GROWTH:
A Clinical Perspective

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GH-IGF Axis: Sites of Defects

Figure 1-3: Mean and published values for the linear growth of normal children, derived from longitudinal growth data of 24 measurements. The rate of growth of the spine is now rapid from birth to age 2 months. Beyond this age, the bone growth rate increases. The mean growth rate for normal children is shown by the solid line. The shaded area represents the 2nd and 98th percentiles, indicating the range of normal growth. The dashed line represents the growth pattern of children with growth hormone deficiency, while the dotted line represents the growth pattern of children with IGF-1 deficiency. The growth pattern of children with growth hormonedeficiency and IGF-1 deficiency is similar, with both groups showing slower growth compared to normal children.
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

Figure 2. Growth hormone secretory pattern in a 12-yr-old male with moderate sexual maturity. Shaded area indicates the period of nocturnal sleep.
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**

Midparental Height (in inches)

- Midparental height for girls = (Father’s height – 5 inches) + (Mother’s height)
- Midparental height for boys = (Mother’s height + 5 inches) + (Father’s height)

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
- 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

- Delayed Puberty
- 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
PATOPHYSIOLOGICAL MECHANISMS OF BIPOTENTIAL GLUCOCORTICOID ACTIONS ON GH SECRETION IN THE RAT

Fig. 11. Schematic representation of the authors' concept of pathophysiologic mechanisms of the biphasic dose-dependent effects of glucocorticoids on the somatotrophic axis. Similar (physiologic) amounts of cortisol are required to support pituitary GH gene transcription and maintain the GH-IR receptor, whereas excessive glucocorticoids suppress GH secretion via augmenting somatostatin release, and reducing CRH secretion, as inferred based on data in the rat. (From B. and Walsch, 1977, Clin Res.)
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>Genetic defect</th>
<th>Phenotype</th>
<th>Inheritance</th>
<th>Murine homolog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesp1</td>
<td>AR</td>
<td>Septo-optic dysplasia, variable involvement of pituitary hormones</td>
<td>Heart/Ripx</td>
</tr>
<tr>
<td>Prdom1</td>
<td>AR, AD</td>
<td>GH, PRL, TSH, LH, and FSH deficiencies, variable degree of ACTH deficiency</td>
<td>Pprop1 (Ames mouse)</td>
</tr>
<tr>
<td>Pouconf1</td>
<td>AR, AD</td>
<td>GH and PRL deficiencies, variable degree of TSH deficiency</td>
<td>Pith/gHt (Small mouse, Jackson mouse)</td>
</tr>
<tr>
<td>Nesf1</td>
<td>AD</td>
<td>Reiger’s syndrome, GHD</td>
<td>Rghpl/2</td>
</tr>
<tr>
<td>Ghrhr</td>
<td>AD</td>
<td>Bioinactive GH molecule</td>
<td>Adgpl</td>
</tr>
<tr>
<td>Gh1</td>
<td>AR</td>
<td>Type I A form of GHD</td>
<td>Gh (spontaneous dwarf rat)</td>
</tr>
<tr>
<td>Gh1</td>
<td>AR</td>
<td>Type I B form of GHD</td>
<td>Gh (spontaneous dwarf rat)</td>
</tr>
<tr>
<td>Gh1</td>
<td>AD</td>
<td>Type II form of GHD</td>
<td>Gh (spontaneous dwarf rat)</td>
</tr>
<tr>
<td>X-linked</td>
<td>AD</td>
<td>Type II form of GHD</td>
<td>Hyopraphrobia thomsonii</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Bioactive GH molecule</td>
<td>Adgpl</td>
</tr>
</tbody>
</table>
Established Genetic Defects Causing IGF Deficiency

<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Mouse Modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGR</td>
<td></td>
<td></td>
<td></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>Starter inactivat</td>
</tr>
<tr>
<td>Primary defects of IGF synthesis</td>
<td>AR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


The GH/IGF axis in GHIS

- Hypothalamus
- Pituitary
- Growth Hormone Receptor
- IGF-I
- Signal Transduction
- GH-BP
- Liver
- Bone
- Circulation

GH and IGF axis diagram.
Growth Hormone-Activated Intracellular Signaling

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

**IGF-I Receptor Mutations: Pre and Postnatal Growth Retardation**

Patient 1

- Patient 1 – nonconsanguineous, 1.4 kg, 38 week pregnancy, normal serum IGF-I, normal GH to provocation.
- Patient was a compound heterozygous for mutations in exon 2 of the IGF-IR gene → binding of IGF-I to IGF-I receptor.


Patient 2

- Heterozygous for a potential mutation in exon 2. Exon 2 is the first exon to encode a substantial portion of the mature receptor → no visible receptor protein was made.


**Inactivating mutations of the IGF-I gene:**

**A Novel Insulin-Like Growth Factor-I Mutation**

- Patient 2 - At birth, weight of 2000 grams, length of 40 cm, and microcephaly. Normal GH and IGF-I high for age.
This is the first report on a homozygous missense mutation in the human IGF-I gene resulting in an IGF-I protein that is hardly capable of interacting with the IGF-IR but with relatively unaffected binding capacity for IGFBPs. This leads to severe effects on growth and development in utero and during childhood.

<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, HES 1</td>
<td>Hypothalamic (idiopathic GH deficiency)</td>
</tr>
<tr>
<td>Pituitary</td>
<td>GHR 1</td>
<td>GH1, PS1, SF1</td>
<td>Hypothalamic hypoplasia</td>
</tr>
<tr>
<td>Hepatocytes, Osteoblasts</td>
<td>G1R Receptor</td>
<td>J2K, Stat 5b, G1R, IGFBPs, RAS</td>
<td>GHR 1</td>
</tr>
<tr>
<td>Chondrocytes</td>
<td>G1R Receptor</td>
<td>IGFI mRNA gene, G1R1 receptor gene</td>
<td>IGFI resistance</td>
</tr>
</tbody>
</table>

Table: Growth Failure Resulting from Reduced GH Secretion or Action.
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)
  - Klinefelter syndrome
  - XY 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