UNDERSTANDING AND RECOGNIZING PRECOCIOUS PUBERTY

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Learning objectives

- ❑ Review the pattern of normal puberty
- ❑ Understand the criteria for, and the possible etiologies of precocious puberty
- ❑ Identify when to pursue further workup and referral for precocious puberty

Why is it important?

- Influence on ultimate height
- Psychosocial development
- May signify an underlying serious condition

Variations of normal

- Vast majority of children with signs of apparent mild early puberty often have variations of normal growth and physical development
  - Possible factors (non-pathologic) associated with earlier puberty include obesity and endocrine disrupting chemicals – some pesticides, plasticizers, plant-derived phytoestrogens in soy, lavender oil, tea tree oil, fennel

Normal Development

- Females:
  - Breast budding (thelarche) is usually first sign
  - Pubic hair (pubarche) may be initial sign in 15%
  - Menarche occurs about 2 years (range 1.5-4yrs) after thelarche
  - Peak height velocity is reached at about 12 years, immediately prior to menarche

Normal Development (cont.)

- Males:
  - Testicular enlargement is earliest sign
  - Peak height velocity occurs at average age of 14 years

Tanner stages

- Tanner I is prepubertal
- Breast enlargement progresses and by Tanner V the areola recesses to the contour of the breast
- Testes enlarge first, followed by length then width of penis
- Pubic hair becomes more curled, darker then by Tanner V spreads to medial thigh

Criteria

- Males considered precocious if sexual development before 9 years

Criteria

- Females used to be considered precocious if before 8 years
  - many now use appearance of secondary sex characteristics before 7 yr in African-American females, 8 yr in Caucasian females
    - consider family history, growth velocity, bone age, rate of pubertal progression, etc. for those between 6-8 years
  - mean menarchal age about 12.2y AA and 12.8y C; statistically, early menarche is defined as <9.5 yr
  - in overweight girls, it is important to distinguish the sex-steroid dependent breast (firm, nodular, and possibly tender) from adipose tissue (soft, homogeneous, and non-tender)

Hormones

- Skeletal maturation parallels progression of chronologic age under influence of growth and thyroid hormones, estrogens, and androgens

- HPG axis active in neonatal/infancy period but then quiescent between 2-8 years of age due to inhibitory influences (possibly gamma-aminobutyric acid – GABA)

Terminology

- Gonadarche is the activation of gonads by pituitary hormones FSH and LH
  - Driven by increase in pulsatile GnRH secretion from hypothalamus
  - GnRH stimulates anterior pituitary to secrete FSH and LH
  - LH stimulates ovaries to secrete estradiol and testes to secrete testosterone
  - FSH promotes development of oocytes or spermatozoa and increases the size of gonads
  - Estradiol causes progressive breast enlargement, the pubertal growth spurt, and rapid bone age advancement
  - Testosterone causes penile enlargement and pubic hair growth in boys and, by conversion to estradiol, causes the male growth spurt

Terminology

- Adrenarche:
  - onset of androgen-dependent signs of puberty (pubic hair, acne, adult body odor)
  - physiologically distinct from gonadarche
  - can begin at 6-8 years with increase in adrenal androgens (DHEA & DHEAS)
  - premature pubarche is not the same as premature adrenarche
    - premature pubarche refers to just some hair without necessarily abnormal increase in levels of adrenal hormones; possibly related to increase in androgen receptor sensitivity
    - premature adrenarche has increase in adrenal hormones, and an advanced bone age

Causes of Isosexual Precocious Puberty

- Central (True and Complete) Precocious Puberty
- Peripheral (Pseudoisosexual) Precocious Puberty
  - gonadotropin independent
  - some people use the term “precocity” since not “true puberty” as central axis is not activated
- Incomplete Precocious Puberty

Etiology of Central (True and Complete)

- Idiopathic (85% in females, 50% in males): with/without hypothalamic hamartoma
- Secondary:
  - Congenital anomalies: hamartoma, hydrocephalus, arachnoid or ventricular cyst, septo-optic dysplasia, empty sella syndrome
  - Postinflammatory: encephalitis, meningitis, abscess, granulomatous disease
  - Radiation therapy
  - Trauma
  - Neoplasms: hypothalamic hamartoma, astrocytoma, ependymoma, glioma (NF), craniopharyngioma
  - Genetics: activating mutations in kisspeptin1 gene and other genes
- Following effective treatment of long-standing pseudoisosexual precocity

Etiology of Pseudoisosexual Prec. Pub.

- Familial male-limited precocious puberty
  - autosomal dominant, male-limited; signs of puberty generally by 4 yrs of age
  - mutation in gene for LH receptor resulting in activation of receptor
  - testosterone production and Leydig-cell hyperplasia occur in setting of prepubertal LH levels
- McCune-Albright syndrome
  - clinical triad of polyostotic fibrous dysplasia, irregular bordered café-au-lait macules, and endocrinopathies
  - due to mutation in G protein (GSα gene); results in activation of adenylyl cyclase in affected tissues

Etiology of Pseudoisosexual Prec. Pub.

