"I think I have a superior brain and an inferior stature, if you really want to get brutal about it."
- Paul Simon

**DISCLOSURES**

NO conflicts of interest

NO financial disclosures

**OBJECTIVES**

1. Understand patterns and physiology of normal growth from birth to young adulthood.
2. Be able to describe how to assess growth in a child.
3. Develop a DDx for short stature / growth failure.
4. Know how to order a basic work-up for short stature.
5. Know growth hormone indications, and how to counsel families regarding this therapy.
6. Develop a working approach to patients of tall stature.

**PATTERNS OF NORMAL GROWTH**

**INTRAUTERINE**

Extrinsic
- Maternal
  - Size and Nutritional status
  - Placental sufficiency

Intrinsic
- Fetal insulin – most influential hormone on fetal size
- Maternal IGF-1, IGF-2 and placental GH
- Fetal GH & Thyroxine – relatively small roles

SGA
- BW < 10% for GA (or more than 2 SD below mean)

IUGR
- Deviation and reduction in expected fetal growth pattern.

**Intrauterine growth deficits → poor growth later in life** (esp. if growth insults occur early in gestation)**

→ SGA can be indication for GH therapy ←
**Patterns of Normal Growth**

**Infancy / Early Childhood**
- Common to cross percentiles (↑ or ↓)
  - 1st 2 years of life
  - Maternal factors – reduced influence
  - Unless permanent intrauterine insult
  - Nutrition, Environment, infant’s hormones – bigger role
- Growth is rapid
  - 24 cm/yr (Year 1)
  - 12 cm/yr (Year 2)
  - 8 cm/yr (Year 3)

**Childhood**
- After 2-3 yrs of life, most healthy children assume “their curve”
  - Genetically determined
  - Stable GV until puberty
  - ~5-7 cm/yr

**Measurements must be done carefully and with great consistency**

**Infancy / Early Childhood**

**Total Adult Height**
- 85% → Pre-pubertal growth
- 15% → Pubertal growth

**Influencing factors:**
- Androgens
- Estrogens
- Nutrition
- Growth Hormone
- Ethnicity

**Childhood**

**Puberty**
- Thyroid Hormone
- Nutrition
- Ethnicity

**Influencing factors:**
- Androgens
- Estrogens
- Growth Hormone

**Growth so long as epiphyses open**
- Once closed epiphyses
  - Estrogen → No linear growth
- Girls → 15 yo
- Boys → 17-18 yo

**Physiology of Growth**

**Growth Hormone**
- Stored in secretory granules
- Released in discrete bursts
- Increased during Stage 4 sleep
- Typically occurring between 11 PM and 2 AM
**Growth Hormone Regulation**

- GHRH
  - Dopaminergic control
  - Clonidine – eg stimulation testing
  - Glucagon and Ghrelin
  - Hypoglycemia – counter-regulatory
- Somatostatin
  - G1-coupled protein
  - Inhibition of GH secretion
  - Regulates pulse frequency of GH
  - Arginine blocks somatostatin inhibition
- Leptin
  - Produced by fat cells
  - Exercise

**Growth Hormone Action**

- **Brain**
  - IGF1Ps
  - IGF1
  - GH
  - Target Tissue
  - Growth

**Anthropometry**

- Measuring sizes and proportions of the human body

**Common measurements for monitoring growth**

- **Newborn and Infant**
  - Length (measured laying down)
  - Weight
  - **FOC** (Fronto-Occipital Circumference)
  - Frontal bossing - Achondroplasia

**ASSESSING A PATIENT’S GROWTH**

- **Childhood and Adolescence**
  - Height
  - (can use arm span as surrogate - e.g. CP with spasticity)
  - Weight and BMI
  - Waist circumference
  - Limb proportions
  - Shortened limbs (rhizomelia, mesomelia, acromelia)
  - Elongated limbs (Klinefelter's and Marfan's)

**Limb Proportions:**

- **Upper Segment**
- **Lower Segment**
ASSESSING A PATIENT’S GROWTH

Limb Proportions:
Upper Segment
Top of head
Symphysis Pubis
Lower Segment
Symphysis Pubis
Floor

Ratio = ~1.7

Similar ratios (> 1) might be seen in achondrodysplasias with limb shortening.
ASSESSING A PATIENT’S GROWTH

Limb Proportions:
Upper Segment
Top of head to Public Symphysis

Lower Segment
Symphysis Pubis to Floor

ASSESSING A PATIENT’S GROWTH

Limb Proportions:
Upper Segment
Top of head to Public Symphysis

Lower Segment
Public Symphysis to Bottom of Feet

Ratio = ~1

ASSESSING A PATIENT’S GROWTH

- Recording data on Growth Curves
  - Two Types – CDC and WHO

  CDC
  (Ages 2 – 20 years)

