GROWTH: A Clinical Perspective

Sharon E. Oberfield, M.D.
Professor of Pediatrics
Columbia University Medical Center
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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>3 to 4 times/year*</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>3 to 4 times/year*</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

Fig. 1. Growth hormone secretory pattern in a prepubertal 12-yr-old male. Shaded area indicates the period of nocturnal sleep.
What is Short Stature?

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

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

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)

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)

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

\[
\text{Midparental height for boys} = \frac{(\text{Mother’s height} + 5 \text{ inches}) + (\text{Father’s height})}{2}
\]

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

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**Growth Deficiency-Prenatal Onset**

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

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

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

Do not show post-natal catch-up growth

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**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
PATHOPHYSIOLOGICAL MECHANISMS OF BISPOTENTIAL GLUCOCORTICOID ACTIONS ON GH SECRETION IN THE RAT

Fig. 13. Schematic representation of the authors' concept of pathophysiological mechanisms of the biphasic dose-dependent effects of glucocorticoids on the somatotropes axis. Smaller (physiological) amounts of corticosteroid are required to support pituitary GH gene transcription and sustain the GH-1 receptor, whereas excessive glucocorticoid suppresses GH secretion via augmenting somatostatin release, and reducing GH1 mRNA synthesis, as inferred based on data in vitro. (From: Wieland and Wollheim, 1982. Ann. Histochem.)

CHRONIC DISEASE

Height curve in a girl with Crohn's disease accompanied by undernutrition. (Stenmark, 1981)
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>Human Gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Mouse Homolog</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHD</td>
<td>AR</td>
<td>Hypogammaglobulinemia, Variable development of primary lymphatics</td>
<td>Rieg1/Spk</td>
</tr>
<tr>
<td>PROFI</td>
<td>AR</td>
<td>GH, PRL, TSH, LH and FSH deficiencies, Variable degree of ACTH deficiency</td>
<td>POU1F1 (Mouse mutant)</td>
</tr>
<tr>
<td>JOUC1F3</td>
<td>AR, AD</td>
<td>GH and PRL deficiencies, Variable degree of TSH deficiency</td>
<td>POU1F1 (Mouse variant, Jackson mouse)</td>
</tr>
<tr>
<td>BAG1</td>
<td>AD</td>
<td>Rieg’s syndrome, IGHD</td>
<td>Rieg/Pitx2</td>
</tr>
<tr>
<td>GH1</td>
<td>AR</td>
<td>IGHD</td>
<td>Global (Stefansson)</td>
</tr>
<tr>
<td>AR</td>
<td>Type IA form of IGHD</td>
<td>GH (Spontaneous dwarfism)</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>Type II form of IGHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked</td>
<td>Type III form of IGHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>Restrictive GH molecule</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The genetic defect for this syndrome is unknown.*


The GH/IGF axis

The GH/IGF axis in GHD
Established Genetic Defects Causing IGF Deficiency (2)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Mutation / Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH1</td>
<td>AR</td>
<td>IGF deficiency. Decreased or normal GHBP</td>
<td></td>
</tr>
<tr>
<td>Transmembrane domain</td>
<td>AR</td>
<td>IGF deficiency. Increased GHBP</td>
<td></td>
</tr>
<tr>
<td>Intracellular domain</td>
<td>AD</td>
<td>IGF deficiency. Increased or normal GHBP</td>
<td></td>
</tr>
<tr>
<td>Intracellular domain (cytoplasm)</td>
<td>AR</td>
<td>IGF deficiency. Normal GHBP</td>
<td>Sheffler syndrome</td>
</tr>
<tr>
<td>Primary defects of IGF synthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Igf1</td>
<td>AR</td>
<td>IGF deficiency. Igf1</td>
<td></td>
</tr>
</tbody>
</table>

Growth Hormone-Activated Intracellular Signaling

- **IGF1 resistance**
- **IGF1 mRNA gene, IGF1 receptor gene**

**Growth Factor**

- **Growth hormone** resistance
- **GHR receptor**
- **J2K, Stat 5b**
- **IGF1, IGFBPs, ALS**

**Hepatocytes, Osteoblasts**

- **Pituitary tumors**
- **Hypoplasia**

**Hypothalamus**

- **Idiopathic GH deficiency**
- **Infiltrative disease**

**Clinical/Lab Presentations**

- **Genomic Organization**
- **Growth Factor Tissue**

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**Table: Growth Failure Resulting from Reduced GH Secretion or Action.**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Growth Factor</th>
<th>Genomic Organization</th>
<th>Clinical/Lab Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophysis</td>
<td>GHHR 1</td>
<td>PTA-1, HESX 1</td>
<td>Hypoplastic (idiopathic GH deficiency) Hypoplastic, infiltrative disease</td>
</tr>
<tr>
<td>Fetal</td>
<td>GH 1</td>
<td>PFR2, J1, J2K, GHR 1</td>
<td>Fetal increase Hypoplasia</td>
</tr>
<tr>
<td>Adipocytes, Osteoblasts</td>
<td>GH Receptor</td>
<td>GH 3</td>
<td>Growth hormone resistance</td>
</tr>
<tr>
<td>Chondrocytes</td>
<td>IGF1 Receptor</td>
<td>IGF1 mRNA gene, IGF1 receptor gene</td>
<td>IGF1 resistance</td>
</tr>
</tbody>
</table>

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**Classification of IGF-I Deficiency and IGF-I Resistance with Clinical and Biochemical Features (1)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>GHSD</th>
<th>GH</th>
<th>GHR</th>
<th>IGF</th>
<th>IGFBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary IGF-I Deficiency</td>
<td>Congenital</td>
<td>Defer to IGF-I Deficiency</td>
<td>No</td>
<td>GH</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary IGF-I Deficiency</td>
<td>Congenital</td>
<td>GH receptor deficiency</td>
<td>Yes</td>
<td>GH</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>GH-GHR signal transduction defect</td>
<td>Yes (rare)</td>
<td>GH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Classification of IGF-I Deficiency and IGF-I Resistance with Clinical and Biochemical Features (2)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GHD</td>
</tr>
<tr>
<td>Tertiary IGF-I Deficiency</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
</tr>
<tr>
<td>GHRH receptor deficiency</td>
<td>No</td>
</tr>
<tr>
<td>GHD</td>
<td>Yes</td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>GHRH inhibiting antibody</td>
<td>Yes</td>
</tr>
<tr>
<td>GHD</td>
<td>Yes</td>
</tr>
<tr>
<td>IGF-I Insensitivity</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
</tr>
<tr>
<td>IGF receptor deficiency</td>
<td>No</td>
</tr>
<tr>
<td>IGF-R signal transduction defects</td>
<td>No</td>
</tr>
</tbody>
</table>

Height, standard deviation score for height

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)
  - Klinefelters syndrome
  - XYY males
  - Marfan syndrome
  - Homocystinuria


Large Size in Childhood
Normal Variants

<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 and bone age in childhood</td>
<td>Normal</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 2. Final Height as Compared with Predicted Adult Height before Treatment with Growth hormone in 80 Children with Idiopathic 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
- Homocysteinuria
- Total lipodystrophy
- Klinefelter syndrome (47, XXY)
- XYY 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