PREP 2017
Pediatric Endocrinology
General session
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- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Practice Changes:

Upon completion of this session, you should be able to:

• Recognize growth chart patterns for common pathologic and non-pathologic conditions
• Describe common milestones and variants in normal puberty
• Describe the appropriate evaluation of early puberty
• Understand the distinction between various forms of pediatric diabetes
• Understand current strategies in insulin management
• ** = mentioned in endocrine content outline
Linear Growth
Normal Parameters to Know

• Growth curves
• Height velocity
• Mid parental height
• Arm span
• Bone ages and other crystal balls
Height Velocity

• Ideally, velocity should be calculated over at least a 6 month period. Using a shorter time period can be less accurate.

• Normal ranges:
  – <4 years old = at least 7 cm/year
  – 4-6 years old = at least 6 cm/year
  – 6 – puberty = at least 5 cm/year
  – Peak velocity is around 13.5 years in boys and 11.5 years in girls.
Mid-Parental Height (Genetic Potential)

- Correct parents’ heights by 5 inches based on gender of child (i.e. correct mother’s height for boys and correct father’s height for girls).

- Average corrected heights of parents.

- Target height is +/- 2 inches of the mid-parental height.
Examples of Mid-Parental Height

- Dad = 72”; Corrected = 67”
- Mom = 64”; Corrected = 69”
- MPH for a boy = (72+69)/2 = 70.5”
- MPH for a girl = (67+64)/2 = 65.5”
Arm Span

• In general the arm span should be less than the height (within 2 cm) in boys before 11 years of age and less than the height (within 2 cm) in girls before 11-14 years of age.
  – Discordant arm span and heights could indicate skeletal dysplasias instead of hormonal deficiencies.
The Bone Age

- The most common method used to read a bone age is the Greulich and Pyle method.

- Assessments are a rough estimate of skeletal maturity

- Experience matters in the reading and interpretation

www.wikidoc.org
Short Stature

Benign
- Constitutional Growth Delay
- Familial Short Stature
- Idiopathic Short Stature

Pathologic
- Endocrine
- Genetic syndromes
- Nutritional Disorders
- Chronic Illnesses/Drugs
Constitutional Delay

- Diagnosis
  - Family history of “late bloomers”
    - Late menarche in mom
    - Continued growth after high school in dad
  - Growth chart pattern
    - Deceleration in growth around 3-6 months of age
  - Delayed bone age (usually around 2-2.5 years behind)
    - Bone age “corrects” short stature to mid-parental height
  - Normal growth velocity for bone age
  - Absence of other medical conditions
Familial Short Stature

• **Diagnosis**
  – Deceleration in growth at 6-18 months of age
  – Growth chart pattern
    • Normal weight
  – Family history (with accurate family heights)
    • Measure both parents if possible; don’t rely on reported heights 😊
  – Normal bone age
  – Normal growth velocity
Growth Curve Comparisons

- Familial Short Stature
- Constitutional Growth Delay
Is There a Problem?

• Get worried if:
  – The history and physical are concerning
    • Head trauma, cranial radiation, medications, low birth weight, lack of weight gain or weight loss, chronic headaches
  – No confirmatory family history of constitutional delay or familial short stature
  – Growth velocity is abnormal
Workup for Concerning Short Stature

- Besides a careful history and physical, most pediatric endocrinologists routinely order:
  - Comprehensive metabolic panel
  - Sedimentation rate or CRP
  - A bone age
  - Thyroid function tests
  - Chromosomes on females
  - IGF-1 and IGFBP-3 levels
  - Celiac panel

- Other lab tests and imaging should be based on the history and physical and a review of the growth chart.
Endocrine Causes of Short Stature

- Hypothyroidism
- Untreated precocious puberty
- Turner syndrome
- Growth hormone deficiency
Growth Hormone Deficiency

- Growth hormone deficiency in the neonate
  - Midline defects
  - Microphallus
  - Hypoglycemia
  - Growth hormone not relevant for growth the first year of life
- Growth hormone in children
  - Decreasing growth velocity
  - Low IGF-1 and low IGFBP-3 levels or low GH levels during stimulation
  - Rapid increase in growth velocity following initiation growth hormone
Puberty
Definitions

PUBERTY

Hypothalamus

Gonads

• Breast development
• Increased testicular size
• Voice
• Muscle mass
• Pubic hair

Adrenals

• Pubic/axillary hair

ADRENARCHE

Pituitary

LH/FSH

GnRH

??

??
Normal Puberty (males)

- **Birth**
  - LH surge in first day of life with increased testosterone for first 48 hours of life

- **Childhood**
  - Suppressed GnRH activity and generally undetectable LH/FSH levels
  - Prepubertal testes (<4 ml or <2.5cm)

- **Puberty**
  - Testicular enlargement (>9 years old)
  - Adrenarche (>9 years old)
  - Growth spurt (Tanner IV)
Normal Puberty (females)

**Birth**
- No LH surge
- Breast tissue may be present due to placental estrogens

**Childhood**
- Suppressed GnRH activity and generally undetectable LH/FSH levels

**Puberty**
- Growth spurt either before or concurrent with thelarche
- Breast tissue develops – thelarche (>8 years old)
- Adrenarche (>8 years old)
Precocious Puberty – Workup

• Diagnostic workup for precocious puberty
  – Ultrasensitive LH
  – AM 17 hydroxyprogesterone
  – Estradiol, testosterone (ultrasensitive)
  – Pelvic/testicular ultrasound
  – Bone age
### Precocious Puberty – Normal Variants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premature Thelarche (Girls)</strong></td>
<td>- