Disorders of Growth and Puberty: How to Recognize the Normal Variants vs Patients Who Need to be Evaluated

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Interpretation of Growth Charts

- Most children follow their standard growth %ile channels after age 3
  - remember that 5% of normal children will fall below the 5th %ile at any age
- Height velocity charts are useful for assessing normality of recent growth
  - for 4-10 yrs of age, 5-6 cm/yr is average
  - growth < 4 cm/yr usually abnormal
  - need wall-mounted device for accuracy

What is the value of a bone age?

- Determined by comparing an X-ray of the hand and wrist to an atlas of standards for boys and girls of different ages
- Most short children have delayed bone ages: finding has limited diagnostic value
- Bone age most useful in assessing potential for future growth
  - 10 y.o. boy with BA of 10 is 78.4% of his adult height; but if BA = 7, he is 72% of adult height
Classification of Short Stature

- Normal variant growth patterns
  - constitutional growth delay
  - familial short stature
- Primary growth failure
  - usually have intrauterine growth retardation
- Secondary growth failure (chronic illness, malnutrition)
- Endocrine disorders (<10%)

Constitutional Growth Delay

- Most common cause of short stature
- Growth slows from 6 months - 2 yrs, then parallel to but below 5th %ile thereafter
- Bone age and onset of puberty usually delayed 2-4 years
  - Bone age useful for making height prediction
- Adult height usually in low-normal range

Familial Short Stature

- Height is below 5th %ile but growth velocity is normal
- Parents are shorter than average
  - Target height = (Mother’s height + father’s height)/2 + 2.5” (for boys); - 2.5” (for girls)
- Bone age within one year of chronologic age; average age of puberty
- Adult height subnormal but appropriate for heights of parents

Primary Growth Failure

- Usually of prenatal onset
  - intrauterine growth retardation noted at birth; birth weight < 2500 gm (5 1/2 lb) at term
- Maternal factors
  - severe malnutrition, hypertension, fetal alcohol syndrome
- Skeletal dysplasias (e.g. achondroplasia)
- Chromosomal disorders (Turner syndrome, Down syndromes)
- Various syndromes with dysmorphic features e.g. Russell-Silver, Noonan
Secondary Growth Failure
(Chronic illness, organ system disease)

- Weight usually more affected than height
- Malnutrition is most common etiology
  - inadequate calories, maternal neglect
- Bowel disease
  - Inflammatory bowel disease (Crohn’s), malabsorption, celiac disease, CF
- Chronic renal disease
  - renal tubular acidosis, chronic renal failure
- Other: cardiopulmonary, chronic anemia

Endocrine Causes of Short Stature

- Make up < 10% of short children
- Clue: height often more affected than weight
  - subcutaneous fat stores preserved
- Growth velocity usually subnormal

Major etiologies:
- Hypothyroidism (primary): acquired
- Glucocorticoid excess
- Growth hormone deficiency

Case #1: Evaluation of short stature
A 6 year old girl is referred who was 7 lb 6 oz at birth but by age 18 months was clearly small for her age. Since then, she is growing slowly and falling further behind her peers. She has never been hospitalized and is on no medications. Her height is well below the 5th %ile and weight is at the 5th %ile.

1) What additional history would be helpful?
2) What do you need to be looking for on PE?
3) Construct a DDx for this patient.
4) What screening laboratory tests would help you evaluate the different possibilities?

Hypothyroidism as a cause of short stature

- Congenital hypothyroidism rarely causes growth failure
  - diagnosed by newborn screening & on treatment within 2 weeks of age
- Suspect acquired hypothyroidism if:
  - normal growth followed by deceleration
  - suggestive symptoms: lack of energy, cold intolerance, dry skin, constipation
  - PE: goiter, puffy facies, ?HR, dry skin
- Diagnosis: low T₄ and very elevated TSH
Glucocorticoid excess as a cause of short stature

- Suspect mainly if child has had recent rapid weight gain and normal growth rate do not have glucocorticoid excess
- Look for trunkal, not generalized obesity
- Endogenous Cushing’s syndrome (pituitary or adrenal tumors) very rare in childhood
- Exogenous glucocorticoids used for asthma, joint disease, etc. often cause poor growth

