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
Image of GH/IGF-1 Axis removed
<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>
Weight

Measurement of height - Stadiometer
  less than 2yrs 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

<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>

Image of fetal and post-natal growth chart removed
<table>
<thead>
<tr>
<th>DATE</th>
<th>AGE</th>
<th>STATURE</th>
<th>WEIGHT</th>
<th>COMMENT</th>
</tr>
</thead>
</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

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

Growth rate (cms/yr)

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 Definitions

- 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
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

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

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
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
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

Emotional deprivation syndrome

Psychosocial dwarfism

All lab tests normal

Source: Undetermined
SHORT STATURE

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

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

normal range is ± 8 cms
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
- FT₄, 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)
Neoatal - 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
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
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

[Image: 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.