M2 - Endocrine, Winter 2008

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Abnormalities of Growth & Development

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To understand the

- determinants of normal growth
- common variations in normal growth
- diagnostic approach to a child with abnormal growth
- principles of management of a child with abnormal growth
Topics **NOT** covered in today’s discussion

- Sexual differentiation
- Ambiguous genitalia and disorders of sexual differentiation
- Pubertal development
- Disorders of pubertal development - delayed / precocious
- Physiology of hormone secretion / action
Determinants of Normal Growth

Normal growth is the aggregate of hormonal, environmental, nutritional, and genetic factors.

Hormonal Factors

- Thyroid - essential for normal growth
  - hypothyroidism is a common cause of severe growth delay
- Sex steroids - bone maturation is dependent on estrogen
  - testosterone can enhance GH secretion
- Glucocorticoids - potent inhibitor of growth
GH/IGF-1 Axis

Image of GH/IGF-1 Axis removed
## Determinants of Normal Growth

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Growth Rate $\text{cms/yr}$</th>
<th>Adult Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Steroids $\uparrow$</td>
<td>Increase</td>
<td>Diminished</td>
</tr>
<tr>
<td>Sex Steroids $\downarrow$</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Thyroxine $\uparrow$</td>
<td>Normal/$\pm$ incr</td>
<td>Normal</td>
</tr>
<tr>
<td>Thyroxine $\downarrow$</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>GH $\uparrow$</td>
<td>Increase</td>
<td>Increased</td>
</tr>
<tr>
<td>GH $\downarrow$</td>
<td>Decrease</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol $\uparrow$</td>
<td>Decrease</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol $\downarrow$</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Normal Growth

- Weight
- Measurement of height - Stadiometer
  - less than 2 yrs of age - length (supine)
  - greater than 2 yrs of age - height (erect)
- Head circumference
- Span
- Upper segment / lower segment ratio

Anthropometric parameters
Normal Growth

Anthropometric parameters

Upper / Lower Segment Ratio

Lower segment: symphysis pubis to floor
Upper segment: Ht (-) lower segment

Image of fetal and post-natal growth chart removed

<table>
<thead>
<tr>
<th>2m</th>
<th>5m</th>
<th>Birth</th>
<th>2yr</th>
<th>6yr</th>
<th>12yr</th>
<th>25yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-natal</td>
<td></td>
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</tr>
</tbody>
</table>
Normal Growth

Growth Velocity

- measured in cms/yr
- should be measured over at least a 6-12 month period
- more the # of height points used to calculate GV - more reliable is the interpretation
- assessment of pubertal status is critical for interpretation of GV
- Normal GV - is a strong argument AGAINST a significant hormonal abnormality
Girls 2-18 yrs

Growth rate (cms/yr)

Age (yrs)

Source: JM Tanner, et al.
Boys 2-18 yrs

Source: JM Tanner, et al.
Normal Growth

- Chronological age
- Dental age
- Bone Age (skeletal maturation)

- beyond the neonatal age - X-ray of L wrist

  comparison with published standards (Greulich & Pyle)

Usefulness - prediction of final height
- age of onset of puberty closely linked to bone age
- corroborates diagnosis, but is never diagnostic

Caveats - imprecise / ethnic variability
SHORT STATURE

- Definition
- Classification
- Etiology
- Evaluation / Diagnostic Approach
- Treatment
Short Stature
height < 3rd percentile
Growth Retardation
growth velocity < 3rd percentile
Short Stature
height < 3rd percentile
Growth Retardation
growth velocity < 3rd percentile

Etiology

Normal Variant ↔ Pathological
**SHORT STATURE**

**Normal Variant**

**Familial / Genetic**
- Final ht appropriate for parental ht
- Normal size at birth
- GV may be ↓ in 0-3 yrs of age
- BA = CA

**Constitutional Delay of Growth & Puberty**
- "Late Bloomer"
  - Family history
  - Normal size at birth
  - Normal GV
  - Delayed puberty
  - BA < CA

