Childhood Growth and Puberty Delay Disorders

MAJ Craig Barstow, MD

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Learning Objectives

1. Establish evidence-based protocols for evaluating pediatric patients for growth and pubertal delay.

2. Consider biases that lead to gender differences in the evaluation and treatment of short stature.

3. Counsel patients regarding the safety, efficacy, cost, risks, and benefits of available treatment options.

4. Develop individualized treatment therapy, and coordinate care as appropriate.

Audience Engagement System
Agenda

1. Failure to Thrive
2. Short Stature
3. Tall Stature
4. Delayed Puberty

Failure to Thrive
Case 1

A 9-month old male infant is brought in by his mother for a well child visit. He is healthy appearing and developmentally normal. He is primarily breast fed but his mother has introduced table foods. When you plot his weight on the CDC growth curve, his weight is below the 5th percentile. The physical exam is normal and the review of symptoms is negative.
Poll Question 1

What is your next, best step?

A. Conduct a detailed nutritional history
B. Plot the infant on the WHO growth chart
C. Order labs for celiac disease
D. Admit to infant for a failure to thrive work up

Which Growth Chart to Use?

2000 CDC Growth Chart
- Data from various sources (NHANES and others)
- Cross-sectional data
- 50% were ever breastfed
- 33% breastfed at 3 months

WHO Growth Chart
- Data from WHO Multicentre Growth Reference Study
- Prospective study of 882 children
- 100% were ever breastfed
- 100% breastfed through 12 months

Which Growth Chart to Use?

• MGRS established standards for healthy children under optimal conditions
• CDC established a reference for how certain children grow in a certain place
• Breast feeding is recommended standard for infant feeding
• Fewer US children are identified as underweight on WHO charts

Recommendations

• Use 2006 WHO growth charts for children < 24 months of age
• Use the 2000 CDC growth charts for children 25-59 months
• Use 2.3rd and 97.7th percentile to define abnormal growth (2 standard deviations)

Breast Feeding vs. Bottle Feeding

- Gain weight faster in the first 3 months
- Gain weight more slowly for the remainder of infancy
Case 2

A 6-week old infant is brought to your office by her mother. She recently visited relatives who noted the infant was small and thin appearing. The child is exclusively breast fed. The pregnancy was unremarkable and the infant was AGA at birth. At two weeks, he had surpassed his birth weight. At today’s visit, his weight is 350 grams less than it was 4 weeks ago and his weight vs. age is < 2.5th percentile.
Poll Question 2

Which of the following are consistent with normal growth for an infant?

A. Lose 10% of body weight after birth
B. Regain birth weight within 7 days
C. Double birth weight by 4-6 months
D. Triple birth weight by 1 year
E. All of the above

Normal Growth Infants

• Lose up to 10% of birth weight
• Regain birth weight within 7 days
• Double weight by 4-6 months
• Triple weight by 1 year

Failure to Thrive

• Abnormal pattern of weight gain
• Insufficient nutrition
  • Inadequate caloric intake
  • Inadequate caloric absorption
  • Increased metabolism
• “Weight faltering”


Failure to Thrive

Progressive loss of growth
• Weight
• Length
• Head circumference
Failure to Thrive - Evaluation

• History: focus on nutrition
• Physical exam
  • Acute or chronic illness
  • Signs of genetic condition
  • Evaluate development
• Plot growth over multiple visits

Failure to Thrive - Evaluation

• Diagnosis is usually made by history and physical
• Laboratory evaluation should be guided by H&P
  • Complete blood count
  • Urinalysis
  • Electrolytes
  • Thyroid function
  • Celiac disease
**Failure to Thrive**

*Inadequate caloric intake (most common cause)*
- Gastroesophageal reflux
- Inadequate breast milk supply or ineffective latching
- Incorrect formula preparation
- Mechanical feeding difficulties
- Neglect or abuse
- Poor feeding habits


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**Failure to Thrive**

*Inadequate nutrient absorption*
- Iron deficiency anemia
- Biliary atresia
- Celiac disease
- Chronic GI conditions
- Cystic fibrosis
- Inborn errors of metabolism
- Milk protein allergy

Failure to Thrive

Increased metabolism
• Chronic infection (HIV, tuberculosis)
• Chronic lung disease
• Congenital heart disease
• Hyperthyroidism
• Inflammatory conditions
• Malignancy
• Renal failure


Evaluation of Breastfeeding

• Pre- and post-feed weights
• Lactation consultation
• Consider supplementation with formula
Case 2 Continued

William and his mother were referred to lactation. Evaluation showed a decreased production of breast milk. The mother was instructed to breast feed for 30 minutes then supplement with formula as tolerated. She was also prescribed a hospital-grade breast pump and encouraged to pump after each breastfeeding. Over the next week the patient gained 48 grams per day.

