M2 - Endocrine, Winter 2008

Lash, R.; Hammer, G.; Menon, R.; Oral, E.
Abnormalities of Growth & Development

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OBJECTIVES

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
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

Anthropometric parameters

- 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

Upper / Lower Segment Ratio

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

Anthropometric parameters

Image of fetal and post-natal growth chart removed

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

Growth rate (cms/yr)

Age (yrs)

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

Growth rate (cm/yr)

Age (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

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

Definitions

SHORT STATURE

Etiology

Normal Variant

Pathological

Proportionate

Disproportionate
Short Stature

Pathological Proportionate

Endocrinopathies
- Hypothyroidism
- GH deficiency
- Cushing’s syndrome

GI
- Malabsorption
- Inflammatory bowel disease
- Celiac disease

Renal
- Chronic renal failure
- Renal tubular acidosis

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

Ht age = 1 yr old
4 yr old boy
No dysmorphic features
Chaotic home situation - abusive father

Admitted to hospital for observation

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

All lab tests normal

Emotional deprivation syndrome
Psychosocial dwarfism

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

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**
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**
Screening Tests

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

KARYOTYPE
- in girls to exclude TURNER
- dysmorphic features

Evaluation Laboratory Tests

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
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
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 ±, † 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

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

Lymphedema

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BY: Johannes Nielsen, et al.
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