M2 - Endocrine, Winter 2008

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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
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Growth Rate 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>
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<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

<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>
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</thead>
<tbody>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Post-natal</td>
<td></td>
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<td></td>
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</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

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

Growth rate (cms/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

Etiology
Normal Variant
Pathological
Propotionate
Disproportionate
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 cm/yr
No dysmorphic features
Chaotic home situation – parent incarcerated – shuttled through couple of foster homes

All lab tests normal

Emotional deprivation syndrome
Psychosocial dwarfism

Adopted by a family
Stable home environment

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

Evaluation
Clinical History

Prenatal
maternal infection, alcohol

Pattern of growth
birth wt and length

Family
onset of puberty

History

Nutrition

Systemic Disease

Drugs
steroids

Neurological
headache, vision, enuresis

Psychosocial
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{[\text{father's ht} + \text{mother's ht}] - 13}{2}

boy = \frac{[\text{father's ht} + \text{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
- FT₄, 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)
- 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)
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

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

BY: Johannes Nielsen, et al.

[Image CC BY 2.0]
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
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
Lymphedema at birth is highly correlated with 45, X karyotype and congenital heart abn.

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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.