Normal Weight Gain in Children

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Weight gain (grams/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>26-31</td>
</tr>
<tr>
<td>3-6</td>
<td>17-18</td>
</tr>
<tr>
<td>6-9</td>
<td>12-13</td>
</tr>
<tr>
<td>9-12</td>
<td>9</td>
</tr>
<tr>
<td>12 and older</td>
<td>7-9</td>
</tr>
</tbody>
</table>

- Catch-up growth is two-three times average rate.

Case 2 Continued

Upon recommendation of the lactation consultant, William was switched to an increased caloric formula for supplementation. Six days later he had gained an average of 83 grams per day. By 4 months of age, his weight vs. age was in the 56th percentile.
### Dietary Reference Intake

<table>
<thead>
<tr>
<th>Age</th>
<th>Kcal per kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6 months</td>
<td>108</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>98</td>
</tr>
<tr>
<td>1 to 3 years</td>
<td>102</td>
</tr>
</tbody>
</table>


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### Catch-up caloric requirements

- Take 50th percentile weight (ideal weight) for age from growth chart
- Multiply ideal weight by Dietary Reference Intake (DRI) for age
- Result is daily caloric catch-up requirement

**Catch-up caloric requirements**

**Example**

- 50\textsuperscript{th} percentile weight for a 3-month old boy is 13 kg
- Dietary Reference Intake (DRI) for 3-months is 108 kcal/kg/day
- Daily caloric catch-up requirement is 
  
  $$13 \text{ kg} \times 108 \text{ kcal/kg/day} = 1,404 \text{ kcal/day}$$

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**Formula Recipes**

<table>
<thead>
<tr>
<th>Calories (kcal) per oz</th>
<th>Water (oz)</th>
<th>Scoops of formula powder</th>
<th>Final volume (oz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>4</td>
<td>2</td>
<td>4 1/2</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>2</td>
<td>4 1/2</td>
</tr>
<tr>
<td>22</td>
<td>3.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>3</td>
<td>5.5</td>
</tr>
<tr>
<td>26</td>
<td>3</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>27</td>
<td>7</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

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*Homan GJ. Failure to thrive: A practical guide. American Family Physician. 2016: 94; 295-299*
Case 3

Mariah is a 9 month infant who has failed to gain adequate weight. Over the course of 3 visits, she has continued to fall off the growth chart. Her current weight vs. age is 0 percentile. Her mother suffers from post-partum depression and has missed several scheduled office visits for Mariah. On this visit, her length has begun to fall of the growth curve.

Indications for Hospitalization

• Extreme parental impairment or anxiety
• Extremely poor parent-child interaction
• Need to precisely document nutritional intake
• Outpatient treatment failure
• Severe malnutrition or dehydration
Red Flags

Consider further evaluation if failure to thrive is not isolated finding
• Developmental delay
• Hypotonia
• Neurological symptoms
• Recurrent vomiting
• Liver dysfunction
• Shortness of breath/difficulty feeding
• Acidosis


Short Stature
Case 4

Ryan is a 10-year old boy who is brought to your office for his annual well child exam. You plot him at the 2nd percentile for height and the 10th percentile for weight. His parents are concerned that he is shorter than all of his classmates and wonder if Ryan should see a pediatric endocrinologist.

Poll Question 3

Which of the following causes of short stature are considered normal variants?

A. Constitutional delay of growth and puberty
B. Familial short stature
C. Idiopathic short stature
D. All of the above
Normal Growth

• Newborn size is a result of intrauterine environment
• Catch up (or catch down) growth between six and 18 months of age
• Reach genetically determine growth curve
  • Mid-parental height
  • Children track along percentile (+/- two large bands)
• Growth hormone predominant role after 2 years of age
• At adolescence, growth increases at puberty
  • Sex hormones predominant role

Short Stature

Defined as a height more than two standard deviations (less than 3rd percentile) below the mean for age

Most children will have a normal variant
• Familial short stature
• Constitutional delay of growth and puberty
• Idiopathic short stature
Poll Question 4

What percentage of children referred for evaluation of short stature will have an identifiable, pathological cause?

