GROWTH: A Clinical Perspective

Sharon E. Oberfield, M.D.
Professor of Pediatrics
Columbia University Medical Center
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Figure 1-6. Linear growth in lunar months during fetal life and for the first postnatal year, shown as a distance curve (above) and as a velocity curve (below). The broken line (below) provides a smooth average velocity rate. The slowing of late fetal growth rate with postnatal catch-up is compatible with the concept of late fetal slowing of growth due to uterine constraint. (Redrawn from Thompson, D`Amy W., The Growth and Form of Fetus Growth, 1981.)
Figure 1-9. Mean and percentiles for the linear growth of male infants and mean for female infants, derived from longitudinal growth values of 90 middle-class white babies. The rate of growth of the males is more rapid than that of the females during the first 3 to 6 months. (From Smith, D. W., Harvey, M. A. S., Rogers, J. E., Greisen, L. G., and Skinner, A. L.: Unpublished observations.)
## 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
Fig. 1. Growth hormone secretory pattern in a prepubertal 12-yr-old male. Shaded area indicates the period of nocturnal sleep.
Fig. 2. Growth hormone secretory pattern in a 12-yr-old male with moderate sexual maturity. 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

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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)*
GROWTH and GROWTH DISORDERS

Obtaining Accurate Measurement of Length

Birth to 24 Months

GROWTH and GROWTH DISORDERS

Obtaining Accurate Measurement of Height

Children Aged 2 to 18 Years
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)

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 Secetion

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

*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*
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
Fig. 13. Schematic representation of the authors’ concept of pathophysiological mechanisms of the biphasic dose-dependent effects of glucocorticoids on the somatotropic axis. Smaller (physiological) amounts of cortisol are required to support pituitary GH gene transcription and maintain the GHRH receptor, whereas excessive glucocorticoid suppresses GH secretion via augmenting somatostatin release, and reducing GHRH secretion, as inferred based on data in the rat. Giustina and Veldhuis, 1998 Endo Rev.
Height curve in a girl with Crohn's disease accompanied by undernutrition. Sizonenko, 1981
Fig. 1. Hypograms obtained for case C. (A) Initial sleep recording; (B) second sleep recording 60 days later (Stage I: wakefulness, sleep stages 1, 2, 3, 4, REM = P1). Long periods of wakefulness and absence of stage IV characterize the initial sleep recording (A). The second sleep recording exhibits a normal sleep organization. (Gill Thalheimer, Ped. Rev., 1962.

FIG. 5. Mean plasma GH concentration (top panels) and mean GH secretion rates calculated by deconvolution analysis (bottom panels) according to sleep stages. Using Duncan's multiple-range test, all groups except the following were different (P < .05): awake vs stage 3 for GH concentration; awake vs stage 1 for pituitary secretion rates. L. Tukey distribution confidence.
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
The GH/IGF axis

The GH/IGF axis in GHD
Established Genetic Defects Causing IGF Deficiency (1)

<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Marine Homolog</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HESX1</strong></td>
<td>AR</td>
<td>Septo-optic dysplasia. Variable involvement of pituitary hormones</td>
<td>Hesx1/Rpx</td>
</tr>
<tr>
<td><strong>PROP1</strong></td>
<td>AR</td>
<td>GH, PRL, TSH, LH and FSH deficiencies. Variable degree of ACTH deficiency</td>
<td>Prop1 (Ames mouse)</td>
</tr>
<tr>
<td><strong>POU1F1</strong></td>
<td>AR, AD</td>
<td>GH and PRL deficiencies. Variable degree of TSH deficiency</td>
<td>Pit1/Ghf1 (Snell mouse; Jackson mouse)</td>
</tr>
<tr>
<td><strong>RIEG1</strong></td>
<td>AD</td>
<td>Reiger’s syndrome. IGHD</td>
<td>Rieg/Pitz2</td>
</tr>
<tr>
<td><strong>IGHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GHRHR</strong></td>
<td>AR</td>
<td>IGHD</td>
<td>Ghrhr (little mouse)</td>
</tr>
<tr>
<td><strong>GHI</strong></td>
<td>AR</td>
<td>Type 1A form of IGHD</td>
<td>Ghr (spontaneous dwarf rat)</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>Type 1B form of IGHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Type II form of IGHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X-linked</td>
<td>Type III form of IGHD. Hypogammaglobulinemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Bioinactive GH molecule</td>
<td></td>
</tr>
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</table>

Established Genetic Defects Causing IGF Deficiency (2)

<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Marine Homolog</th>
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</thead>
<tbody>
<tr>
<td>GHR</td>
<td></td>
<td></td>
<td>Ghr</td>
</tr>
<tr>
<td>Extracellular domain</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>Stat5b knockout</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</td>
<td>Igf1</td>
</tr>
</tbody>
</table>

Response of serum somatomedin to administration of human growth hormone, 2.5 mg bid, for 4 days in patients with hyposomatotropic dwarfism (○) and Laron dwarfism (●). (Reprinted from Daughaday et al., 1969.)
Figure 4. A 22-year-old man with GHRD, political leader of his community, writer, poet, and artist, with his 17-year-old bride. Testing for the carrier state for the codon 180 mutation of the GHR of this young woman was of great interest to this couple.

