GROWTH: A Clinical Perspective

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Note to Students About Slides:

This represents a skeleton of the lecture.

All pictures of patients and patients graphs have been removed to maintain patient confidentiality.

I hope this is helpful to the class.
Normal Growth and Development

Expected Growth Rate Per Year

<table>
<thead>
<tr>
<th>Age</th>
<th>Inches/Year</th>
<th>Cm/Year</th>
<th>Frequency of Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>9-11</td>
<td>18-25</td>
<td></td>
</tr>
<tr>
<td>12 to 24 months</td>
<td>4-5</td>
<td>10-13</td>
<td>3 to 4 times/year*</td>
</tr>
<tr>
<td>24 to 36 months</td>
<td>3-4</td>
<td>7.5-10</td>
<td></td>
</tr>
<tr>
<td>3 years to puberty</td>
<td>2-2.5</td>
<td>5-6</td>
<td>Annually</td>
</tr>
</tbody>
</table>

* More frequently if growth abnormality is suspected
What is Short Stature?

**Definition**
- Height SDS < -2 for age and sex
- Approximately 3% of all children

**Figure 2. Differential diagnosis of short stature.** IUGR = intrauterine growth retardation. (Modified from Rimoin DL, Borochowitz Z, Horton WA. *West J Med* 144:710, 1986, with permission)
Assessment of Suspected Growth Abnormalities

Auxologic Data

• Abnormally slow growth rate
  – Ages 3 to 12 years: Less than 2 inches/year (5 cm/year)
• Downwardly crossing centile channels on growth chart after the age of 18 months
• Height below third percentile (-2 SD)
• Height significantly below genetic potential (-2 SD below midparental height)

Blood Tests

• Complete Blood Count
• Erythrocyte Sedimentation Rate
• Serum Electrolytes and Chemistries
• Thyroid Hormone Levels
• Exercise-Induced GH Level
• IGF-1 Level
• Chromosomal Analysis (Karyotype)
• Tissue Transglutaminase Antibody
• Gliadin Antibodies (IGG, IGA)

History and Physical Examination

• Birth History – Small for Gestational Age, Intrauterine Growth Retardation
• General History – Chronic Illness
• Family History – Genetic, Psychosocial
• Physical Examination – Proportions, Abnormalities
• Growth Chart – Growth Velocity, Age of Onset, Change in Growth Pattern

Additional Measurements in Assessing Short Stature

• Head Size
• Body Proportions
• Sexual Maturation
• Skeletal Maturation
Assessment in Growth

Calculating Midparental and Target Heights

Midparental Height (in inches)

- Midparental height for girls: \( \frac{(\text{Father’s height} - 5 \text{ inches}) + (\text{Mother’s height})}{2} \)
- Midparental height for boys: \( \frac{(\text{Mother’s height} + 5 \text{ inches}) + (\text{Father’s height})}{2} \)

Target Height
- Midparental Height ± 2 SD
  - (1 SD = 2 inches)

Differential Diagnosis of Growth Abnormalities

**Assessment of Growth Hormone Secretion**

- **Provocative stimuli**
  - Arginine-insulin
  - Clonidine
  - L-dopa ± propranolol
  - Glucagon
  - Others

- **Physiologic tests**
  - Exercise-stimulated
  - Serial sampling

**Growth Deficiency-Prenatal Onset**

*Exogenous Causes-Secondary Growth Deficiencies*
- Maternal Malnutrition
- Toxemia
- Hypertension
- Renal or Cardiac Disease
- Nicotine
- Ethanol
- Hydantoins

*Endogenous Causes-Primary Growth Deficiencies*
- Chromosomal Abnormalities, e.g. Turner’s Syndrome
- Osteochondrodysplasias
- Multiple Malformation Syndromes

May or may not show post-natal catch-up growth

**Postnatal Growth Deficiency**

- Nutritional
  - Neglect, Malabsorption
- Cardiac Defect
- Renal Dysfunction
- Growth Hormone Deficiency
- Thyroid Hormone Deficiency
- Metabolic Disorders
  - Hypercalcemia, Glycogen Storage Disease, Poorly Controlled Diabetes Mellitus, Salt Wasting Syndrome

Specific treatment results in catch-up growth
Familial Short Stature

- Annual Growth Rate Normal
- Height at or Below 3rd Percentile
- No Systemic or Endocrine Disease
- Pubertal Growth Spurt at Normal Age
- Skeletal Age Equal to Chronological Age
- Ancestors Relatively Short

Constitutional Growth Delay

- Retarded bone age
- Normal predicted adult height in context of family pattern
- No organic or emotional cause for growth failure

Table 1. Principal Clinical Features in 13 Cases of Cushing’s Syndrome in Children*

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truncal Obesity, moon face, buffalo hump</td>
<td>13</td>
</tr>
<tr>
<td>Short Stature (10th percentile or less)</td>
<td>11</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>11</td>
</tr>
<tr>
<td>Acne</td>
<td>11</td>
</tr>
<tr>
<td>Flushed cheeks</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10†</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>7</td>
</tr>
<tr>
<td>Cutaneous striae</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
</tbody>
</table>

† Diastolic pressure of 90 mm Hg or higher
Prevalence of GHD: Utah Growth Study

- 114,881 measurements available for evaluation in 1st year
  - 1,334 children with heights > 2 SD below the mean
  - 52 children referred for further evaluation of growth problems
- 79,495 measurements available for evaluation in 2nd year
  - 578 children with height < 3rd percentile and growth rate < 5 cm/y
  - 503 of 578 children available for follow-up were evaluated further
- 16 new cases of GHD diagnosed
- 17 GH-treated GHD children not identified because of normal growth rates
- Estimated prevalence of GHD in the United States: 1:3,480