When to suspect GH deficiency as the cause of short stature

- Height usually well below 5th %ile
- With time, patient’s height falls further behind
  - growth velocity usually below 4 cm/year
- Nothing in history or on exam to suggest a significant chronic illness
- Even if weight ↓, SC fat stores are adequate

When to suspect GH deficiency

- Evidence of other pituitary deficiencies
  - TSH: see ↓TSH with non-elevated TSH
  - ACTH: severe fatigue, hypoglycemia, low am cortisol levels
  - ADH: inability to concentrate urine due to diabetes insipidus
  - LH and FSH: very delayed puberty or arrested puberty
Causes of GH deficiency

- Hypothalamic dysfunction
  - idiopathic (either isolated GHD or multiple deficiencies)
  - CNS tumors (esp. craniopharyngioma)
  - congenital brain malformations (septo-optic dysplasia, holoprosencephaly)
  - exogenous (head trauma, CNS infection)

- Pituitary GH deficiency
  - defective gene for GH; congenital aplasia
  - tumors (craniopharyngioma), histiocyte
  - surgery, CNS irradiation

Diagnosis of GH deficiency

- Screening Tests
  - random GH levels are useless
  - IGF-1/somatomedin-C is decreased in 70-80% of GHD children
  - IGF binding protein-3: similar accuracy

- Gold standard is still provocative testing: commonly used agents include
  - clonidine p.o
  - insulin hypoglycemia
  - L-dopa, arginine I.V.

- Failure to GH to > 10 ng/ml after two tests is considered diagnostic of GHD

Growth Hormone Therapy

- Given by SC injection
  - daily better than q.o.d; b.i.d no better than q.d

- In GH deficiency, see 1st year increase in growth rate from 3-4 cm/yr to 9-12 cm/yr

- Waning effect after 1st year, but continue to have catch-up growth until patient reaches height %ile channel appropriate for genetic potential

- Can usually achieve normal adult height

GH Therapy for Non-GH Deficient Short Stature

- In children with constitutional growth delay or “idiopathic” short stature, growth rate improves in 1st year, but effect on adult height is limited (1-3”)
  - Is it worth $10-30,000/yr?

- In Turner syndrome (mean adult ht 4’9”), GH can add 3-5” to predicted adult height

- In chronic renal insufficiency, GH therapy can produce catch-up to normal range

Growth hormone therapy in a girl with Turner syndrome showing a large increase over the initially predicted ht of 4’5”
Assessment of Puberty: Females
- Breast development is usually the first sign
- Age at which breasts develop seems to be earlier than in past
  - 6% of white and 25% of black girls already have breast tissue by age 8 yrs
- Pubic hair: due to adrenal androgens
  - can appear in normal girls as early as 6-8 yrs
- Menarche: occurs 2-4 yrs after breasts
  - average age = 12.7 years

Assessment of Puberty: Males
- Testicular enlargement (>2.5 cm) due to ↑ gonadotropin secretion is the first reliable sign
- Increased linear growth, growth of penis and pubic & facial hair, voice change are due to ↑ androgens
  - these changes occur 1-2 yrs later
- Most boys start puberty age 11-13
  - onset before age 9 or no evidence of puberty by age 14 should be evaluated

Case #2: Evaluation of early puberty
A 4 year old girl is seen because for the past year parents have noted growth of sparse but curly pubic hair and an adult-type underarm odor, but little if any breast tissue.
1) What additional history would be helpful?
2) Why is assessment of growth so important?
3) What is most important on physical exam?
4) What is the most likely diagnosis?