Figure 1. The Family of Patients 8, 9, and 10. From left to right, this photograph shows a sister, 25 years old (height, 158.8 cm); a brother, 18 years old (164.7 cm); Patient 9; the father, 52 years old (165 cm); Patient 8; a brother, 12 years old (135.9 cm); a sister, 8½ years old (115.4 cm), and the mother, 46 years old (166.7 cm), holding Patient 10.
IUGR and Postnatal Growth Failure with IGF-I Gene Deletion

- 15-year-old with severe prenatal and postnatal growth failure with homozygous partial deletion of IGF-I gene
- No response to GH therapy administered from age 11 to 12.7 years


Growth Hormone-Activated Intracellular Signaling

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>GHD⁺</th>
<th>Ht SDS</th>
<th>GH</th>
<th>GHBP</th>
<th>IGF-I</th>
<th>IGFBP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary IGF-I Deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Defect in IGF-I</td>
<td>No</td>
<td>-.9 [IUGR]</td>
<td>High</td>
<td>Normal</td>
<td>Very low</td>
<td>Normal</td>
</tr>
<tr>
<td>Acquired Alagille syndrome</td>
<td>No</td>
<td>Varies</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Secondary IGF-I Deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital GH receptor deficiency</td>
<td>Yes</td>
<td>-4 to -12</td>
<td>High</td>
<td>Low/nl/high</td>
<td>Very low</td>
<td>Low/nl/low</td>
</tr>
<tr>
<td>GH-GHR signal transduction defect</td>
<td>Yes (Arab) No (Pakistani)</td>
<td>-3.4 to -6</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Very low</td>
</tr>
<tr>
<td>Acquired Catabolic states/chronic illness</td>
<td>No</td>
<td>Normal-low</td>
<td>High</td>
<td>Low/nml</td>
<td>Low</td>
<td>n/l/low</td>
</tr>
</tbody>
</table>

*phenotype
Ht SDS, standard deviation score for height


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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>Hypothalamus</td>
<td>GHRH ↓</td>
<td>• PTX 1, HESX 1</td>
<td>• Hypothalamic (idiopathic GH deficiency)</td>
</tr>
<tr>
<td>Pituitary</td>
<td>GH ↓</td>
<td>• PROP 1, PIT 1, LHX 3, GH 1, POU1F1</td>
<td>• Pituitary tumors</td>
</tr>
<tr>
<td>Hepatocytes, Osteoblasts</td>
<td>GH Receptor ↓</td>
<td>• GHR 1</td>
<td>• Growth hormone resistance</td>
</tr>
<tr>
<td>Chondrocytes</td>
<td>IGF1 Receptor ↓</td>
<td>• IGF1 mRNA gene</td>
<td>• IGF1 resistance</td>
</tr>
</tbody>
</table>

Table: Growth Failure Resulting from Reduced GH Secretion or Action.
### Classification of IGF-I Deficiency and IGF-I Resistance with Clinical and Biochemical Features (2)

<table>
<thead>
<tr>
<th>Condition</th>
<th>GHD</th>
<th>Ht SDS</th>
<th>Biochemistry</th>
<th>GH</th>
<th>GHB P</th>
<th>IGF-I</th>
<th>IGFBP-3</th>
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</thead>
<tbody>
<tr>
<td><strong>Tertiary IGF-I Deficiency</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHRIH receptor deficiency</td>
<td>No</td>
<td>-4.3 to -8.9</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>GHD</td>
<td>Yes</td>
<td>≤3</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH inhibiting antibodies</td>
<td>Yes</td>
<td>≤-3 to -8.5</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>GHD</td>
<td>Yes</td>
<td>Varies</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>IGF-I Insensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF receptor deficiency</td>
<td>No</td>
<td>Severe/IUGR</td>
<td>High</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>IGF-IGFR signal transduction defects</td>
<td>No</td>
<td>-2 to -4.6</td>
<td>Normal</td>
<td>?</td>
<td>High</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

*phenotype

Ht SDS, standard deviation score for height

Growth Velocity in Turner Syndrome

Height velocity in patients with Turner syndrome compared to the normal range; single measurements.

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

Figure 5-1. Linear growth of a child with Russell-Silver syndrome who was small from prenatal life, had a consistently low rate of linear growth with attainment of short adult height, and showed no acceleration of growth during two trials of human growth hormone therapy. (From J. M. Tanner and R. H. Whitehouse.)
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 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></th>
<th>Familial Tall Stature</th>
<th>Familial Rapid Maturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental stature</td>
<td>Tall</td>
<td>Average</td>
</tr>
<tr>
<td>Onset of rapid growth</td>
<td>Infancy</td>
<td>Infancy</td>
</tr>
<tr>
<td>Facial appearance and bone age in childhood</td>
<td>Normal</td>
<td>Advanced</td>
</tr>
<tr>
<td>Onset of adolescence</td>
<td>Normal</td>
<td>Early</td>
</tr>
<tr>
<td>Final height attainment</td>
<td>Usual age</td>
<td>Early age</td>
</tr>
<tr>
<td>Adult stature</td>
<td>Tall</td>
<td>Average</td>
</tr>
</tbody>
</table>
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