Established Genetic Defects Causing IGF Deficiency (1)

<table>
<thead>
<tr>
<th>Murine Homolog</th>
<th>Phenotype</th>
<th>Inheritance</th>
<th>Mutant gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Type III form of IGHAD</td>
<td>AR</td>
<td>IGHDAD</td>
</tr>
<tr>
<td>TFE3</td>
<td>Type II form of IGHAD</td>
<td>AR</td>
<td>IGHDAD</td>
</tr>
<tr>
<td>Rieg/Pitx2</td>
<td>Reiger's syndrome</td>
<td>AR</td>
<td>IEG1</td>
</tr>
<tr>
<td>Pit1/Ghf1</td>
<td>Pituitary hormone deficiencies</td>
<td>AR</td>
<td>PROP1</td>
</tr>
<tr>
<td>Hesx1/Rpx</td>
<td>Septo-optic dysplasia</td>
<td>AR</td>
<td>HESX1</td>
</tr>
<tr>
<td>Prop1</td>
<td>GH, PRL, TSH, LH and FSH deficiencies</td>
<td>AR</td>
<td>PROP1</td>
</tr>
<tr>
<td>Prop1</td>
<td>GH, PRL, TSH, LH and FSH deficiencies</td>
<td>AD</td>
<td>PROP1</td>
</tr>
<tr>
<td>GHRHR</td>
<td>GH, PRL, TSH, LH and FSH deficiencies</td>
<td>AD</td>
<td>GHRHR</td>
</tr>
<tr>
<td>Gh1</td>
<td>GH, PRL, TSH, LH and FSH deficiencies</td>
<td>AD</td>
<td>GH1</td>
</tr>
<tr>
<td>GH</td>
<td>GH, PRL, TSH, LH and FSH deficiencies</td>
<td>AR</td>
<td>GH</td>
</tr>
</tbody>
</table>

The genetic defect for this syndrome is unknown: Lopez-Bermejo A, Buckway CK, Rosenfeld RG, TEM 11:39-49, 2000
### Established Genetic Defects Causing IGF Deficiency (2)

<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Mutant formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>AR</td>
<td>IGF deficiency. Increased or normal GHBP</td>
<td>GH&lt;sup&gt;-/-&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>IGF deficiency. Increased GHBP</td>
<td>GH&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>IGF deficiency. Normal GHBP</td>
<td>GH&lt;sup&gt;-/-&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>IGF deficiency. Increased or normal GHBP</td>
<td>GH&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IGF deficiency. Normal GHBP</td>
<td>Stat5b knockout</td>
</tr>
<tr>
<td>Primary defects of IGF synthesis</td>
<td>AR</td>
<td>IGF deficiency</td>
<td></td>
</tr>
</tbody>
</table>

Growth Hormone-Activated Intracellular Signaling

AGA vs SGA

- **AGA**
  - Birth weight and length within 2 SD of mean for gestational age
- **SGA**
  - Birth weight and/or length at least 2 SD below mean for gestational age
  - Other definitions
    - Birth weight <2500 g, gestational age ≥37 wk
    - Birth weight or length <3rd, <5th, or <10th percentile for gestational age
    - Ponderal index less than –2 SD

Causes of Tall Stature and Excessive Growth

- Normal variants: Constitutional tall stature
- Endocrine disorders
  - Growth hormone excess
  - Disorders of sexual maturation
    - Precocious puberty
    - Virilization
    - Feminization
  - Hypogonadism
- Nonendocrine disorders
  - Cerebral Gigantism (Sotos syndrome)
  - Klippel-Feil syndrome
  - Marfan syndrome
  - Homocystinuria

Large Size in Childhood

<table>
<thead>
<tr>
<th>Familial Tall Stature</th>
<th>Familial Rapid Maturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental stature</td>
<td>Tall</td>
</tr>
<tr>
<td>Onset of rapid growth</td>
<td>Infancy</td>
</tr>
<tr>
<td>Facial appearance</td>
<td>Normal</td>
</tr>
<tr>
<td>and bone age in</td>
<td></td>
</tr>
<tr>
<td>childhood</td>
<td></td>
</tr>
<tr>
<td>Onset of adolescence</td>
<td>Normal</td>
</tr>
<tr>
<td>Final height attainment</td>
<td>Usual age</td>
</tr>
<tr>
<td>Adult stature</td>
<td>Tall</td>
</tr>
</tbody>
</table>

Figure 1: Final height as compared with predicted adult height before treatment with growth hormone in 82 children with id-i-methad short stature who reached adult height.

Causes of Increased Statural Growth

Prenatal Onset
- Maternal diabetes mellitus
- Beckwith-Wiedemann Syndrome
- Cerebral Gigantism

Postnatal Onset
- Exogenous obesity
- Pituitary GH excess
- Marfan syndrome
- Sexual precocity and virilizing syndromes
- McCune-Albright syndrome
- Homocystinuria
- Total lipodystrophy
- Klinefelter syndrome (47, XXY)
- XY karyotype
- Hyperthyroidism

Wise nature did never put her precious jewels into a garret four stories high: and therefore... exceeding tall men had ever very empty heads.

Francis Bacon