Growth and Pediatric Growth Hormone Use

What does an Adult Endocrinologist need to know?

October 30, 2015
Objectives

- Know the normal rates of growth during childhood
- Understand mid-parental height
- Distinguish between constitutional delay, genetic short stature and GH deficiency
- Review use of growth hormone in other children
  - Turner syndrome
  - Prader-Willi syndrome
  - SGA without growth recovery by 2 years
  - Idiopathic Short Stature
Growth: normal and abnormal
Why understand growth?

- Everyone does it!
- A top question parents have about their kids
- A top question kids have about themselves
- Problems with growth may be a clue to other issues
- On every board exam forever....
What is normal growth?

- Year One → 25 cm/yr
- Year Two → 10-12 cm/yr
- Year Three → >8 cm/yr
- Year Four → >7 cm/yr
- Childhood → 5-6 cm/yr
- Puberty → 8-10 cm/yr

When puberty starts 85% of growth is already completed!
How do you know a child is growing normally?

- Measure the child correctly
- Plot on an appropriate growth chart
  - Or let your computer do that…
- Look at the chart with your brain engaged
General Principles of Growth

- Any chronic disease can adversely affect growth
- Short stature can have adverse psychosocial effects
- Terriers don’t have Great Dane puppies
- Growth in the first 1-2 years is primarily nutritionally driven
- Children generally find “their” percentile by age 2
- Beware of the change in “height” that occurs when a child begins to be measured in the standing position.
- 3% of all kids will always be short
Normal growth

Growth Chart 2 to 20 Years: Boys

Growth Chart 2 to 20 Years: Girls

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10/20/2015
So what if…

- A child is short
- A child is shorter than the family
- A child is growing slowly
- …
History

- Pregnancy, intrauterine problems, gestational length, delivery issues
- Birth weight and length
- Nutritional intake
- Chronic illness / conditions / medications
- Pattern of growth since birth
- Psychosocial issues
Family History

- Parent heights
- Grandparent heights
- Sibling heights
- Parent pattern of puberty (early/late)
  - Women – age of menarche
  - Men – age that vertical growth completed
- Family illnesses/syndromes/diseases
Mid-parental height

Average of the parent’s percentiles

- For boys: \((\text{father} + \text{mother} + 5 \text{ inches}^*)/2\)
- For girls: \((\text{father} + \text{mother} - 5 \text{ inches})/2\)

Family-adjusted target height range is

MPH +/- 3-4 inches

13 cm ~ 5 in
Mid parental height and family adjusted target height range

Mom 5’4”
Mom’s height adjusted
Family adjusted target height range
Mid-parental Ht
Dad 5’7”
Boy’s growth chart, right side

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Physical Exam

- Height and weight
  - Plot it on the APPROPRIATE chart!
  - EMR usually only has one set of charts
    - Down syndrome?
    - Turner syndrome?
    - Many many others
- Calculate BMI and plot it (again, EMR…)
  - kg/m² (kg÷m÷m)
- Look for any sign of hidden or chronic illness
- Look for evidence of hormone problems
- Look for stigmata of syndromes
Wall fixed stadiometer!

- Harpenden **Stadiometer**
- Accu-Hite Stadiometer

Seca Portable Stadiometer

Not as good!

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5. STADIOMETERS FOR MEASURING CHILDREN AND ADOLESCENTS

Stadiometers are available in two types. The first type is permanently fixed to the wall in a clinic area. The second type is portable. The most common failing of a portable stadiometer is a base that is too small. When the base is too small, the stadiometer is not stable and entirely perpendicular to the floor.

