Disorders of growth and Puberty: Distinguishing Normal Variants From Problems Which Need to be Referred

M-3 lecture outline ------- Paul Kaplowitz, MD

I. Assessment of growth
A. Interpretation of standard growth charts
   1. most children maintain growth along standard percentile channels after age 3
   2. deviation from this pattern based on a single measurement is most often based on a faulty measurement, but progressive deviation based on 2-3 points in a concern
   3. a child with Ht slightly < 5th percentile is often a short-normal child and need not be referred if the growth rate is normal
B. Use of height velocity charts
   1. help assess normality of growth rate at different ages of based on accurate measurements at least 4-6 mon apart
      a. wall-mounted devices far better than platform scales
   2. between 4-10 years, height velocity 5-6 cm/ yr is average
   3. height velocity < 4 cm/yr is usually subnormal unless it occurs after the peak of the pubertal growth spurt
C. Interpretation of bone age
   1. determined by comparing hand/ wrist x-rays to an atlas of standard X-rays of hands of different sages and both sexes
   2. most short children have delayed bone age
      a. this finding thus has very limited diagnostic value
   3. bone age useful in predicting adult height

II. Classification of short stature
A. Normal variant patterns
   1. constitutional growth delay – most common: healthy child growing parallel to and below 5th percentile; bone age and puberty delayed and adult height in low-nl range (5’5-5’9)
   2. familial short stature
      a. short parents: growth rate normal; bone age ~ chron age
      b. adult height short but appropriate for genetic potential
   3. patients with above average features can be followed by PCP
B. Primary growth failure
   1. usually prenatal onset (intrauterine growth retardation: BW < 2500 g in term infant)
   2. diverse category includes maternal factors (fetal alcohol syndrome), skeletal dysplasia (achondroplasia), chromosomal disorders (Turner, Down syndrome), and various syndromes with characteristic dysmorphic features
   3. adult height usually moderately to severely compromised
C. Secondary growth failure (systemic non-endocrine disease)
1. clue: weight usually more affected than height  
2. malnutrition is most common etiology in this category  
   a. inadequate calories: poverty, maternal neglect  
   b. bowel disorders: inflammatory bowel disease, malabsorption, celiac disease, cystic fibrosis  
   c. chronic renal disease (RTA, chronic renal failure)  
   d. severe cardiopulmonary disease  
   e. chronic anemia (e.g. sickle cell)  

D. Endocrine disorders: make up < 5% of all short kids  
1. clue: height either equally or more affected than weight  
2. hypothyroidism  
   a. congenital: diagnosed on newborn screening by low T4/ high TSH and started treatment by 2 weeks of age → no growth failure  
   b. acquired: usually due to Hashimoto’s thyroiditis; presents with goiter, hyperthyroid symptoms, and/ or growth failure  
3. glucocorticoid excess: endogenous (Cushion’s Disease rare in childhood) or due to exogenous oral steroid therapy  
   a. see trunkal obesity accompanied by poor linear growth  
   b. patients with simple (exogenous) obesity are tall for age; do not generally need an endocrine evaluation  
4. growth hormone deficiency (see below)  

III. Growth hormone Deficiency  
A. Suspect this Dx in patients who are very short and are falling further below the 5th percentile with age (most grow < 4 cm/ yr)  
   1. occasionally also Dx GH deficiency in children of normal height who start to cross the percentile channels (see B-3 below for causes)  
B. Cause is usually a deficiency of hypothalamic GRF  
   1. most cases are idiopathic (no anatomic lesion seen on MRI)  
   2. coexisting deficiencies of TSH (low T4/normal TSH), ACTH, LH, FSH, and ADH may provide diagnostic clues  
   3. organic causes include trauma (esp. craniopharyngioma), radiation, trauma, infection, septo-optic dysplasia (congen)  
C. Diagnostic tests  
   1. random GH levels are useless due to the pulsatile nature of GH secretion (levels are low most of the day)  
   2. IGF-1/Somatomedin C and IGF-BP3 are useful screening tests  
   3. Provocative tests: clonidine, L-dopa, arginine, insulin  
      a. failure to increase GH to > 10 ng/ml after stimulation with 2 of above agents is the “gold standard” for GH deficiency  
      b. note that some kids of normal height “fail” GH testing  
D. Growth hormone therapy  
   1. given by SC injection daily (or 6 days/week); doses bases on weight (0.2-0.3 mg/kg/week) – cost is $10- 30,000/ year)
2. GH-deficient patients typically increase growth rate from 3-4 cm/yr to 9-12 cm/yr during first year of therapy
3. Response wanes after first year but continue to have catch-up growth until they reach the 10th-50th percentile, then they follow this percentile channel until they reach a normal adult height
4. GH also improves growth at least initially in non-GHD kids, though effect is not as dramatic
   a. in "idiopathic" short stature, effect on adult height is small (0-3” in various studies) relative to the cost and effort
   b. GH FDA-approved for growth failure due to renal disease and in Turner syndrome, where both acute increases in growth and improved adult height have been demonstrated