A. 25%
B. 15%
C. 5%
D. < 1%

Short Stature

5% of children referred for evaluation of short stature will have an identifiable pathological cause

• Growth hormone deficiency
• Hypothyroidism
• Celiac disease
• Turner syndrome

Short Stature – Initial Evaluation

• History and physical evaluation
• Accurate growth assessment
• Calculate growth velocity
• Bone age evaluation

History and Physical Evaluation

• Chronic disease
• Renal, hepatic or gastrointestinal complaints
• Medication history
• Dysmorphic features
Accurate Growth Assessment

- Use appropriate growth charts
- Correctly measure the child
- Plot growth at every visit
- Obtain two measurements at least 3-6 months apart
- Calculate growth velocity

Mid-parental Height

Girls
- \([\text{Paternal height (in)}-5 \text{ in} + \text{maternal height (in)}]/2\)

Boys
- \([\text{Paternal height (in)}+5 \text{ in} + \text{maternal height (in)}]/2\)

Most children have a projected height within 4 inches of mid-parental height
Normal Growth Velocity by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Growth Velocity (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>23 to 27 cm (9.06 to 10.63 in)</td>
</tr>
<tr>
<td>12 months to 1 year</td>
<td>10 to 14 cm (3.94 to 5.51 in)</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>8 cm (3.15 in)</td>
</tr>
<tr>
<td>3 to 5 years</td>
<td>7 cm (2.76 in)</td>
</tr>
<tr>
<td>5 years to puberty</td>
<td>5 to 6 cm (1.97 to 2.36 in)</td>
</tr>
<tr>
<td>Puberty</td>
<td>Girls: 8 to 12 cm (3.15 to 4.72 in)</td>
</tr>
<tr>
<td></td>
<td>Boys: 10 to 14 cm (3.94 to 5.51 in)</td>
</tr>
</tbody>
</table>

Bone Age Evaluation

- Left hand and wrist radiographs
- Results compared against standard
- Bone age calculated

- Constitutional delay of growth and puberty and endocrine disorders will have a delayed bone age
Case 4 Continued

You perform an initial evaluation of Ryan. His father is 177 cm (69 inches) tall and his mother is 164 cm (64 inches) tall. Ryan’s growth velocity has been 5 cm per year for last 3 years. His physical exam is normal and he reports neither GI nor endocrine symptoms. His bone age is consistent with an 8-year old boy.
Short Stature Evaluation

Dysmorphic patient
- If proportionate growth
  - Consider genetic syndrome
  - Down syndrome, Turner syndrome
- If growth NOT proportionate
  - Evaluate for chondrodystrophy
Short Stature Evaluation

Growth velocity $\geq 5$ cm / year
And delayed bone age
• Constitutional delay of growth and puberty

Child born AGA, falls to 3rd percentile during catch-down growth
Delayed onset of puberty which results in normal height

Short Stature Evaluation

Growth velocity $\geq 5$ cm / year
And normal bone age
• Familial short stature
Projected height consistent with midparental height
• Idiopathic short stature
Short Stature Evaluation

Growth velocity < 5 cm / year
And delayed bone age
• Consider endocrine disorders

Weight tends to be normal or increased

Lab Evaluation

For an asymptomatic child with idiopathic short stature
• Full laboratory evaluation is expensive and low yield
• Two diseases most frequently identified
  • Celiac disease
  • Growth hormone axis problem

Lab Evaluation

If no etiology is suggested by history and physical:
• CBC
• CMP
• Bone Age
• ILGF-1
• IGFBP3

• Karyotype in girls


Short Stature – Differential Diagnosis

Normal variants
• Constitutional delay of growth and puberty
• Familial short stature
• Idiopathic short stature
Short Stature – Differential Diagnosis

Chronic disease
• Anemia
• Celiac disease
• Chronic renal insufficiency
• Inflammatory bowel disease

Short Stature – Differential Diagnosis

Endocrine Disorders
• Achondroplasia
• Acquired growth hormone deficiency
• Congenital growth hormone deficiency
• Congenital hypothyroidism
• Intrauterine growth deficiency
• Primary nutritional deficiency
Short Stature – Differential Diagnosis

Genetic conditions
• Turner syndrome

Referral to Pediatric Endocrinology

• IUGR who do not catch up by 2 years
• Height more than 3 SD below the mean (< 1\textsuperscript{st} percentile)
• Growth velocity < 5 cm (2 inches) per year
• No onset of puberty by 14 years for boys and 13 years for girls
• Projected height more than 2 standard deviations (10 cm or 4 inches) below the midparental height
• Bone age more than 2 SD below chronological age
• Diagnosis for which growth hormone is indicated

Indications for Growth Hormone

- Idiopathic short stature
- Turner syndrome
- Chronic renal failure
- Prader-Willi syndrome
- Small for Gestational Age
- Noonan syndrome
- Short-stature homeobox-containing gene deficiency

Treatment: Growth Hormone

- Daily injections for several years
- Adverse events are rare
- Four years of treatment
  - Costs $100,000- $120,000
  - Results in average growth of 3.7 cm (1.46 inches)
Case 4 Continued

Ryan’s parents are both within normal adult height and Ryan’s mid-parental height is 50\textsuperscript{th} percentile. His growth velocity has consistently been 5 cm per year. His bone age is delayed. Basic labs are unremarkable.

Poll Question 5

What is Ryan’s most likely diagnosis?

