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

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
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

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
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 Fetal</th>
<th>5m Fetal</th>
<th>Birth</th>
<th>2yr Post-natal</th>
<th>6yr Post-natal</th>
<th>12yr Post-natal</th>
<th>25yr Post-natal</th>
</tr>
</thead>
</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
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 $< 3$rd percentile

Growth Retardation
growth velocity $< 3$rd percentile
Short Stature
height < 3rd percentile

Growth Retardation
growth velocity < 3rd percentile

Etiology

Normal Variant ↔ Pathological
**SHORT STATURE**

**Normal Variant**

**Familial / Genetic**

- Final height appropriate for parental height
- 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
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
All lab tests normal
Emotional deprivation syndrome
Psychosocial dwarfism

Source: Undetermined
SHORT STATURE

Pathological Disproportionate

Skeletal Abnormalities
- Dysplasia
- Achondroplasia
- Rickets
- Vertebral anomalies

Dysmorphic Syndromes
- Turner
- Down
- Russell-Silver
- Prader-Willi
- Pseudo-hypoparathyroidism
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
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

**Evaluation Laboratory Tests**

**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
SHORT STATURE

GH Deficiency (GHD) Causes

- Tumor - craniopharyngioma
- Trauma - surgery / irradiation
- Idiopathic
- Congenital Aplasia / Hypoplasia / Septic-optic dypslasia
- 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.

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
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
5 yr old girl
GV = 3.0 cm/yr
subtle dysmorphic features - clinodactyly, webbing of neck ±, † 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.
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**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Failure</td>
<td>80-100%</td>
</tr>
<tr>
<td>Gonadal Dysgenesis</td>
<td>80-100%</td>
</tr>
<tr>
<td>Inverted/widely spaced nipples</td>
<td>60%</td>
</tr>
<tr>
<td>Nail dysplasia</td>
<td>60-80%</td>
</tr>
<tr>
<td>High narrow palate</td>
<td>60-80%</td>
</tr>
<tr>
<td>Cardiac malformation</td>
<td>40-60%</td>
</tr>
<tr>
<td>Renal dysplasia</td>
<td>40-60%</td>
</tr>
<tr>
<td>Low hairline/webbing</td>
<td>30-40%</td>
</tr>
<tr>
<td>Pigmented nevi</td>
<td>common</td>
</tr>
</tbody>
</table>
Turner Syndrome
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.