Pediatric Growth Hormone Deficiency: Identification, Diagnosis, & Management
Kent Reifschneider, MD
CHKD / EVMS
Norfolk, VA

Conflict of Interest
• Speaker bureau and advisor for Pfizer
• Board member of The Human Growth Foundation

THANK YOU!

Objectives
• Review the literature regarding measurement accuracy
• Discuss accurate measurement techniques
• Identify normal verse abnormal growth patterns
• Review differential diagnosis for poor growth
• Case studies
Importance of Accurate Growth Measurement

• Incorrect measurements = Inaccurate assessment

• A 2004 study showed growth to be measured accurately in only 30% of children¹


Accurate Height Measurement Technique

• No shoes, hair ornaments, braids, etc²

• Heels together, legs straight, arms at sides, shoulders relaxed²

• Patient should inhale deeply and stand fully erect²

• Height should be plotted on patient’s chart at each visit


Accurate Length Measurement Technique
Evaluating Growth (cont’d)

• Normal growth velocity:
  – Most rapid in first year of life (up to 22 cm/yr)¹
  – Slows to 7-8 cm/yr, ages 2–4 years²
  – Declines further to ~ 5-7 cm/yr, mid-childhood¹
  – Increases to 10–12 cm/yr, during pubertal growth spurt¹

• Serial measurements over at least 6 months are required for growth velocity calculation.

• Velocity standards are required for correct evaluation of data¹

². CDC growth chart. 2000. www.cdc.gov/growthcharts

Causes of Abnormal Growth

• Normal Variants
  – Familial Short Stature
  – Constitutional Delay
  – Prenatal Factors → Postnatal Growth
  – Low Birth Weight (SGA)
  – Congenital Anomalies
  – Nutritional Deficiency
  – GER, FTT, Eating Disorders
  – Chronic Disease
    – Common – GI, Renal, Neurologic
    – Less Common – Cardiac, Pulmonary
  – Medications
    – Steroids, Stimulant medications
  – Endocrine
    – Hypothyroidism
    – GH Deficiency
    – Cushing Syndrome
    – Early or late puberty
  – Genetic Syndromes
    – Down
    – Turner
    – Prader-Willi
    – Pseudohypoparathyroidism
    – Russell-Silver
  – Bone Disorders
    – Achondroplasia, etc

Normal Variants

Short Stature with normal growth rate

• Familial Short Stature
  – Short stature with normal onset of puberty
  – FH of short stature
  – BA = CA
  – Final height short but within target range

• Constitutional Delay
  – Short stature with delayed puberty (late bloomer)
  – FH of slow growth and delayed puberty in ~50–75%
  – BA < CA
  – Final height normal or low normal
Auxological Signs of Pediatric GHD

- Short stature
- Low growth velocity for age (<25th% for bone age)
- Crossing centiles in a downward direction
- Auxology is helpful as an indication for evaluation for pediatric GHD; however, it doesn't differentiate children with pediatric GHD from other causes of growth problems
  - Screening tests can help differentiate endocrine from non-endocrine causes of growth failure

Etiologies of Pediatric GHD – Congenital

- Multiple genetic causes of pediatric GHD have been identified
  - Examples include abnormalities of the GH gene, the GHRHR gene, or the Pit-1 gene (PDX1FS gene)
- May be associated with structure defects:
  - Agenesis of corpus callosum
  - Hydrocephalus
  - Septo-optic dysplasia
- May be associated with midline facial defects:
  - Cleft lip/palate
  - Single central incisor

Etiologies of Pediatric GHD – Acquired

- Trauma
- CNS infection
- Hypophysitis
- Primary or secondary CNS tumors, particularly of the hypothalamus or pituitary (e.g., craniopharyngioma, glioma, germinoma, histiocytosis)
- Cranial irradiation
Idiopathic Pediatric GHD

- Majority of pediatric GHD cases
- Presentation may be in early childhood with severe growth failure and other clinical features of GHD
- Affected infants usually have a normal weight and length at birth, but impairment of linear growth may occur within the first 2 years of life
  - This growth pattern suggests that GH may not be an essential growth factor in utero
- History may include difficult delivery, recurrent hypoglycemia, and/or prolonged jaundice