- Equipment must be used for the purpose for which it was designed
- No tapes, yardsticks or graphics attached to the wall
- No carpet under stadiometer
- Stadiometer must be stable, calibrated and dedicated to the purpose

A sequential evaluation approach

- Short/growing slowly & underweight-for-height
- Short/growing slowly & appropriate weight-for-height
- Short/growing slowly & overweight-for-height
- Tall/growing rapidly
Short/growing slowly & underweight-for-height

- Evaluation of nutritional issues first, then for chronic illness
- Later consideration of hormonal concerns (less likely).
- A dietary recall / referral to a dietician
  - macro- and micro-nutrient issues
  - specific food avoidance
  - intentional dieting
  - use of laxatives or diuretics
  - “nutritional supplements” or herbal preparations.
- ROS: body image, stool pattern and quality, swallowing problems, abdominal pain.
- Laboratory testing: Prealbumin, cholesterol, UA, ESR, CBC, tTG, IgA, BUN, creatinine, ALT.
- Additional testing (sweat test, stool for fecal fat, occult blood & parasite) if symptoms/family hx
Short/growing slowly & underweight-for-height

- May include those with GI disease or other chronic illness
- Common in constitutional delay
- Common with ADHD
- Bone age often delayed
- Weight velocity
- decline started prior to height velocity decline
- Weight age < Height age
  - Age at which weight or height would be 50th percentile
HA = 4.75 yrs

WA = 3.75 yrs
Short/growing slowly & appropriate weight-for-height

- Evaluation of chronic illness and genetics first
- Then hormonal problems
- Detailed family history: parental heights, parental pubertal pattern, and heights of aunts, uncles and grandparents
- Family history can suggest explanations
  - constitutional delay of growth and puberty
  - chromosomal deletions or re-arrangements
- A bone age x-ray
  - need for referral for further evaluation (if more than -2 SD delayed)
  - re-assure families that the child most likely has/will have delayed puberty (if -1 to -2 SD.)
- Laboratory testing: ESR, CBC, IgA, tTG IgA, BUN, creatinine, free T4, TSH, IGF-1, Karyotype (girls)
Short/growing slowly & appropriate weight-for-height

- Genetic short stature most commonly
- Chronic illness with reasonably maintained nutrition
- Turner syndrome
Idiopathic Short Stature

Men 1.2% = 63"

Women 1.2% = 58.5"

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Short/growing slowly & overweight-for-height

- Evaluate hormonal and genetic problems.
- Dietary review: excessive intake, inappropriately calorie-dense foods
- Review of familial heights and pubertal patterns AND detailed information concerning overweight, heart disease, hypertension, hyperlipidemia, diabetes, hormone problems
- ROS: fatigue, dry skin and/or hair, constipation, purple non-healing striae, low muscle strength, history of bone fracture
- Laboratory testing: free T4, TSH, IGF-1, karyotype, general screen for overweight-related morbidity (random/fasting serum glucose, total cholesterol level/fasting lipid profile
  - Hypercortisolism: rare
- Bone age x-ray
Short/growing slowly & overweight-for-height

- Cushing
- Hypothyroid
- Growth Hormone deficiency
Growth hormone Deficiency
Growth hormone history

http://www.ghresearchsociety.org/GRS%20history.htm
Eight FDA approved indications for Growth Hormone

- Childhood GH deficiency (1985)
- CRI pre-transplant (1993)
- HIV wasting in adults (1996)
- Turner syndrome (1996)
- Adult GH deficiency (1997)
- Prader-Willi syndrome (2000)
- SGA without growth recovery (2001)
- Idiopathic Short Stature (2003)
Growth hormone deficiency

- Estimated incidence 1:10,000
  - 1:4000-1:60,000
- Etiology
  - Anatomic
  - Post-surgical
  - Post-radiation
  - Post-traumatic
  - Inflammatory/Infiltrative
  - Genetic
  - Idiopathic
Growth hormone deficiency

- Isolated GH deficiency vs. poly-pituitary hormone deficiency

- GH effects:
  - Linear growth
  - Bone metabolism
  - Adipose tissue
  - Muscle tissue
Growth hormone deficiency

Classically present with:

- Marked growth retardation
- Diminished growth velocity
- Delayed skeletal maturation
- Low IGF-1 and IGF-BP3
- Poor GH response to stimulation testing

Most children with GHD dx have partial GHD or GH insufficiency
Growth hormone deficiency - Evaluation

■ Evaluation for short stature / slow growth
  □ Growth velocity is low
  □ IGF-1 is low (or lowest quartile)
  □ No other etiologies