- Gonadal/extragonadal tumors
  - Estrogen-secreting: ovarian cyst, granulosa cell, calcifying Sertoli cell tumors, Peutz-Jeghers syndrome
  - Testosterone-secreting: Leydig cell, teratoma
  - Human chorionic gonadotropin-secreting: hepatoblastoma, germinoma, choriocarcinoma
- Adrenal
  - Congenital adrenal hyperplasia: 21-hydroxylase, 11 beta-hydroxylase deficiency
  - Adenoma, carcinoma
  - Glucocorticoid resistance
- Exogenous sex hormones
- Primary hypothyroidism (TSH shares the alpha chain of gonadotropins)

A word about hCG

- Human chorionic gonadotropin
  - shares structural homology of subunit with LH
  - has an LH-like action
  - stimulates Leydig cells to make testosterone (leading to male precocious puberty)
  - in females, one would need both LH and FSH to make estradiol (although hCG may have some weak FSH-like activity)

Incomplete Prec. Puberty (cont.)

- Premature thelarche
  - onset most common between 2-3 yrs of age
  - unilateral or bilateral
  - frequently regresses without intervention
  - bone age not significantly advanced
  - observe and reassure
  - CPP may develop in 10%

Incomplete Prec. Puberty (cont.)

- Premature pubarche/adrenarche
  - usually benign and non-progressive
  - might have physical signs from adrenal androgens (small amounts of acne, pubic hair, axillary hair/odor)
  - not virilized (no cliteromegaly, no growth spurt, and bone age not or only slightly advanced)
  - one of the most common reasons for referral; children develop pubic hair and axillary odor before ages 8 in girls and 9 in boys
  - 20% incidence of functional ovarian hyperandrogenism in girls so need close follow-up into young adulthood
- Premature menarche

Key Findings on History/Physical Exam

- Height velocity (>95th %tile for age)
  - Height velocity curves
    - Reflect variation between early, average, and late maturity
    - Some generated many years ago (1970s)
  - Increase/crossing of growth percentiles with standard growth charts
    - Do not reflect differences in timing of early vs late maturing children
- Boys:
  - Voice change
  - Acne
  - Facial hair
- Girls:
  - Breast tissue development
  - Vaginal discharge

Diagnostic evaluation

- When multiple signs of precocious puberty are present
- Progressive precocious puberty and/or rapid increase in height velocity
- Avoid ordering labs/imaging for patients with isolated findings without other signs of puberty (isolated thelarche, isolated pubarche)

Diagnostic evaluation

- Baseline labs may include:
  - Bone age study
  - FSH
  - LH
    - LH of >0.3 IU/L is the most reliable screening test for CPP
      Consider stimulation test if <0.3 and CPP is still suspected
    - LH concentrations in the prepubertal range (<0.2 mIU/mL) are consistent with peripheral precocity or benign pubertal variant
  - estradiol or testosterone

When to Refer

- When bone age/initial labs are abnormal
  - If initial workup is normal, may watch for 6 months, then repeat workup as necessary
- When there is progression of precocious puberty

More specific evaluation

- Precocious pubic hair
  - If bone age normal, can get DHEAS to verify that it is benign premature adrenarche
  - If bone age advanced:
    - get DHEAS and if high, abdominal CT to look for adrenal tumor
    - in females, also get17-OHP to evaluate for CAH

Ref: Root AW. *Pediatrics in Review.* 2000, 21 (1) 10-19.

More specific evaluation

- Precocious penile enlargement
  - Obtain a 17-OHP to evaluate for CAH

Ref: Root AW. *Pediatrics in Review.* 2000, 21 (1) 10-19.

More specific evaluation

- Precocious thelarche
  - If bone age normal, mostly likely benign premature thelarche
  - If bone age advanced:
    - if LH elevated, likely central precocious puberty and should get MRI of brain
    - if LH not elevated, then check estradiol level, pelvic ultrasound, look for exogenous estrogen

Ref: Root AW. *Pediatrics in Review.* 2000, 21 (1) 10-19.

More specific evaluation

- Precocious menarche
  - If bone age normal, can get a pelvic ultrasound to evaluate for masses, foreign body
  - If bone age advanced:
    - if LH elevated, likely central precocious puberty and should get MRI of brain
    - if LH not elevated, then check estradiol level, pelvic ultrasound, look for exogenous estrogen

Ref: Root AW. *Pediatrics in Review.* 2000, 21 (1) 10-19.

More specific evaluation

- Precocious testicular enlargement: check testosterone level, if elevated then:
  - Bilateral testicular enlargement:
    - if LH elevated, likely CPP, get MRI of brain
    - if LH not elevated, then consider familial male-limited precocious puberty, or look for exogenous androgen
    - check hCG level, and if elevated look for potential neoplasm
  - Unilateral testicular enlargement: check testicular ultrasound

Ref: Root AW. *Pediatrics in Review.* 2000, 21 (1) 10-19.