  WHO
  (Ages 0 – 24 months)

  Established with predominantly breast-fed infants; high-quality, longitudinal studies to create “standards” of ideal growth

ASSESSING A PATIENT’S GROWTH

Other growth assessments
- Account for puberty
  - Tanner Staging (PH, B and T)
  - Growth Velocity (cm/yr)
    - Annualized from 3-6 month average
  - Skeletal Maturation
  - Bone Age

ASSESSING A PATIENT’S GROWTH

Bone Age
- Left hand and wrist by convention
- Allows for visualization of growth plates
- Utilized to estimate remaining growth potential
- “Advanced” or “Delayed”
- Estrogen → drives BA advancement

ASSESSING A PATIENT’S GROWTH

Predicting Adult Height
- Frequently is biggest concern
- Calculating a Target Height
  - Mid-parental Height (MPH)
  - See Adjust MPH
    - Add 2.5 cm for males
    - Subtract 2.5cm for females
  - Use bone age
ASSESSING A PATIENT’S GROWTH

EVALUATION OF SHORT STATURE

Building a DDx H&P+ Labs

"Everybody’s Different"
- Variant of normal (e.g. constitutional delay)
- Genetic or Familial Short Stature
- "No Gas in the Tank"
- Under-nutritioned
- Malabsorption (CF, Celiac, etc.)
- "Something hormonal"
- Growth Hormone Deficiency (Acquired or congenital)
- HYPOthyroidism
- HYPERcortisolim

"Chromosomes & Syndromes"
- Turner Syndrome (45 XO, Mosaics)
- Prader-Willi Syndrome (chromosome 15 – imprinting)
- Other (Russell-Silver, Cornelia de Lange)
- Underlying Medical Condition
- Kidney Disease (e.g. RTA)
- Congenital Heart Disease
- Poorly controlled DM
- Medication Side-effect
- SGA

EVALUATION OF SHORT STATURE

MCC short stature

- Constitutional Delay
  - Official dx made at adult ht and as a “dx of exclusion”
  - (our “dx” is identifying a pattern of growth)
  - MC presentation
    - Patient with NV status – except delayed bone age
    - Normal height parents
    - Other (+) h/o constitutional delay in parent
    - Normal BW and length
    - Slowed GV in 1st yr of life with tracking (nl GV) since

EVALUATION OF SHORT STATURE

"Everybody’s Different"
- Constitutional Delay (cont.)
  - Delayed puberty

Initial WORK-UP (before Endo referral)

- Well-documented:
  - Birth history
  - PMH
  - GV (if reliable past heights available)
  - Pubertal status
  - Predicted height (as well as any known sibling heights)
  - TSH, FT4
  - Bone Age
  - IGF-1, IGF-BP3
  - Chemistry
  - Karyotype (if female – ask for 40 cell count)
  - CBC and/or ESR (if suspicion for chronic disease)
  - Celiac panel
CASE #1 – SHORT STATURE

CC: Short stature

HPI: 6 yo male
BH: FT and AGA
PMH:
• No chronic conditions
• No surgeries
• No Malignancy or radiation
Diet: Regular pediatric diet – no significant issue
FH: (+) constitutional delay - MOC

ROS: Negative
• No steroid exposure
• No precocious puberty

Parental Heights
• MOC – 163 cm (64 inches)
• FOC – 171 cm (67 inches)
• Predicted $\Rightarrow \frac{[64 + 5] - 67}{2} = 68$ inches $\Rightarrow 5 \text{ ft 8 in} \sim 25\%$

What tests would NOT be considered an appropriate part of this child’s initial work-up:

A. Thyroid Function Tests (TSH and Free T4)
B. Celiac Panel
C. Early morning serum GH
D. IGF-1 and IGF-BP3
E. Gonadotropins (FSH and LH)
F. Bone Age
G. Chemistry (BMP)
H. ESR
I. CBC
J. Karyotype
CASE #1 – SHORT STATURE

Standard Work-up for CC of short stature

A. Thyroid Function Tests (TSH and Free T4)
B. Celiac Panel
C. IGF-1 and IGF-BP3
D. Bone Age
E. Chemistry (BMP)
F. Karyotype

Laboratory Results:

• Thyroid
  - TSH 2.1 (0.6 – 5.5)
  - FT4 1.0 (0.8 – 1.7)
• Celiac
  - TTG IgA negative
  - Total serum IgA 112 (29 – 256)
• IGF-1 70 (37 – 192)
• IGF-BP3 1835 (1500 – 3400)
• Chemistry – wnl
• Bone Age – delayed

“I think this picture is most consistent with constitutional delay or a late bloomer who will ultimately enter puberty late but reach his expected genetic height potential.”

“I would like to see him back in 3-4 months to track his growth.”

What would be the next most appropriate course of action?