■ GH stimulation testing
Growth hormone stimulation testing

- Arginine IV infusion
  - stimulate hypothalamus through the adrenergic pathway and ↑ GHRH (release GH)
  - increases insulin production (↓BG & release GH)
  - decrease somatostatin production (release GH)

- Glucagon IV injection
  - ↑ insulin secretion to compensate for elevated serum glucose levels (↓BG & release GH).
GH stimulation testing

- Failed stimulation = All GH levels under 7-10
- Quality of test (hypoglycemia)
- Simultaneous test for HPA adequacy
GHD on stimulation testing: what next?

- MRI brain, with & without contrast, focus on hypothalamus and pituitary.
- SMN (Statement of medical necessity)
- Choose a GH product!
GH products

- **Genentech: Nutropin AQ Nuspin**
  - Vial and pen

- **Lilly: Humatrope**
  - Vial and pen

- **NovoNordisk: Norditropin**
  - Pen

- **Serono: Saizen**
  - Vial, pen, needle-less jet injector, easypod

- **Pharmacia: Genotropin**
  - Pen, miniquick*, mixer

- **Omnitrope**
  - Vial, pen

- **Zomacton…**

*Miniquick is the only non-preservative GH
GH treatment

Treatment

- Recombinant GH
- SQ injection nightly
- 0.3 mg/kg/week
  - Pubertal dosing up to 0.7 mg/kg/week
GH follow up

- Follow growth velocity, IGF-1, thyroid function
  - monitor for complications: hyperglycemia, low cortisol, lipid panel, occasional LFT or CBC

- Continue until:
  - Completed growth (<1 cm growth in 3-4 months)
  - Acceptable height (the teen wants to stop)
  - Bone epiphyses fused/near fused (girls 14.5, boys 16)

- Discuss Adult GH treatment!
Other indications for GH

- Turner syndrome
- Prader-Willi syndrome
- SGA without growth recovery by 2 years
- Idiopathic Short Stature
Turner Syndrome
Growth in Turner Syndrome

- 95% of girls experience growth failure
- Disproportionate increase in weight
- 50% of affected girls have no stigmata except short stature and ovarian failure
- Untreated adult height 143 cm = 4’8” (av)
  - 50% of girls are <5th %tile at 1.5 years
  - 75% of girls are <5th %tile at 4 years
Growth Hormone in Turner Syndrome

- GH treatment approved for use in girls with Turner syndrome 1996
- Most girls with Turner syndrome do not have classic Growth hormone deficiency
- Additional issues of puberty induction timing, use of low-dose estrogen (or oxandrolone.)
Prader-Willi syndrome
Growth in Prader-Willi syndrome

- Average height untreated
  - Male: 155 cm (61”)
  - Female: 148 cm (58”)
- Reduced Growth hormone secretion
  - Normalizes linear growth
  - Increased lean body mass with decreased fat mass
  - Increased BMD
  - Improved body strength and agility
GH treatment in Prader Willi

60 pre-pubertal Dutch kids with PWS
Followed for 8 yrs continuous GH
GH tx 1 mg/m2/day SQ
  1 mg/m2/d ≈ 0.035 mg/kg/d
LBM increased first year then remained stable
Percent body fat SDS and BMI SDS decrease first year and then remain stable
Height SDS and head circumference SDS completely normalized
IGF-1 SDS increased to +2.36 SDS the first year and remained stable
GH treatment did not adversely affect glucose homeostasis, serum lipids, blood pressure, and bone maturation.
GH treatment in Prader Willi

- GH treatment is under investigation in 4-30 month babies with positive preliminary results
  - Improved lean body mass
  - Pace of motor development *may be* increased

- Sleep associated Deaths
  - Sleep study prior to GH tx
  - Withhold GH if BMI > 4SD or severe abnl sleep study
SGA without growth recovery by 2 years
SGA without growth recovery by 2 years

