are not present

- **by age 13 years in girls
(or primary amenorrhoe at 15.5-16y)**
- **by age 14 years in boys**

Pubertal development is inappropriate

the interval between first signs of puberty and menarche in girls/completion genital growth in boys is > 5 years

GnRH or gonadotropin dependent I.

Idiopathic

sporadic or familial (associated with constitutional growth delay)

Chronic diseases

with bone age delay and growth retardation due to different pathophysical mechanisms (malnutrition, anemia, acidosis, hypoxia,...anorexia nervosa, cystic fibrosis, chronic renal insufficiency,..)

Psychosocial deprivation

GnRH or gonadotropin dependent II.

Hypogonadotropic hypogonadism

Gonadotropin deficiency

LH only (fertile eunuch syndrome)

FSH and LH

- **Congenital (genetic, syndromes) - Kallman syndrome –mutation of KAL gene,
mutation of DAX1 gene, Prader-Willi syndrome ,...**
- **Acquired - cranial irradiation, hemosiderosis, granulomatous disease**

Associated with others pituitary hormones deficiencies

- **Congenital – empty sella syndrome, genetic-transcription factors, disruption
of pituitary stalk (breech delivery),...**
- **Acquired – tumors, inflammation, irradiation, trauma....**

Syndromes Associated with Pubertal Delay

- Prader-Willi syndrome
- Laurence Moon syndrome
- Septo-optic dysplasia
- Bardet-Biedl syndrome

Gonadotropin independent (hypergonadotrophic)

Boys

Congenital

Anorchia

**Chromosomal abnormalities (Klinefelter syndrome,
Noonan syndrome...)**

Acquired

Autoimmune inflammation (APS)

Radio or chemotherapy

Traumatic

Surgery

Gonadotropin independent (hypergonadotrophic hypogonadism)

Girls

Congenital

Bilateral ovarian torsion

Chromosomal abnormalities (Turner syndrome, pure gonadal dysgenesis, Noonan syndrome...)

Acquired

Autoimmune inflammation (APS)

Radio or chemotherapy

Traumatic

Surgery

Investigating Delayed Puberty

- Investigations depend on clinical presentation, but may include
 - Bone age
 - Hormone levels (FSH, LH, estradiol, testosterone,, TSH)
 - Karyotype
 - Hormone stimulation tests
 - GnRH stimulation test
 - Imaging
 - MRI if gonadotropins high & no obvious cause of hypogonadotropic hypogonadism

Treatment of delayed puberty

- Treat underline cause
- Testestrone
- estrogen