A. Refer to GI for FTT
B. Order Growth Hormone Stimulation test
C. Send chromosomal microarray
D. Refer to genetics
E. Sweat test screen for CF
F. Brain MRI
G. Make the resident decide
**CASE #1 – SHORT STATURE**

**Stimulation tests (general principles)**
- Low hormone production
  - Under-stimulated Gland
  - Under-functioning Gland

**Speed up car down hill?**
- Foot off brake
- Foot on gas

**Interpretation:**
- FAILED test c/w GHD

**Time** | **GH level** | **Reference Range**
--- | --- | ---
0 minutes | 1.2 | Normal > 10
30 minutes | 3.5 | Intermediate 5-10
60 minutes | 4.9 | Subnormal <5
90 minutes | 4.0 |

**Indications for GH Therapy**
- GHD (congenital or acquired)
- Chronic Renal Failure
- Turner Syndrome
- Prader-Willi Syndrome (sleep study before)
- SGA or IUGR
- Idiopathic Short Stature

**What to expect from GH therapy?**

### Treatment Goals
- **GHD**
- **Turner**
- **SGA/IUGR**
- **Idiopathic**
- **CRF**

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*Modified from Endocrine University 2015, Dr. Peter Tebben*
CASE #2 – DELAYED PUBERTY

CC: Amenorrhea

- HPI: 17 yo female who has “never” had a period
- BH: FT, no complications, mild IUGR; (+) pedal edema
- PMH: No previous evaluations
- FH: MOC with late menarche (15-16 yo)
- Meds: No chronic meds or exposure to radiation
- Parental Heights – MOC (52 in.) and FOC (60 in.)

CASE #2 – DELAYED PUBERTY

Physical Exam:

- Short stature
- Pubertal Status
  - Tanner 1-2 breast
  - Tanner 4 pubic hair
- High-arched palate
- Pigmented Nevi
- Increased Upper-to-Lower segment ratio
- Broad, shield-like chest
- Wide-spaced nipples
- Increased carrying angle

CASE #2 – DELAYED PUBERTY

This patient has Turner syndrome; which of the following is NOT true concerning Turner Syndrome?

A. These patients have an increased risk of Chronic Lymphocytic Thyroiditis, celiac disease, obesity and DM
B. Not truly growth hormone deficient
C. Up to 30% will experience spontaneous pubertal development.
D. Some will have potential to become pregnant
E. Have increased risk of cardiac anomalies and HTN, but no increased risk for renal anomalies.

CASE #2 – DELAYED PUBERTY

Clinical Presentation

- Relatively common (~ 1:2000)
- Any age
- Frequently short stature and delayed puberty
  - Chromosomes in SS girl
  - Often without other physical stigmata

May present for other frequent comorbidities:

- Amenorrhea
- HTN and/or murmur (Coarctation, bicuspid aortic valve)
- Renal anomalies (e.g. horseshoe kidney – frequently incidental finding)

Pubertal staging can vary

- 20-30% spontaneous pubertal development
CASE #2 – DELAYED PUBERTY

Given their increased risk for various comorbidities, which are true regarding screening tests and schedules for Turner Syndrome patients?

A. At time of diagnosis, a hearing evaluation and an orthodontic evaluation (if > 7 yo) should be considered.
B. Cardiac echo or MRI q 3-5yr after dx
C. Teenage and adult girls screened annually for fasting lipids and BG
D. Thyroid and lipid screen annually
E. Bone Mineral Density q 3-5 yr

All of the above are correct

CASE #2 – DELAYED PUBERTY

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Screening Tests – AT DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>Cardio (4 pt BP's, MRI or Echo, ECG)</td>
</tr>
<tr>
<td>Renal U/S, hearing, growth/pubertal development; Support group referral</td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>Hip dislocation, scoliosis/kyphosis</td>
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<tr>
<td>4-10 years</td>
<td>TFT's, celiac</td>
</tr>
<tr>
<td>Orthodontia (age ≥ 7)</td>
<td></td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>Same as 4-10 year old screens</td>
</tr>
<tr>
<td>Ovarian function, BMD (age ≥ 18)</td>
<td></td>
</tr>
<tr>
<td>Liver enzymes, fasting BG, lipids,</td>
<td></td>
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</tbody>
</table>