**Abbreviations:**
- BA = bone age
- CA = chronological age
14 yr old boy
h/o “shortest in his class”
h/o “always a small boy”
h/o father did not “grow” till he entered college

Prepubertal
GV = 5.0 cm/yr
Normal BUN / ESR
Normal Free T4 & TSH
Low-normal IGF-1
Normal IGFBP3 (for Tanner stage)
Bone age = 11.5 yrs

MRI
Normal

Testosterone 50 mg / q 4wks x 3 doses

Source: Undetermined
Short Stature
height < 3rd percentile
Growth Retardation
growth velocity < 3rd percentile

Etiology
Normal Variant
Pathological
Proportionate
Disproportionate

Definitions
SHORT STATURE
Proportionate
Disproportionate
Hypothyroidism
GH deficiency
Cushing's syndrome

Endocrinopathies
Hypothyroidism
GH deficiency
Cushing's syndrome

Malabsorption
Inflammatory bowel disease
Celiac disease

GI

Renal
Chronic renal failure
Renal tubular acidosis

Renal

Chronic Systemic Illness
Cardiac
Pulmonary
Liver
Infection

IUGR
Malnutrition

Psychosocial Dwarfism
Emotional Deprivation Syndrome

SHORT STATURE
Pathological Proportionate
4 yr old boy
Voracious appetite / drinks urine – toilet bowl
Withdrawn / flat affect
No dysmorphic features
Chaotic home situation – abusive father

Ht age = 1 yr old

All lab tests normal
4 yr old boy
No dysmorphic features
Chaotic home situation - abusive father

Emotional deprivation syndrome
Psychosocial dwarfism

Admitted to hospital for observation

Source: Undetermined
6 yr old girl
GV = 3.0 cm/yr
No dysmorphic features
Chaotic home situation – parent incarcerated – shuttled through couple of foster homes
Adopted by a family
Stable home environment

Emotional deprivation syndrome
Psychosocial dwarfism

All lab tests normal

Source: Undetermined
Skeletal Abnormalities
- Dysplasia
- Achondroplasia
- Rickets
- Vertebral anomalies

Dysmorphic Syndromes
- Turner
- Down
- Russell-Silver
- Prader-Willi
- Pseudo-hypoparathyroidism

SHORT STATURE
Pathological Disproportionate
SHORT STATURE

**Prenatal**
- maternal infection, alcohol

**Pattern of growth**
- birth wt and length

**Family History**
- onset of puberty

**Nutrition**

**Systemic Disease**

**Drugs**
- steroids

**Neurological**
- headache, vision, enuresis

**Psychosocial**

**Evaluation Clinical History**
**SHORT STATURE**

**Anthropometric**
- ht, wt, head circ., arm span, U/L ratio

**Nutritional state**

**Tanner Staging for Pubertal Development**
- First sign of puberty on PE:
  - ♀ breast dev / ♂ incr in testicular volume

**Dysmorphic Features**

**Neurological exam**

**Thyroid Gland**

**Evaluation Physical Exam**
SHORT STATURE

Target Height (in cms)

\[
girl = \frac{[father's \ ht + mother's \ ht] - 13}{2}
\]

\[
boy = \frac{[father's \ ht + mother's \ ht] + 13}{2}
\]

normal range is ± 8 cms
SHORT STATURE

Evaluation
Diagnostic Approach

Key Parameter - Growth Velocity

Normal GV
Familial
Constitutional

Impaired GV
Malnutrition
Chronic systemic illness
IUGR
Psychosocial
Chromosomal abnormalities
Endocrine
Malabsorption
Bone dysplasias
**SHORT STATURE**

**Screening Tests**

- CBC, ESR, BUN
- FT$_4$, TSH
- IGF-1, IGFBP3
- Tissue Transglutaminase ab

**Evaluation Laboratory Tests**

- KARYOTYPE
  - in girls to exclude TURNER
  - dysmorphic features

- RADIOLOGICAL
  - bone age
  - skeletal survey
SHORT STATURE

Growth Hormone Deficiency (GHD)
Short Stature

GH Deficiency (GHD)
Signs & Symptoms

- Neonatal - normal size / hypoglycemia / jaundice / micropenis / midline defect
- Decreased growth velocity
- Delayed dentition / mid-facial hypoplasia
- Increase in adiposity
SHORT STATURE

