M2 - Endocrine, Winter 2008

Lash, R.; Hammer, G.; Menon, R.; Oral, E.

<http://hdl.handle.net/2027.42/64949>
http://hdl.handle.net/2027.42/64949
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 cms/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
Upper / Lower Segment Ratio

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

Normal Growth

Anthropometric parameters

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>Post-natal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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

Age (yrs)

Growth rate (cms/yr)

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 $\leftrightarrow$ 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
- $BA < CA$

**Notes**

- $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
Hypothyroidism
GH deficiency
Cushing’s syndrome
Malabsorption
Inflammatory bowel disease
Celiac disease
Chronic renal failure
Renal tubular acidosis
Cardiac
Pulmonary
Liver
Infection
Psychosocial Dwarfism
Emotional Deprivation Syndrome
SHORT STATURE
Pathological
Proportionate
GI
Endocrinopathies
Renal
Chronic Systemic Illness
IUGR
Malnutrition
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
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

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

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

Skeletal Abnormalities
- Dysplasia
- Achondroplasia
- Rickets
- Vertebral anomalies

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

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**
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\ \pm\ 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
**Screening Tests**

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

**KARYOTYPE**
- in girls to exclude TURNER
- dysmorphic features

**RADIOLOGICAL**
- bone age
- skeletal survey
SHORT STATURE

Growth Hormone Deficiency (GHD)
Neonatal - normal size / hypoglycemia / jaundice / micropenis / midline defect

Decreased growth velocity

Delayed dentition / mid-facial hypoplasia

Increase in adiposity
Tumor - craniopharyngioma
Trauma - surgery / irradiation
Idiopathic
Congenital Aplasia / Hypoplasia / Septic-optic dypslasia
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**

**GH Deficiency Diagnosis**

**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
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 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
Turner Syndrome

BY: Johannes Nielsen, et al.
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.
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.