Outline
- Review factors influencing growth
- Differential diagnosis
- Diagnostic studies
- Therapeutic options, i.e. growth hormone
- Discussion of selected growth charts

Growth
- Growth is a fundamental process of childhood that should be followed longitudinally by the primary care physician.
- Ongoing systemic pathologies may impact growth, although typically for a pathology to be that severe, other symptoms would also be manifested.
The Short Child

Definitions

- **Short stature**: absolute height-for-age below a designated cut-off, e.g. height <3%ile
- **Growth failure**: interval of poor growth velocity, e.g. growth velocity <5%ile; for individuals still within the normal curves, crossing two major percentile curves

Growth velocity chart
Short Stature: common components

• Familial short stature
• Constitutional growth delay

Genetic height

• Mid-parental target height calculation:
  – Average parents’ heights; add 2.5” for male, subtract 2.5” for female
• Provides framework for evaluating genetic influences of growth, but deviation from the midparental target height can occur (+/- 2-3 inches)
• Short stature tracking along path of mid-parental target height does not discount a well-described pathology that produces the phenotype

Short Stature: DDx

• Chronic disease
  – ‘Silent’: chronic renal failure, celiac disease, inflammatory bowel disease
• Nutrition
• Genetic/Chromosomal
  – Turner syndrome
• Skeletal dysplasia
• Endocrine pathology
  – GH deficiency
  – Hypothyroidism
• Birth history of small-for-gestational age (no catch-up)
• Medications

Evaluation

• Review growth chart; assess growth velocity
• Bone age

• General screening labs, e.g. CBC, comprehensive metabolic panel, ESR
• Karyotype (girls)
• TSH, free T4
• Tissue transglutaminase, serum IgA
• IGF-I, IGF BP-3 to assess for GH deficiency
Poor yield of screening tests to identify a pathological diagnosis

1373 new patients coded for short stature

N=235

1138 excluded:
- height >3% percentile (58%); prior growth velocity <5 cm/y (6.5%); history, review of symptoms, or physical exam suggest underlying diagnosis (29%); incomplete medical chart (6.5%)

23% familiar short stature, 41% constitutional delay of growth and maturation, 36% idiopathic short stature

1.3% (n=3) w/ a new pathological diagnosis

Celiac, abnormal tTG – parents refused biopsy, possible IGF-1 receptor defect – lost to follow

98.7% (n=232) w/out a pathological diagnosis

GH deficiency

- Etiology
  - Hypopituitarism (congenital/genetic)
    - Multiple hormone vs. isolated GH deficiency
  - Iatrogenic: neurosurgical vs. radiation
  - Mass lesion
  - Trauma
- Diagnosis
  - Screening with serum IGF-I, IGF BP3
  - Low levels of IGF-I (± IGF BP3) are consistent with GH deficiency, therefore consider GH stimulation test with two provocative stimuli

Avoid ordering screening tests looking for chronic illness or endocrine cause, including CBC, CMP, IGF-1, thyroid tests, and celiac antibodies in healthy children who are growing at or above the 3rd percentile for height with a normal growth rate (i.e. not crossing percentiles) and with appropriate weight gain.

GH secretion is pulsatile
GH Research Society
Consensus Guidelines

- Evaluation for GH deficiency is warranted:
  - Height >3 SD below mean
  - Height >1.5 SD below mid-parental height
  - Height >2 SD below mean and growth velocity >1 SD below mean; change in height SD >0.5 for children >2 yr
  - Growth velocity >2 SD below mean x1 yr, or >1.5 SD below mean x2 yrs

Problems with GH stimulation tests

- Non-physiologic
- Arbitrary definitions
- Impacted by age dependency & sex steroids
- Limited accuracy
- Poor reproducibility
- Expense, discomfort, risks

Adapted from Rosenfeld & Cohen in Sperling’s Pediatric Endocrinology

Turner syndrome:
a common genetic condition associated with short stature

‘Pharmacologic’ use of GH

- Although Turner syndrome is not associated with GH deficiency, several studies have demonstrated an increase in final adult height in GH-treated girls
- Similarly, other conditions with associated short stature yet lacking classical, severe GH deficiency have also been demonstrated to improve growth velocity (and final adult height)

Rosenfeld et al., J Peds 1998
Paradigm shift

- As GH has been demonstrated to lead to improved height in conditions not associated with GH deficiency, FDA-approved indications for its use continue to evolve.
- This has begun to shift the focus from determining the underlying cause for poor growth to identifying which patients would most benefit from GH treatment.

Peak GH predicts response to exogenous GH poorly

GH: FDA approved indications

- GH deficiency (pediatric)
- Chronic renal insufficiency
- Turner syndrome
- Adult GH deficiency
- AIDS-associated wasting (adult)
- Prader-Willi syndrome
- SGA with failure of catch-up growth
- Noonan syndrome
- Genetic abnormalities of the SHOX gene
- Idiopathic short stature

Definition: Idiopathic Short Stature

- Short stature >2.25 SD below the mean in height for age and who are unlikely to catch up in height
- Extrapolates to final adult height of <5’3” in boys, 4’10” in girls
- Term ‘idiopathic’ implies other etiologies for short stature excluded
Psychosocial detriment

• Generally held assumption that short stature is associated with more life challenges
  — Teasing and juvenilization
  — Perception by others
  — Self-esteem
• Presumably, improving one’s height should relieve the psychosocial burden from being short

GH costs

• As a recombinant biosynthetic product, GH is now available in an ‘unlimited’ supply
• Annual cost for 30 kg child estimated at $15-20K/year (Allen, Pediatrics 2006)
• Excluding patients with GH deficiency, final height increase has been estimated at 0.5-1.0 cm/yr treatment, equating to costs of $35K/inch final height (Finkelstein et al., Arch Pediatr Adolesc Med 2002)

Endocrinologist’s dilemma:
wear of many hats

• Physician
• Scientist
• Patient advocate
• Psychologist
• Ethicist
• Insurance consultant
• Economist

Physician comfort level

• All children growing at >2 SD from mean (or significantly less than channel of mid-parental target height) should have careful consideration of possible etiologies
• Growth velocity >2 SD from mean warrants evaluation
• Children who meet FDA approved criteria for treatment with GH should have opportunity to meet with a pediatric endocrinologist to discuss potential risks and benefits of treatment
• Use of stringent criteria for diagnosis of idiopathic isolated GH deficiency
• Children at >5%ile would have to demonstrate compelling evidence to consider GH treatment
(Fictional) cases

- Options
  - (1) routine monitoring
  - (2) schedule additional follow up for monitoring
  - (3) diagnostic studies
    - Bone age x-ray
    - CBC, comprehensive metabolic panel
    - Other lab studies
  - (4) refer to Pediatric Endocrinology
Aromatase inhibitors can improve height in delayed puberty

Gain in height SDS

Mid-parental target height

T = testosterone
Lz = letrozole
Pl = placebo