GROWTH: A Clinical Perspective

Pathophysiology Lecture
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“If you can look into the seeds of time
And say which grain will grow and which will not”
-Macbeth, Act 1, Scene 3
GH-IGF Axis: Sites of Defects

**HYPOTHALAMUS**
- Hypothalamic dysfunction
  - Transcription factors
  - GHRH or ghrelin genes

**PITUITARY**
- Pituitary dysfunction
  - Transcription factors
  - GHRH receptor
  - GH gene

**LIVER**
- Abnormal GH–signal transduction: JAK/STAT/MAPK
  - GH receptor
  - IGFBP-3
  - Other IGFBPs

**GROWTH PLATE**
- Defects of the type I IGF receptor
  - Growth
  - Post-receptor defects

**Defects of IGF-I synthesis**
- Defects of IGF transport/clearance

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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'Arcy W.: On Growth and Form. Cambridge, Cambridge Uni-
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 (From Smith, D. W., Harvey, M. A. S., Rogers, J. E., Greitzer, L. G., and Skinner, A. L.: Unpublished observations.)
Mean age and range when a new growth channel had been achieved.

Catch-up growth begins soon after birth.
Mean age and range when a new growth channel had been achieved

Mean age and range when the slowdown in linear growth began
## 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>Annually</td>
</tr>
<tr>
<td>3 years to puberty</td>
<td>2-2.5</td>
<td>5-6</td>
<td></td>
</tr>
</tbody>
</table>

* More frequently if growth abnormality is suspected
Means for upper to lower segment ratios. Note the rapid change in childhood, when the legs grow faster than the trunk.
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.
Fig. 1. A, The mean (±SE) 24-h concentrations of GH for the five study groups are illustrated. B, The mean (±SE) area under the GH concentration vs. time curve for individual GH pulses, as identified by the Cluster pulse detection algorithm, is presented. C, The number of GH pulses (mean ± SE), as detected by the Cluster algorithm, in the 24-h GH concentration profiles for subjects in the five study groups are graphed. In each panel, any two vertical bars not identified by the same letter represent statistically different values (P < 0.05); bars sharing a common letter represent statistically indistinguishable values (P > 0.05).
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)
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
# Calculating Midparental and Target Heights

Midparent Height (in inches)

<table>
<thead>
<tr>
<th>Midparental Height for Girls</th>
<th>((\text{Father’s height} - 5 \text{ inches}) + (\text{Mother’s height}))</th>
<th>(\frac{2}{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midparental Height for Boys</td>
<td>((\text{Mother’s height} + 5 \text{ inches}) + (\text{Father’s height}))</td>
<td>(\frac{2}{2})</td>
</tr>
</tbody>
</table>

Target Height

Midparental Height ± 2 SD

(1 SD = 2 inches)
GH – IGF Axis

Stimulation of GH
- Deep sleep
- α-Adrenergic
- Fasting
- Acetylcholine
- Sex steroids
- Stress
- Amino acids
- Hypoglycemia

Inhibition of GH
- Obesity
- β-Adrenergic
- Glucocorticoids
- High FFA
- Hyperglycemia
- Hypothyroidism
- IGF-I

Inhibition of IGF-I
- Undernutrition
- Acute illness
- Chronic illness
- GH receptor deficiency
- GHR antibodies
- IGF-I receptor deficiency

Adapted from Rosenbloom AL, et al. Trends Endocrinol Metab 1994;5:296–303. Permission for use of figure has been requested from the publisher.
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
Figure 2. Plasma levels (mean and range) of somatomedins according to age in normal children.
## 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

### Infections
- Rubella
- Cytomegalic Inclusion Virus
- Toxoplasmosis
- Syphilis

### 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
Patient picture will go here.
Patient picture will go here.
Constitutional Growth Delay

- Delayed Puberty
- Retarded bone age
- Normal predicted adult height in context of family pattern
- No organic or emotional cause for growth failure
Patient picture will go here.
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 (10\textsuperscript{th} 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
Patient picture will go here.
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.
Sazonenko, 1981
Prevalence of GHD: Utah Growth Study

- 114,881 measurements available for evaluation in 1\textsuperscript{st} 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 2\textsuperscript{nd} year
  - 578 children with height < 3\textsuperscript{rd} 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
<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Murine Homolog</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GHD owing to hypothalamic-pituitary dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Developmental abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>HESX1</em></td>
<td>AR</td>
<td>Septo-optic dysplasia. Variable involvement of pituitary hormones</td>
<td><em>Hesx1/Rpx</em></td>
</tr>
<tr>
<td><em>PROP1</em></td>
<td>AR</td>
<td>GH, PRL, TSH, LH and FSH deficiencies. Variable degree of ACTH deficiency</td>
<td><em>Prop1</em> (Ames mouse)</td>
</tr>
<tr>
<td><em>POU1F1</em></td>
<td>AR, AD</td>
<td>GH and PRL deficiencies. Variable degree of TSH deficiency</td>
<td><em>Pit1/Ghf1</em> (Snell mouse, Jackson mouse)</td>
</tr>
<tr>
<td><em>RIEG1</em></td>
<td>AD</td>
<td>Reiger's syndrome. IGHD</td>
<td><em>Rieg/Pitx2</em></td>
</tr>
<tr>
<td><strong>IGHD</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>GHRHR</em></td>
<td>AR</td>
<td>IGHD</td>
<td><em>Ghrhr</em> (little mouse)</td>
</tr>
<tr>
<td><em>GH1</em></td>
<td>AR</td>
<td>Type 1A form of IGHD</td>
<td><em>Gh</em> (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&lt;sup&gt;c&lt;/sup&gt;</td>
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</tr>
<tr>
<td></td>
<td>AD</td>
<td>Bioinactive GH molecule</td>
<td></td>
</tr>
</tbody>
</table>

