“WHY IS JOHNNY SO SHORT?”
EVALUATING SHORT STATURE AND WHEN TO REFER

ASHLEY SMITH, PA-C
Endocrinology Associates
Scottsdale, AZ
Secretary, American Society of Endocrine Physician Assistants
Arizona State Association of Physician Assistants Spring CME Conference March 10, 2018

OBJECTIVES

Growth disorders
• Differentiate between normal and pathological growth and when is appropriate to refer to a specialist
• Recognize the pertinent personal and family history as well as physical exam findings in evaluating short stature
• Interpret skeletal age, mean parental height, and serological studies
• Illuminate the etiology of short stature using clinical presentation and objective evaluation

Pubertal Disorders/Contrasexual development
• Review of normal pubertal development
• Distinguish benign from pathological premature pubertal development
• Identify the pathogenesis of adrenogenital disorder
• Discuss the effects of precocious puberty and adrenogenital disorder on final height

GROWTH DISORDERS
SHORT STATURE ETIOLOGIES

- Constitutional Growth Delay
- Familial Short Stature
- Idiopathic Short Stature
- Small for Gestational Age
- Growth hormone (GH) Deficiency
  - Head trauma/cranial radiation
  - Achondroplasia
  - Noonan Syndrome
- Growth hormone (GH) Deficiency
- Prader-Willi Syndrome
- Turner Syndrome
- Precocious Puberty
- Down Syndrome
- Fetal – Alcohol Syndrome
- Hypothyroidism
- Congenital Adrenal Hyperplasia
- Systemic disease
- Anemia
- Inflammatory Bowel Disease
- Cardiovascular Disease
- Chronic Kidney Disease
- Celiac disease
- Type 1 Diabetes Mellitus
- Cushing’s Syndrome

GROWTH EVALUATION

- Gender-specific growth percentiles
- Abnormal growth patterns:
  - Crossing 2 growth percentiles
  - Failure to “catch up” by age 2 years

ABNORMAL GROWTH: HISTORY

- Birth history
  - Gestational age
  - Birth weight/length
  - Birth Trauma/Hypoglycemia/jaundice (may indicate GH deficiency)
  - PMH: head trauma, radiation exposure, systemic disease
  - Fam hx: consanguinity, “late bloomers,” short stature

- Mean parental height (MPH)
  - Males
    - Final height (cm) = [father's height + (mother's height + 13cm)]/2
  - Females
    - Final height (cm) = [mother's height + father's height – 13cm)]/2

Mean parental height (MPH)

- Males
  - Final height (cm) = [father's height + (mother's height + 13cm)]/2
- Females
  - Final height (cm) = [mother's height + father's height – 13cm)]/2
ABNORMAL GROWTH: HISTORY

- Eating habits
  - Malnutrition, failure to thrive (FTT), food intolerances
- ROS
  - Fatigue, lethargy, weight loss
  - Skin pallor, dryness, café au lait spots, striae, bruising, hair loss, brittle nails
  - Thelarche, palpitations, chest pain
  - Increased abdominal adiposity, abdominal pain/bloating, diarrhea, constipation, flatulence, change in stool consistency, hematochezia
  - Pubarche, polyuria

ABNORMAL GROWTH: EXAM

- Overweight/obesity, bradycardia, hypo- or hypertension
- Skin pallor, dryness, café au lait spots, striae, bruising
- Syndromic or round facies, webbed neck, posterior hair line, conjunctival pallor, loss of outer third of eyebrows
- Limb atrophy/shortening, wide carrying angle, scoliosis, hypotonia
- Thelarche, widely spaced nipples, arrhythmia, murmur
- Central adiposity, abdominal tenderness, bowel sounds
- Pubarche

SHORT STATURE SYNDROMES

TURNER SYNDROME

NOONAN SYNDROME
Skeletal age:

- **Skeletal age/Bone age (BA)**
- Radiograph of left hand/wrist
- Use conversion factor to predict adult height
- **Delayed:** constitutional growth delay, hypothyroidism, GH deficiency, chronic illness
- **Normal:** familial short stature
- **Advanced:** precocious puberty
CONSTITUTIONAL GROWTH DELAY: "LATE BLOOMERS"