IV. Disorders of puberty
A. Normal puberty
   1. females: breast first sign – mean age of onset now 10 years (earlier in black girls) with normal range of 7-13 years; menses typically start 2-3 years after thelarche
   2. males: increase in testicular size (to > 2.5 cm) is earliest sign; normal range is 9-14 years
   3. pubic hair can appear at the same time, earlier, or later than above; is related to increased adrenal androgen secretion, not activation of the hypothalamic-pituitary-gonadal axis
B. Common normal variants of puberty – don’t need to refer
   1. premature thelarche: isolated early breast development without other signs of puberty such as growth spurt; usually seen in girls < 3 years old
   2. premature pubarche (adrenarche): appearance of pubid and/or axillary hair typically in 3-7 year old girls or boys without other signs of androgen excess
   3. pubertal gynecomastia: significant breast tissue in boys typically seen in mid-late puberty due to physiologic increase in conversion of testosterone to estrogen; endocrine evaluation is rarely helpful
C. Precocious puberty
   1. central (true) precocious puberty: due to early activation of the HPG axis with enlarging gonads, increase in LH, FSH, sex steroids
      a. idiopathic (~90% in females, 50% in males = MRI negative)
      b. CNS tumors: astrocytomas, gliomas, hamartomas
      c. Congenital malformation: cysts, hydrocephalus
   2. peripheral precocious puberty: gonadotropin-independent
      a. gonadal sex-steroid secreting tumors
      b. non-salt losing congenital adrenal hyperplasia (males)
      c. virilizing adrenal tumors
      d. familial male precocious puberty: activating LH receptor mutation
   3. treatment of central precocious puberty:
a. prevents progression of physical changes of puberty and menses, slows growth and rapid advancement of bone age to prevent adult short stature
b. best treatment: monthly dose of a depot preparation of a synthetic GnRH analogue (Lupron) – works by blocking pulsatile stimulation of pituitary by endogenous GnRH

D. Delayed puberty in boys (onset after 14 years)
1. constitutional delayed puberty: very common, boys typically short, healthy, BA delayed by 2 or more years
   a. can either wait for spontaneous puberty or give a brief course of androgen Rx (e.g.) 4 monthly injections of testosterone) to trigger puberty if the patient is anxious

2. gonadotropin deficiency: can be either isolated (e.g. Kallmann’s syndrome with anosmia) or associated with multiple pituitary deficiencies, such as GH, TSH, ACTH
   a. if fail to progress over a course of androgens, will need long-term androgen replacement

3. primary hypogonadism (testicular failure): most common causes are radiation, orchiopexy, or Klinefelter’s (47,XXY)
   a. major diagnostic clue is small to absent testes
   b. diagnosis confirmed by finding of increased LH & FSH due to decreased negative feedback

E. Delayed puberty in girls
1. constitutional delay much less common that in males
2. extreme thinness (e.g. anorexia nervosa) and/or heavy exercise (gymnasts, ballet dancers, swimmers) often delay puberty
3. gonadal dysgenesis (Turner syndrome): complete or partial monosomy of the X chromosome (50% are 45, XO)
   a. short stature seen in > 90%; mean adult height 4’9"
   b. common physical features include webbed neck, high-arched palate, cubitus valgus, upturned fingernails
   c. in girls > 10 years old, increased LH & FSH are typically found
   d. definitive diagnosis requires peripheral blood karyotype
   e. with estrogen and progestin replacement, menses occur but fertility only possible with egg transfer