CASE #2 – DELAYED PUBERTY

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Screening Tests – ONGOING MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>Cardiac</td>
</tr>
<tr>
<td>1st eval nl</td>
<td></td>
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<tr>
<td>• then prn symptoms</td>
<td></td>
</tr>
<tr>
<td>• Life-events (pregnancy, transition to adult care, etc)</td>
<td></td>
</tr>
<tr>
<td>• Or redo imaging – q 5-10 yr</td>
<td></td>
</tr>
<tr>
<td>• Only Echo at dx  MRI</td>
<td></td>
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<tr>
<td>1st eval abnl</td>
<td></td>
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<tr>
<td>• Per specialist’s recommendations</td>
<td></td>
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<tr>
<td>ENT and Audiology ANNUALLY</td>
<td></td>
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<tr>
<td>BP ANNUALLY</td>
<td></td>
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<tr>
<td>School Age</td>
<td>Liver enzymes and TFT's ANNUALLY</td>
</tr>
<tr>
<td>Dental / Orthodontic prn</td>
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</tr>
<tr>
<td>Educational and social progress ANNUALLY</td>
<td></td>
</tr>
<tr>
<td>Teensagers and Adults</td>
<td>Liver enzymes and TFT's ANNUALLY</td>
</tr>
<tr>
<td>Celiac prn</td>
<td></td>
</tr>
<tr>
<td>Age-appropriate screen of pubertal development</td>
<td></td>
</tr>
</tbody>
</table>

CASE #3 – TALL STATURE

CC: 7yo male self-referred for “early growth spurt”.

- **HPI:**
  - Noted increased linear growth x 1 yr
  - Child is currently at 75-90%
  - Feel he has become more moody as well
  - MOC and FOC
  - Didn’t “grow” until high school
  - Both are 25-50% height
- **PHI:**
  - FT, AGA; no chronic medications.
  - Surgeries: None (desired circ but told “he was too big”)
  - FH: Late-bloomers in parents:

- **Physical Exam:**
  - Ht and wt 75-90%
  - Limb proportions within normal ranges for age
  - Adult body odor noted
  - Tanner 2-3 pubic hair noted with sparse axillary hair
  - Testes 3 cc in size
  - Phallic appears enlarged
CASE #3 – TALL STATURE

What is the appropriate next step in evaluation?
A. Karyotype  
B. Brain MRI  
C. 17-Hydroxyprogesterone, DHEA-S, Testosterone and BA

What are the most likely complications of missing diagnosis?
A. Increased risk of breast cancer and infertility  
B. Increased risk of sz’s and pituitary deficiencies  
C. Compromised adult height, infertility, and small testes.

CASE #3 – TALL STATURE

17-OHP  1252   (< 120)
Testosterone  26   (< 2-3 for pre-pubertal)
DHEA-S  184   (13 -83 for pre-pubertal)

Congenital Adrenal HYPERplasia (CAH)

- Classical
  - Self-inducing
  - Simple Virilising
    - Generalized newborn male genitalia missed
  - Peripherally precocious puberty (ages 3-7 yr)
    - Tanner stage 4 or 5
    - [oa/ [oa] + elevated LH]
- Non-classical
  - Mild 21-hydroxylase deficiency

Typically just need glucocorticoid therapy

- ↑ Androgens → ↑ Estrogens → premature close of epiphyses → SHORT
- Therapy shuts off excess ACTH-mediated adrenal stimulation

DIFFERENTIAL DIAGNOSIS

<table>
<thead>
<tr>
<th>Growth Period</th>
<th>Etiology</th>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal</td>
<td>Maternal</td>
<td>Transient neonatal hypo-glycemia/calcemia, cardiac anomalies.</td>
</tr>
<tr>
<td></td>
<td>Congenital</td>
<td>Hypoplasia, meningoencephalitis, ocular, visceral, endocrine, neurological</td>
</tr>
<tr>
<td>Childhood</td>
<td>Obesity</td>
<td>Exogenous estrogen, virilization, precocious puberty</td>
</tr>
<tr>
<td></td>
<td>Constitutional</td>
<td>Early onset, non-accelerating growth, delayed maturation</td>
</tr>
<tr>
<td></td>
<td>Marfan</td>
<td>Arachnodactyly, arm span &gt; height, pectus, long narrow face</td>
</tr>
<tr>
<td></td>
<td>Pituitary</td>
<td>Gigantism, endocrine, precocious puberty</td>
</tr>
<tr>
<td>Adolescence +</td>
<td>Constitutional</td>
<td>Diagnostic criteria – otherwise normal child</td>
</tr>
<tr>
<td>Adult</td>
<td>Marfan</td>
<td>Arachnodactyly, short stature, Intellectual disability</td>
</tr>
<tr>
<td></td>
<td>Pituitary</td>
<td>Gigantism, endocrine, precocious puberty</td>
</tr>
</tbody>
</table>

MONITORING GROWTH – KEY POINTS

- Patterns of normal growth are multifactorial and vary based on patient age and pubertal status.
- Short stature is a very common complaint and commonly is not pathologic.
- A systematic approach to short stature helps complete a reasonable patient work-up before an endocrine referral.
- GH therapy, where medically indicated, is a safe and effective therapy for growth failure.
- Although not a common “complaint”, tall stature should always be scrutinized, as several pathologic causes can commonly exist.