- Most common cause of short stature
- Possible fam hx of constitutional growth delay
- Deceleration in growth and weight in infancy, then follow normal growth curves
- Normal height velocity
- Lower weight vs height/FTT
- **Chronological age > BA**
- Predicted height inside of 2.5 SD of MPH
- Diagnostic key: **delayed pubertal onset**
- Height and weight increased before sexual maturity
- Treatment: reassurance

FAMILIAL SHORT STATURE

Fam Hx of short stature
- Check mean parental height!
Findings:
- Normal weight/overweight
- Normal pubertal stages
- Normal height velocity
- Chronological age = BA
- Predicted height inside of 2.5 SD of MPH
Treatment:
- Typically reassurance
- Growth hormone is controversial
FDA-APPROVED INDICATIONS FOR GH THERAPY IN PEDIATRICS

- Constitutional Growth Delay
- Familial Short Stature
- Idiopathic Short Stature
- Small for Gestational Age
- GH Deficiency
- Achondroplasia
- Noonan Syndrome
- Prader-Willi Syndrome
- Turner Syndrome
- Down Syndrome
- Fetal – Alcohol Syndrome
- Hypothyroidism
- Systemic disease
- Anemia
- IBD
- CKD
- CVD
- Celiac disease
- Type 1 DM
- Cushing’s Syndrome

GROWTH HORMONE PHYSIOLOGY

- Somatotropin
  - Synthesized by somatotrophs in the anterior pituitary
  - Release is pulsatile
  - Action:
    - Stimulates growth and cell reproduction
    - Stimulates production of cartilaginous and muscle tissue
    - Stimulates hepatic production of insulin-like growth factor 1 (IGF-1)
- Somatostatin (growth hormone inhibiting hormone)
  - Secreted by hypothalamus
  - Provides negative feedback

GH: A COUNTERREGULATORY HORMONE

- In response to hypoglycemia
  - Pancreas: Decreased insulin and increased glucagon
  - Sympathetic nervous system: Increased epinephrine/norepinephrine
  - Pituitary: Increased GH and ACTH
  - Increased IGF-1 and cortisol
  - Increased hepatic glycogenolysis and gluconeogenesis
PATHOLOGICAL SHORT STATURE:
GROWTH HORMONE DEFICIENCY

- Measurement of GH level and age-adjusted IGF-I is required
  - IGF-I is more stable and a reflection of GH secretion and action
  - Used for screening, diagnosis, and monitoring of growth hormone deficiency
- Clinical features of GH deficiency
  - Body is proportionate
  - Delayed puberty
  - Overweight
  - Symptoms of pituitary adenoma

GROWTH HORMONE DEFICIENCY: DIAGNOSIS

- Consider GH stim test
  - Most diagnoses are made based on GH/IGF-I levels and clinical picture
  - May be required for insurance approval
- GH stimulation test/insulin tolerance test:
  - Measure GH in response to induction of hypoglycemia
  - Gold standard for diagnosing GH deficiency/pituitary dwarfism
  - Positive result: Peak GH < 5.0 μg/L

PATHOLOGICAL SHORT STATURE:
SMALL FOR GESTATIONAL AGE (SGA)

- Birth weight below 10th percentile for age
- Most infants play “catch up” and cross percentiles into normal ranges by 2 yo
- Pathological growth:
  - Persistent low length (-2 SD) after 2 years old
  - Tx with GH should be considered
PATHOLOGICAL SHORT STATURE:
IDIOPATHIC SHORT STATURE

- No phenotypic or pubertal anomalies
- All other etiologies ruled out
- Current height <3rd percentile for age
  - >2 SD below the mean for age (AAP)
  - >2.25 SD below the mean for age (FDA)
- Predicted height > 2.25 SD below MPH
- BA >2 SD below mean for age
- May have low IGF-1 but pass GH stim test

GROWTH HORMONE THERAPY:
INITIATING TX

- Subcutaneous daily injection of recombinant human growth hormone (rhGH)
- Must treat prior to closer of epiphyseal plate
- Dosed according to weight and indication
- Requires use of a specialty pharmacy