<sup>c</sup> The genetic defect for this syndrome is unknown.
Patient picture will go here.
Patient picture will go here.
Patient picture will go here.
The GH/IGF axis in GHIS

- Hypothalamus
- GHRH
- SMS
- PITUITARY
- GH
- GH-BP
- Liver
- IGF-R
- IGF-I
- ALS
- IGFBP-3
- 150 kD complex
- Bone
- CIRCULATION
- GROWTH
- Signal Transduction
Established Genetic Defects Causing IGF Deficiency

<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Murine Homolog</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHI</td>
<td></td>
<td></td>
<td></td>
</tr>
<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.)
FIG. 4. A 32-yr-old man with GHRD, political leader of his community, writer, poet, and artist, with his 17-yr-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 (156.7 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

New Insights About The Growth Hormone Receptor (GHR)

- Previously it was believed that growth hormone binding to the GHR causes dimerization of the GHR which allows JAK2 to come together and initiate tyrosine phosphorylation.

- However, this model has been shown to be incorrect.

Image From: Biochemistry, 6th Edition by: Berg, Tymoczko, and Stryer
New Insights About The Growth Hormone Receptor (GHR) cont’d…

• Several studies have confirmed the GHR is already constitutively dimerized prior to growth hormone binding. Instead, the binding of growth hormone appears to cause a conformational shift in this dimer with rotation in the intracellular domain.

• This aligns the JAK2 on each dimer allowing tyrosine phosphorylation to begin. It also appears that usually the JAK2 domains are too close together and inhibition of kinase activity occurs via a pseudo-binding inhibitory domain. As growth hormone binds to the GH receptor, not only is there rotation of the GHR dimer complex but there is also a widening of the gap between individual intracellular GHR domains. This appears essential for activation of JAK 2.

Data originally presented by Dr. Michael Waters at LWPES/ESPE meeting in September 2009.
Fig. 1. Model for GHR activation. The hormone binds first to receptor 1, then sits there until vibrational movement locates tryptophan 104 of receptor 2-adjacent binding site 2 of hormone. Binding to site 2 realigns the receptors such that receptor 1 is raised and rotated relative to receptor 2 because of the asymmetric placement of the receptor binding sites on the hormone. This realignment is transmitted through the TMD, aligning JAK2 kinases bound to box1 of the receptor, which facilitates their activation by transphosphorylation, so initiating the GH signaling cascades.

IGF-I receptor mutations:
IGF-I Receptor Mutations: Pre and Postnatal Growth Retardation

Summary of Clinical Cases of GH-IGF-1 Mutations

- Mutations can occur in all pathway components:
  - GH
  - GHR
  - STAT 5B
  - IGF-1
  - IGF-1R
  - ALS-binding protein

**COMMON CHARACTERISTIC IS:** DECREASED IGF-1 BIOACTIVITY which may result in pre/postnatal growth failure, cognitive defects, delayed bone age and physical development
Specific Mutations (as of 2009)

- **GHR (i.e. Laron)** – many reported cases
  - $\uparrow$GH, $\downarrow\downarrow$IGF, $\downarrow\downarrow$IGFBP3, and $\downarrow\downarrow$GH BP
    (Only 2 cases reported with nl GHR and GH BP. Did not respond to GH and actually have mutations STAT 5 B, Kofoed, Hwa)
- **IGF1**: homozygous for IGF1 gene deletion (Woods et al.)
- **IGF1**: point mutation in IGF1 gene $\rightarrow$ blunted inactivation of IGF-1R (Walenkamp et al.)
- **IGF-1R gene** – 4 cases (point mutations, nonsense mutations, and heterozygous mutation in exon 7 of IGF-1R gene)
  - Actually have $\uparrow$IGF1 levels
- **IGFBP** – no reports
- **ALS gene** – 11 reports (nl GH, $\downarrow$IGF1 and IGFBP3)
### 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></td>
<td></td>
<td></td>
<td>• Hypothalamic infiltrative disease</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></td>
<td></td>
<td></td>
<td>• Hypoplasia</td>
</tr>
<tr>
<td>Hepatocytes, Osteoblasts</td>
<td>GH Receptor ↓</td>
<td>• GHR 1</td>
<td>• Growth hormone resistance</td>
</tr>
<tr>
<td></td>
<td>J2K, Stat 5b ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IGF1, IGFBPs, ALS</td>
<td></td>
<td></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>
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

*Underwood, LE & Van Wyck, JJ. Williams Textbook of Endocrinology, 1992, p. 1125*

Sotos' Syndrome of Cerebral Gigantism

Fig. 3.—Height chart of Cases 1 and 2.

Fig. 5.—Head circumference chart of Cases 1 and 2.
Patient picture will go here.
Patient picture will go here.
GROWTH HORMONES

LOTIONS

DIETARY SUPPLEMENTS
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