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
## 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 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

2m 5m Birth 2yr 6yr 12yr 25yr
Fetal Post-natal

Image of fetal and post-natal growth chart removed
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 (cm/yr)

Age (yrs)

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

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

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

Ht age = 1 yr old

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

Dysplasia
Achondroplasia
Rickets
Vertebral anomalies

Pathological Disproportionate

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 onset of puberty

History 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{[\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
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)
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.
Proximate 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.
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/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.
Turner Syndrome

**Lymphedema**

- Lymphedema at birth is highly correlated with 45,X karyotype and congenital heart abn

CC:BY 2.0
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.