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
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 $\text{cm/yr}$</th>
<th>Adult Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Steroids</td>
<td>Increase</td>
<td>Diminished</td>
</tr>
<tr>
<td>Sex Steroids</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Normal/± incr</td>
<td>Normal</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>GH</td>
<td>Increase</td>
<td>Increased</td>
</tr>
<tr>
<td>GH</td>
<td>Decrease</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Decrease</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol</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**
**Normal Growth**

**Anthropometric parameters**

**Upper / Lower Segment Ratio**

<table>
<thead>
<tr>
<th>Time</th>
<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>
<td></td>
</tr>
<tr>
<td>Post-natal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lower segment:** symphysis pubis to floor

**Upper segment:** Ht (-) lower segment

Image of fetal and post-natal growth chart removed
Girls 2-18 yrs

Source: Undetermined
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

Age (yrs)

Growth rate (cms/yr)

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 Definitions

- 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

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

Definitions

- Short Stature
  height < 3rd percentile
- Growth Retardation
  growth velocity < 3rd percentile

Etiology

Normal Variant
Pathological

Proportionate
Disproportionate
SHORT STATURE

Endocrinopathies
Hypothyroidism
GH deficiency
Cushing’s syndrome

GI
Malabsorption
Inflammatory bowel disease
Celiac disease

Renal
Chronic renal failure
Renal tubular acidosis

Pathological Proportionate

Chronic Systemic Illness
Cardiac
Pulmonary
Liver
Infection

IUGR
Malnutrition

Psychosocial Dwarfism
Emotional Deprivation Syndrome
4 yr old boy

Voracious appetite / drinks urine - toilet bowl
Withdrawn / flat affect
No dysmorphic features
Chaotic home situation - abusive father

All lab tests normal
Admitted to hospital for observation

4 yr old boy
No dysmorphic features
Chaotic home situation – abusive father

Emotional deprivation syndrome
Psychosocial dwarfism

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
SHORT STATURE

Pathological Disproportionate

Skeletal Abnormalities
- Dysplasia
- Achondroplasia
- Rickets
- Vertebral anomalies

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

Evaluation
Clinical History

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
First sign of puberty on PE:
♀ breast dev / ♂ incr in testicular volume

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

Nutritional state

Tanner Staging for Pubertal Development

Dysmorphic Features

Neurological exam

Thyroid Gland
SHORT STATURE

Evaluation
Diagnostic Approach

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

Key Parameter - Growth Velocity

Normal GV
- Familial
- Constitutional

Impaired GV
- Malnutrition
- Chronic systemic illness
- IUGR
- Psychosocial
- Chromosomal abnormalities
- Endocrine
- Malabsorption
- Bone dysplasias

Evaluation Diagnostic Approach
SHORT STATURE

Screening Tests

CBC, ESR, BUN
FT₄, TSH
IGF-1, IGFBP3
Tissue Transglutaminase ab

KARYOTYPE
◊ in girls to exclude TURNER
◊ dysmorphic features

Evaluation
Laboratory Tests

RADIOIOLOGICAL
◊ 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 dypslasia
- Genetic Defects -
  - Isolated Growth Hormone Deficiency (IGHD)
  - PROP1 / POU1F1 (Pit1)
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
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
Growth hormone deficiency
- Turner syndrome
- Renal disease, before transplant
- Small for gestational age
- Prader-Willi syndrome
- Idiopathic short stature
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

$GV = 3.0 \text{ cm/yr}$

subtle dysmorphic features - clinodactyly, webbing of neck ±, t carrying angle

$GV = 3.0 \text{ cm/yr}$

Normal Free T$_4$ & TSH

Normal IGF-1

Normal IGFBP3

Bone age = 5.0 yrs

Karyotype = 45,X

TURNER SYNDROME

Source: Undetermined
**Turner Syndrome**

- 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
Turner Syndrome

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
Turner Syndrome

CC BY 2.0
BY: Johannes Nielsen, et al.
Lymphedema at birth is highly correlated with 45,X karyotype and congenital heart abn.
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.