GROWTH HORMONE THERAPY:
ADVERSE EFFECTS

- Slipped capital femoral epiphysis (SCFE)
- Fractured growth
- Knees or hip pain with limp
- Pseudotumor cerebri: Ask about HA!
- Hyperglycemia/Insulin resistance
  - Monitor A1c
  - Ask about polyuria/polydipsia
- Musculoskeletal effects
  - Scoliosis
  - "Growing pains"
- Sleep apnea
- Gynecomastia
- Increased conversion from thyroxine (T4) to triiodothyronine (T3) without hypothyroidism

Slipped capital femoral epiphysis
GROWTH HORMONE THERAPY:
MONITORING

- Monitor age- and gender-specific IGF-I levels
- Safety, not efficacy
- Monitor bone age annually
- Reassess predicted height vs target height/MPH
- Duration of tx

PUBERTAL DISORDERS

RACE-ADJUSTED NORMAL RANGES
- Boys: age 9-14 yo
- Girls:
  - Adrenarche: after age 8
  - Thelarche: age 8-14 yo
  - Menarche: two years following thelarche
  - Associated with bone age
  - Age at onset is inversely related to predicted height

NORMAL VARIATIONS
- Benign premature thelarche: onset prior to age 3
  - If present after age 7 or 8, may progress to precocious puberty
- Premature adrenarche: elevated DHEA
  - More common in girls
  - Absence of additional pubertal development
**Precocious Puberty**

- Age at onset of pubertal development 2 SD earlier than population norms
- Secondary sex characteristics prior to age 8 in girls and age 9 in boys
- Rapid linear growth leads to premature skeletal maturation and short stature: check bone age!

**Central Precocious Puberty:** Gonadotropin-dependent
- Elevated gonadotropin releasing hormone (GnRH) → elevated gonadotropins → elevated gonadal steroids

**Peripheral Precocious Puberty:** Gonadotropin-independent
- Elevated gonadal steroids despite low gonadotropins

**Central Precocious Puberty: Gonadotropin-Dependent**

- **Causes**
  - Idiopathic*
  - CNS tumors or abnormalities
  - Girls > boys
  - Reproductively normal progression, but premature
  - Short stature
    - Early exposure to gonadal steroids leads to premature closure of epiphyseal plate

**EVALUATION**

- **Serological studies:**
  - LH, FSH, estradiol or testosterone
  - LH/FSH ratio >1 suggests puberty
  - +/- DHEA-S, +/- progesterone

- **Imaging:**
  - MRI brain/pituitary
  - Bone age: Advanced
  - Pelvic US shows normal ovaries/uterus for pubertal stage but premature for age

**TREATMENT**

- **GnRH analogue**
  - Binds to GnRH receptors
  - Initial increase in gonadotropins
  - Subsequent desensitization and down-regulation of gonadotropins
PERIPHERAL PRECOCIOUS PUBERTY: GONADOTROPIN-INDEPENDENT

- Rare cause of precocious puberty
- Approximately 50% of cases of precocious puberty in boys
- Causes:
  - Exposure to gonadal steroids outside of hypothalamic-pituitary-gonadal axis (eg tumor, exogenous)
  - Congenital adrenal hyperplasia
  - McCune-Albright Syndrome F > M

Treatment: target underlying condition

CONTRASEXUAL DEVELOPMENT

CONGENITAL ADRENAL HYPERPLASIA
CONGENITAL ADRENAL HYPERPLASIA:
21-HYDROXYLASE DEFICIENCY

ACTH

NO NEGATIVE FEEDBACK FROM CORTISOL

1) Increased adrenal or gonadal androgens
   - Acne, clitoromegaly, hirsutism, initial tall stature with ultimate short adult stature
   - Early exposure to gonadal steroids leads to premature closure of epiphyseal plate
   - Tx: GnRH analog

2) Cortisol deficiency
   - Hypoglycemia and decreased response to illness
   - May need emergency stabilization
   - Tx: Hydrocortisone (glucocorticoid and mineralocorticoid)

3) Aldosterone deficiency
   - Salt-wasting, hypotension
   - May or may not be present in CAH
   - Tx: Fludrocortisone (mineralocorticoid)

QUESTIONS?