M2 - Endocrine, Winter 2008

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<http://hdl.handle.net/2027.42/64949>
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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
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</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

*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

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
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
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

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

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

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

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

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

Skeletal Abnormalities
- Dysplasia
- Achondroplasia
- Rickets
- Vertebral anomalies

Pathological Disproportionate

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
Target Height (in cms)

\[
girl = \left( \frac{\text{father's ht} + \text{mother's ht}}{2} \right) - 13
\]

\[
boy = \left( \frac{\text{father's ht} + \text{mother's ht}}{2} \right) + 13
\]

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
SHORT STATURE Evaluation Laboratory Tests

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)
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)
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
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 ±, t 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

CC BY 2.0 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/widely spaced 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.