GH Deficiency (GHD) Causes

- Tumor - craniopharyngioma
- Trauma - surgery / irradiation
- Idiopathic
- Congenital Aplasia / Hypoplasia / Septic-optic dysplasia
- Genetic Defects -
  - Isolated Growth Hormone Deficiency (IGHD)
  - PROP1 / POU1F1 (Pit1)
Criteria for diagnosing GH deficiency

Clinical (NOT laboratory) diagnosis
- GV < 2 SD
- Low IGF-1 & IGFBP-3
- Provocative GH Level < 7-10 ng/ml

Corroborative evidence
- Delayed BA
- Related pathology
SHORT STATURE

Measurement of GH

- Spontaneous pulsatility of GH precludes random measurement
- Provocative test after overnight fast
  - Insulin induced hypoglycemia is the “Gold standard”

IGF-1 / IGFBP3

- Altered by nutritional status
- Normal range related to age & pubertal status
SHORT STATURE

Growth hormone deficiency
Turner syndrome
Renal disease, before transplant
Small for gestational age
Prader-Willi syndrome
Idiopathic short stature

Treatment
Indications for GH Therapy
SHORT STATURE

Treatment
GH Replacement Therapy

s/c injection
7 days/wk

Side Effects
- Secondary/tertiary hypothyroidism
- Worsening of scoliosis
- Slipped capital femoral epiphysis
- Pseudotumor cerebri

Monitor
GV, Free T4, IGF-1, IGFBP3
8½ yr old girl
h/o poor growth x 12-18 months
recent h/o vague headaches
school performance has recently deteriorated
recent episodes of enuresis

Prepubertal
GV = 1.5 cm/yr
Low Free T₄, Normal TSH
Low IGF-1 & IGFBP3
Karyotype = 46 XX
Bone age = 6 yrs

MRI
craniopharyngioma

Source: Undetermined
8½ yr old girl
h/o poor growth x 12-18 months
h/o vague abdominal discomfort

Prepubertal
GV = 2.5 cm/yr
Normal Free T4 & TSH
Low IGF-1
Normal IGFBP3
Karyotype = 46 XX
Bone age = 7.5 yrs

Decreased serum albumin, microcytic anemia
ESR - 30

Tissue transglutaminase antibodies +ve
Small Intestine Biopsy - CELIAC DISEASE

Source: Undetermined
5 yr old girl
GV = 3.0 cm/yr
subtle dysmorphic features - clinodactyly, webbing of neck ±, ↑ carrying angle
GV = 3.0 cm/yr
Normal Free T₄ & TSH
Normal IGF-1
Normal IGFBP3
Bone age = 5.0 yrs

Karyotype = 45,X
TURNER SYNDROME

Source: Undetermined
Described in 1938 by Dr. Henry Turner

**Most common sex chromosomal abnormality in females -- X chromosome**

**Frequency 1:1500 to 1:2500 in live born infant girls**

**15% of spontaneous abortions = TS**
Turner Syndrome

Karyotype 45, X

Image of Turner Syndrome
Karyotype removed
**Clinical Features - Postnatal**

- Growth Failure: 80-100%
- Gonadal Dysgenesis: 80-100%
- Inverted/ widespaced nipples: 60%
- Nail dysplasia: 60-80%
- High narrow palate: 60-80%
- Cardiac malformation: 40-60%
- Renal dysplasia: 40-60%
- Low hairline/webbing: 30-40%
- Pigmented nevi: common
Lymphedema at birth is highly correlated with 45,X karyotype and congenital heart abn
If you slept through this lecture... the 4 points to remember

- **Growth velocity (and NOT height)** is the key anthropometric parameter
- **Normal growth velocity virtually excludes a pathological cause for short stature**
- **Always exclude Turner’s synd in a girl with short stature**
- **Diagnosis of a child with growth problems is made more on CLINICAL and less on laboratory criteria**