- >86% born SGA will catch up in length by 1 yo
- 7-10% of children born SGA will remain > or = -2 SD for height into adulthood
  - Those born -2 SD for weight have a relative risk of 5.2 for being short at adulthood compared with those born AGA
  - Those born -2 SD for height have a relative risk of 7.1 for being short at adulthood compared with those born AGA
SGA without growth recovery by 2 years

- GH tx dose 1 mg/m2/d, up to 0.48 mg/kg/wk
- No GH stimulation testing required?
- Limited side effects
  - No increase in metabolic syndrome or insulin resistance
  - Despite high dosing compared to GH deficient population (0.3 mg/kg/wk)
- Estimated increase 11 cm (4.3”)
Idiopathic Short Stature

Randy Newman – Short People

…They got little hands
And little eyes
And they walk around
Tellin' great big lies
They got little noses
And tiny little teeth
They wear platform shoes
On their nasty little fett

Well, I don't want no Short People
Idiopathic Short Stature

GH approved in 2003 for the long term treatment of children with idiopathic short stature with growth rates unlikely to permit attainment of adult height in the normal range

- More than -2.25 SD
  - under the 1.2 percentile
- Persistent low growth rate <1.75”/yr
- No evidence of systemic disease, malnutrition, hypothyroidism, GHD
Idiopathic Short Stature

Men 1.2% = 63”

Womyn 1.2% = 58.5”

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Idiopathic Short Stature

- GH dose 0.37 mg/kg/wk
- Must rule out GHD, systemic disease, malnutrition, hypothyroidism
- Longer term studies lacking
- ISS treatment has fallen out of favor
  - With Pediatric Endocrinologists
  - With Insurance companies
“At a cost approximating $40/mg of hormone, the yearly cost of treating a short child with GH ranges from $5,000 to $40,000 (approximate mean, $18,000–20,000).”

“In the absence of disease, there is no rationale for defining a cutoff for treatment. For example, how does one justify treating a boy whose height prediction is 5 ft. 3 in. but not one whose height prediction is 5 ft. 3 and 1/32 in.?”

“…we must ensure that the benefits of GH clearly exceed its short- and long-term risks.”

J Clin Endocrinol Metab, July 2004, 89(7):3138–3139
GH treatment: dosing

- GHD 0.3 mg/kg/wk
- GHD pubertal up to 0.7 mg/kg/wk
- Turner syndrome 0.35 mg/kg/wk
- Prader-Willi syndrome 7 mg/m2/wk
- SGA without catch up 0.48 mg/kg/wk
- ISS 0.37 mg/kg/wk
Endocrine Society Statement on Possible Association Between GH Therapy in Childhood and Later Stroke August 25, 2014


- Possible association GH tx childhood among “low risk patients” (isolated GH deficiency, idiopathic short stature and small for gestational age) and increased risk for stroke (both hemorrhagic and ischemic stroke) in young adulthood in France
  - 11 out of the 6,874 GH recipients had a fatal or non-fatal stroke.
  - Death Certificates, not medical records review
  - Low response rate on mailed questionnaires
  - Poor choice of comparison cohort

- Same group (2012) association between childhood GH therapy for low risk indications and mortality risk in adulthood
  - Contradicted by concurrent studies, study design weaknesses
Just published

Risk of Neoplasia in Pediatric patients receiving Growth Hormone Therapy – a report from the Pediatric Endocrine Society Drug and Therapeutics Committee
Quotations

“A dwarf on a giant’s shoulders sees farther of the two.” George Herbert (1593–1633)

"The bias towards tallness and against shortness is one of society's most blatant and forgivable prejudices.“ John Kenneth Galbraith 6'6"
Online resources

Educational video

The Human Growth Foundation
The Magic Foundation
The Child Growth Foundation
Consensus Statements

Genentech
Lilly
NovoNordisk
Serono
Pharmacia
Omnitrope
Short Persons Support

NOSSA - NATIONAL ORGANIZATION OF SHORT STATURED ADULTS, INC.

Equal Treatment - Not Special Treatment

ShortStuff.org

Scams!!!
In the end we are all big and small, short and tall, wise and foolish, and only a small part of this amazing world.

-Kathleen C. Moltz

Questions?