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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
GH/IGF-1 Axis

Image of GH/IGF-1 Axis removed
<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

- **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>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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Post-natal | | | | | |

Post-natal Growth Chart
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

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

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

Endocrinopathies
- Hypothyroidism
- GH deficiency
- Cushing’s syndrome

Renal
- Chronic renal failure
- Renal tubular acidosis

GI
- Malabsorption
- Inflammatory bowel disease
- Celiac disease

Chronic Systemic Illness
- Cardiac
- Pulmonary
- Liver
- Infection

IUGR
- Malnutrition

Psychosocial Dwarfism
- Emotional Deprivation Syndrome

Pathological Proportionate
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
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 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

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)

\[
girl = \frac{[father's \, ht + mother's \, ht] - 13}{2}
\]

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

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
**SHORT STATURE**

**Screening Tests**

- CBC, ESR, BUN
- FT$_4$, 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)
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 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
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
8 1/2 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 T\textsubscript{4}, 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.
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
**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

Lymphedema

- 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.