Auxological Criteria for GHD Evaluation

- Investigation should be initiated if a child exhibits one or more of these features:
  - Severe short stature
  - Height >2.25 SD below the mean for age or >2 SD below the midparental height percentile
  - Midparental height = (father's height + mother's height)/2 + 6.5 cm for boys, - 6.5 cm for girls
  - Growth velocity <25th% for bone age


Conclusions

- Pediatric GHD is defined as short stature or slow growth caused by the absence or inadequate production of GH in children
- Multiple etiologies have been identified; may also be idiopathic
- Diagnosis is complex
  - Based on clinical, auxological, biochemical, and radiological evaluations
- GH therapy is proven to improve growth in children with pediatric GHD
- Routine follow-up of patients receiving GH therapy should be performed by a pediatric endocrinologist

Management of Short Stature in Children Born Small for Gestational Age

Objectives of Presentation

• Define small for gestational age (SGA)
• Review the etiology of SGA
• Discuss methods of identifying children who are born SGA
• Review evidence for the use of growth hormone (GH) in children who are born SGA and fail to manifest catch-up growth by 2 years of age
• Discuss assessment and monitoring of children who are candidates for GH therapy

Etiology of SGA
SGA: Pathophysiology (Hypothesis)

- Fetal response to prolonged nutrient deficiency late in gestation may be permanently reset to a slow growth rate, with a degree of resistance to GH, insulin-like growth factor (IGF-I), and insulin.
  - Therefore, a subset of children born SGA may have:
    - Slow growth rate as a manifestation of a degree of GH or IGF-I resistance
    - Increased risk of cardiovascular and metabolic diseases in later life

Gluckman PD, Harding JE. Hom Res. 1997;48(suppl 1):11-16.

Identifying Children Born SGA

- For correct diagnosis of SGA, birth length must be measured precisely
  - 2 people required for accuracy
  - Infant on back, centered on board, lying straight with shoulders and buttocks flat against surface
  - Infant’s eyes looking straight up and toes pointing upward with feet flat against footpiece, both legs fully extended


Catch-up Growth in Children Born SGA

- ~90% of children who are born SGA experience catch-up growth by age 2 years and will achieve a height greater than ~2 SDS (~3rd percentile)\(^1,2\)
  - 80% or more of infants caught up in the first 6 months of life\(^2\)

Growth Failure in Children Born SGA

- In some children born SGA, the growth pattern falls away from age- and gender-specific growth curves.

Rationale for GH Evaluation

- Children who have not experienced catch-up growth by age 2 years have higher risk of short stature (less than -2SDA) as adults, especially those with low birth weight.

Conclusions: Management of Short Stature in Children Born SGA

- Children born SGA who fail to exhibit catch-up growth by 2 years of age are unlikely to catch up, and may be candidates for GH therapy.
- Treatment of children with GH for up to 6 years has been effective and well tolerated in clinical trials.
- Early initiation of therapy may result in better growth response.

What is Normal Growth?  
...It depends!

Important Questions

- Referent point (gender, MPH)
- Birth, PNH (trauma, meningitis) & NET
- Medications
- Activities
- TSS
- Hair, vision, hearing or signs of hypothyroidism
- P.E.
- Arm span, Tanner, skeletal exam, & growth velocity
What if this was a girl?

Turner Syndrome
Clinical Features

• Short Stature ~100
• Gonadal failure >95
• Characteristic faces 60
  - micrognathia, high-arched palate, low-set ears
• Cardiovascular anomalies 30-50
• Renal abnormalities 40
• Skeletal abnormalities 40-50
  - short metacarpals, cubitus valgus, scoliosis
• Endocrine abnormalities 30-40
  - autoimmune thyroiditis
  - Type 2 diabetes
• Webbed neck 25
• Edema of hands/feet 25
Evaluation

- Confirm accurate measurements
- Compare to genetic potential and Hx
- Follow growth velocity
- Similar to FTT plus hormones & Bone age
  - CBC - CMP
  - UA - ESR
  - TSH/T4 - IGF-1/IGF-BP3*
  - IgA with TTG abs - Bone age*

Nutrition

- ALL JUICE IS BAD!
- LOW FAT MILK IS GOOD!
- Diet soda?
- N.E.A.T. vs Exercise
References

14. Wollmann HA. Horm Res. 1998;49(suppl 2) 1-6.