Premature Adrenarche
- Isolated growth of pubic and/or axillary hair in boys or girls <7-8 years old
  - most common in females and blacks
  - usually get adult-type axillary odor
- Due to a precocious increase in secretion of weak androgens (DHEA) by the adrenals
  - not related to activation of HPG axis
- If growth rate is normal; no virilizing signs, one can exclude pathological androgen disorder and follow clinically without referring

Premature Thelarche
- Isolated early growth of breast tissue without other signs of puberty
  - no growth acceleration, genital changes, or menses; serum LH, estradiol usually not ↑
- Most often seen in girls < 3 years; if seen < 1 year, may have persisted from newborn
- If growth is normal and breast changes little over time, can follow clinically without lab tests or referral
Pubertal gynecomastia
- Common for boys in mid-late puberty to develop glandular breast tissue
- Related to rising testosterone production and conversion to estradiol
- More common in obese than thin boys
- Pathologic causes are very rare
- Endocrine evaluation usually not helpful
- Referral is appropriate in severe cases, especially if there is emotional distress

Differential diagnosis of precocious puberty
- Normal variants
  - premature thelarche
  - premature adrenarche
- Central (true) precocious puberty
  - mediated by rise in LH and FSH
  - gonads bilaterally enlarged
- Peripheral precocious puberty
  - independent of gonadotropins
  - gonads usually not enlarged (prepubertal)

Central (True) Precocious Puberty
- For girls, definition of when puberty is precocious has recently changed:
  - old: < 8 yrs; new: < 7 yrs (white girls); < 6 yrs (lack girls)
- For boys, puberty onset < 9 years is considered abnormal
- In girls, one recent student shows 80% below age 6 and 98% age 6-8 are idiopathic (normal MRI)
- in boys, incidence of organic etiologies more common

Causes of precocious puberty
- CNS tumors
  - usually astrocytomas or gliomas
- hamartomas
  - developmental defect in 4th ventricle
- congenital CNS anomalies
- CNS trauma, infections

Treatment of Central Precocious Puberty
- Best therapy is synthetic long-acting GnRH analogs (e.g. Depot Lupron given monthly IM)
  - blocks pulsatile stimulation of pituitary gonadotropes by endogenous GnRH
  - Prevents progression of pubertal changes and onset of menses
  - Slows rapid growth acceleration and stops rapid ↑ of BA; prevents loss of adult height
  - Cost: $6000-10,000/year; need to be sure that benefit is great enough to justify

Case # 3: Evaluation of delayed puberty
A 15 year old boy is concerned because he has not started to physically mature. His PMH is non-contributory. He looks 12-13 years old; ht/wt are just < 5th %ile. Penis and pubic hair are prepubertal but a modest ↑ in testicular size is noted.

1) What family history would be useful?
2) What diagnostic studies might be helpful?
3) What is the most likely diagnosis?
4) Would you offer this boy any therapy?
### Delayed Puberty in Boys

**failure to progress by age 14**

- Constitutional growth delay (common)
  - most boys look healthy but often thin; often have positive FH
  - bone age delayed 2-4 yrs; height potential normal
  - will eventually mature but waiting is often stressful
    - may get teasing and social isolation
    - as other boys have their growth spurt, these boys fall further behind

### Delayed Puberty in Girls

**failure to progress by age 13**

- Constitutional delay relatively uncommon in girls compared to boys

- If patient is very thin, think of anorexia (distorted body image) or ↑↑↑↑ exercise
  - especially gymnasts, ballet dancers, swimmers

- If patient is short, think of Turner syndrome (even if no obvious physical features)
  - LH, FSH are good screens for gonadal failure

### Treatment of boys with constitutional delayed puberty

- Waiting eventually resolves problem but may not address present concerns of pts
- 4 month course of androgen therapy (e.g. IM depot testosterone 100 mg/mo x 4) results in excellent growth spurt and genital growth cost: about $30-$50
- At follow-up visit 4 months after androgens stopped, see ↑ in testicular size and serum testosterone → puberty is progressing

### Gonadotropin deficiency (rare)

- isolated (e.g. Kallmann syndrome w/ anosmia)
- associated with other pituitary deficiencies
- Primary testicular failure
  - s/p testicular radiation, orchiopexy
  - history, ↑ LH & FSH usually diagnostic

### Clinical Evaluation: Endocrine Studies

![Graph showing endocrine studies for Turner syndrome](image-url)