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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
## 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 2 yrs of age - length (supine)
  - greater than 2 yrs of age - height (erect)
- Head circumference
- Span
- Upper segment / lower segment ratio
Normal Growth

Upper / Lower Segment Ratio

Lower segment: symphysis pubis to floor
Upper segment: Ht (-) lower segment

Anthropometric parameters

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

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
$GV = 5.0 \text{ cm/yr}$
Normal BUN / ESR
Normal Free $T_4$ & 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

Definitions

- 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

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

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

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 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

Pathological Disproportionate
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
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)
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
- 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.
Producative 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
- 7days/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
● 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
<table>
<thead>
<tr>
<th>Clinical Features - Postnatal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth Failure</strong></td>
<td>80-100%</td>
</tr>
<tr>
<td><strong>Gonadal Dysgenesis</strong></td>
<td>80-100%</td>
</tr>
<tr>
<td>Inverted/widespaced nipples</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Nail dysplasia</strong></td>
<td>60-80%</td>
</tr>
<tr>
<td><strong>High narrow palate</strong></td>
<td>60-80%</td>
</tr>
<tr>
<td><strong>Cardiac malformation</strong></td>
<td>40-60%</td>
</tr>
<tr>
<td><strong>Renal dysplasia</strong></td>
<td>40-60%</td>
</tr>
<tr>
<td><strong>Low hairline/webbing</strong></td>
<td>30-40%</td>
</tr>
<tr>
<td><strong>Pigmented nevi</strong></td>
<td>common</td>
</tr>
</tbody>
</table>
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.