Management and Treatment

- Objectives in management of True Precocious Puberty:
  - Detection and treatment of an expanding intracranial lesion
  - Arrest of premature sexual maturation until normal age of puberty onset
  - Attainment of normal mature height
  - Prevention of emotional disorders and alleviation of parental anxiety
  - Reduction of risk of sexual abuse and early sexual debut

Management & Treatment (cont.)

- Focus management of underlying disorder if CPP due to specific remediable anatomic abnormality of CNS
- Idiopathic CPP (or hypothalamic hamartoma):
  - inhibit HPG axis with long-acting GnRH agonists (e.g., leuprolide acetate) available as monthly injections, every 3 months, or as implant
  - agonists work by downregulating GnRH receptors and altering synthesis of gonadotropins
  - suppression often occurs within 4-8 weeks
  - monitor efficacy clinically, radiographically, and hormonally

Management & Treatment (cont.)

- Effects of GnRHa:
  - cessation of menses
  - regression or halt in the progression of sexual characteristics in both genders
  - rates of linear growth and skeletal maturation decline (thus attaining greater adult height)
- Therapy often halted by 11-12 years of age in girls, and 12-13 years of age in boys, as age peers achieve their pubertal development
- After discontinuation of therapy, HPG rapidly returns to pubertal state; menses usually occur within 6-18 months

Management & Treatment (cont.)

- Pseudoisosexual Precocious Puberty:
  - Treat primary disease
    - excise gonadal, adrenal, and other tumors
    - cortisol for CAH
    - thyroxine for hypothyroidism
    - ovarian cysts often regress spontaneously
    - ketoconazole to inhibit testosterone synthesis in familial male-limited precocious puberty and McCune-Albright syndrome
    - testolactone (an aromatase inhibitor) or tamoxifen (which blocks actions of estrogen) in girls for hyperestrogenemia in McCune-Albright
  - After suppression of gonadotropin-independent sex hormone secretion, some may evolve into having CPP and may need treatment with GnRHa

Management & Treatment (cont.)

- Premature thelarche
  - frequently regresses without intervention
  - observe and reassure
  - CPP may develop in 10%
- Premature adrenarche
  - usually benign and non-progressive
  - 20% incidence of functional ovarian hyperandrogenism in girls so need close follow-up into young adulthood

Management & Treatment (cont.)

- Psychosocial aspects
  - often tend to be shy and withdrawn when in company of age peers
  - because of appearance, adults often expect more advanced sexual and maturational behavior
  - need to provide appropriate counseling to parents and teachers with regard to expecting age- (not appearance-) appropriate behavior
  - need to provide safeguards to prevent sexual abuse / pregnancy

Rapid Tempo Puberty

- No formal definition exists
  - Start of puberty is within normal range, but subsequent milestones are achieved more than 2 SD ahead of expected mean age of occurrence
  - In girls, typical interval from breast budding (Tanner stage 2) to menarche (usually associated with at least Tanner stage 4 breasts) is 2.4 ± 1.1 years
  - In boys, the usual time from pubertal onset (Tanner stage 2 testes) to adult testicular volume is 3.2 ± 1.8 years
- Exact etiology is unknown
  - Possibly modified by family genetics, h/o low birth weight/SGA, rapid and/or excessive growth in early childhood (especially if having been born SGA), diet, diminished physical activity, other factors

Ref: Nakamoto JN, Chan Y-M, Geffner ME. Puberty. Allen D, Nadeau K, Kappy M, Geffner M (eds). Principles and Practice of Pediatric Endocrinology. McGraw-Hill, 2020)

Rapid Tempo Puberty

- Typically affected adolescent usually presents to medical attention nearly or even fully developed already having marked height acceleration early
- Often missed in first affected child in family because of infrequency of visits to PMD for WCC visits in this age group
- No proven treatment strategies since often identified late
  - If reasonable remaining growth potential, transient interruption of the HPG axis may be considered using GnRH analogs without or with added GH
  - These drugs not FDA-approved to treat rapid tempo puberty

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Summary - Key Points

- Males considered precocious if sexual development before 9 years
- Females considered precocious if before 8 years; many use appearance of secondary sex characteristics before 7 yr in African-American females, 8 yr in Caucasian females
- Consider organic disease in females in the “in-between zone” (or any other time) if clinical findings are suggestive (i.e., rapid height velocity, bone age maturation, rapid change in pubertal status, etc.)
- Adrenarche can begin at 6-8 years with increase in adrenal androgens (DHEA & DHEAS)

Summary - Key Points

- Causes of isosexual precocious puberty:
  - Central (True and Complete) Precocious Puberty
  - Pseudoisosexual Precocious Puberty
  - Incomplete Precocious Puberty

Summary - Key Points

- Management/treatment:
  - CPP: focus management of underlying disorder if due to specific remediable anatomic abnormality of CNS; may need to inhibit HPG axis with long-acting GnRH agonists
  - pseudoisosexual precocious puberty: treat primary disease
  - premature thelarche and/or premature adrenarche: follow closely for possible future signs of CPP or functional ovarian hyperandrogenism

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