A. Familial short stature
B. Idiopathic short stature
C. Celiac Disease
D. Constitutional delay of growth and puberty
Tall Stature

Defined as a height more than two standard deviations (greater than 97th percentile) above the mean for age

- Much less likely to be referred to pediatric endocrinology
- Intervention is usually not needed
Tall Stature - Differential

Normal variants
• Constitutional advancement of growth
• Familial tall stature

Endocrine disorders
• Hyperthyroidism
• Obesity
• Pituitary gigantism
• Precocious puberty

Genetic conditions
Disproportional overgrowth
• Beckwith-Wiedemann syndrome
• Homocystinuria
• Klinefelter syndrome (XXY)
• Marfan syndrome

Proportionate overgrowth
• Fragile X syndrome
• Sotos syndrome
• Weaver syndrome
Case 4 Continued

Ryan is now 12 and his parents return to your office. They are concerned because his remains shorter than his school-aged peers and he has not started puberty. They again want to know if he should see a pediatric endocrinologist.
Poll Question 6

When should you consider the diagnosis of delayed puberty?

A. No signs of puberty at 2 SD above the mean
B. No signs of puberty at 13 years for girls
C. No signs of puberty at 14 years for boys
D. All of the above

Hormonal Changes in Puberty

1. Hypothalamus increases pulsatile secretion of gonadotropin releasing hormone (GnRH)
2. GnRH stimulate anterior pituitary to increase pulsatile secretion of gonadotropins: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)
3. FSH and LH stimulate sex steroidogenesis
   - Estradiol in girls
   - Testosterone in boys
Disorders of Puberty

Precocious Puberty
• Onset of puberty at age 2-3 SD below mean
  • Before 8 years in girls
  • Before 9 years in boys

Delayed Puberty
• Absent signs of puberty at age 2-3 SD above mean
  • By 13 in girls
  • By 14 in boys

Puberty

1. Gonadarche – physical changes of puberty
   Triggered by GnRH
   • Girls – starts with breast development (mean age 10)
   • Boys – starts with testicular enlargement (mean age 11.5)

2. Adrenarche – development of axillary hair, body odor, mild acne
   Triggered by adrenal androgens
Disorders of Puberty Initial Workup

- FSH
- LH
- Testosterone (boys)
- Estradiol (girls)
- Bone age radiography

Additional testing is guided by history and physical

Delayed Puberty

Possible additional evaluation
(Guided by history of physical exam)
- TSH
- Prolactin
- ILGF-1
- Celiac disease
- Diabetes mellitus
- Karyotype
- Brain imaging
Delayed Puberty

Differential Diagnosis

- Constitutional delay of growth and puberty
- Hypergonadotropic hypogonadism (FSH and LH above prepubertal range)
- Hypogonadotropic hypogonadism (FSH and LH in prepubertal range)
  - Functional – chronic disease, stress or poor nutrition
  - Persistent – congenital abnormality of HPG axis or CNS pathology

Constitutional Delay of Growth and Puberty

Most common cause of puberty delay
- 70% boys
- 30% girls
- 75% of parents have a history of puberty delay
FSH and LH in prepubertal range
Hypogonadotropic hypogonadism

Functional
• Celiac disease
• Diabetes mellitus
• Hyperthyroidism
• Hypothyroidism
• Inadequate nutrition
• Inflammatory bowel disease

Hypogonadotropic hypogonadism

Persistent Genetic
• Congenital GnRH
• Kallmann syndrome

Persistent Acquired
• CNS trauma, surgery or radiation
• CNS tumors
Hypergonadotrophic hypogonadism

- Chemotherapy, radiation or trauma to gonads
- Klinefelter syndrome (boys)
- Oophoritis or orchitis
- Turner syndrome (girls)

Treatment: Delayed Puberty

Jump-start therapy for constitutional delay of growth and puberty
- Boys > 14 years
  - Testosterone monthly injections
- Girls > 15 years
  - Estradiol overnight transdermal patch
Poll Question 7

Ryan’s growth and bone age are still consistent with his previous work up. He still has no gastrointestinal or endocrine symptoms. His FSH and LH are both in the prepubertal range. What is his most likely diagnosis?

A. Hypergonadotrophic hypogonadism
B. Constitutional delay of growth and puberty
C. Functional hypogonadotrophic hypogonadism
D. Turner syndrome

Practice Recommendations

1. Measure weight and height over more than one visit. (LOE C)
2. Use World Health Organization growth charts for children up to 2 years of age and Centers for Disease Control growth charts for children to to 20 years of age. (LOE C)
3. Routine lab testing is rarely indicated for failure to thrive. Lab evaluation for short stature should be guided by the history and physical. (LOE C)
4. Boys without testicular growth by 14 years and girls without breast development by 13 years should be evaluated for delayed puberty.

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Questions
Additional Reading

