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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</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/( \pm ) 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**
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></td>
<td></td>
<td>Post-natal</td>
<td></td>
<td></td>
<td></td>
</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

Growth rate (cms/yr)

Age (yrs)

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

Age (yrs)

Growth rate (cms/yr)

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
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

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

Source: Undetermined
Short Stature
- height < 3rd percentile
- Growth Retardation
  - growth velocity < 3rd percentile

Definitions
- Proportionate
- Disproportionate

Etiology
- Normal Variant
- Pathological
Hypothyroidism
GH deficiency
Cushing’s syndrome
Malabsorption
Inflammatory bowel disease
Celiac disease
Celiac disease
Chronic renal failure
Renal tubular acidosis
Cardiac
Pulmonary
Liver
Infection
Infection
IUGR
Malnutrition
Psychosocial Dwarfism
Emotional Deprivation Syndrome

**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

**Pathological Proportionate**

IUGR
Malnutrition
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

Emotional deprivation syndrome
Psychosocial dwarfism

4 yr old boy
No dysmorphic features
Chaotic home situation - abusive father

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

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
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
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
**SHORT STATURE**

**Treatment**

**Indications for GH Therapy**

- 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 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

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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
Karyotype 45, X
**Turner Syndrome**

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**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

CC BY 2.0
BY: Johannes Nielsen, et al.
Lymphedema

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

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.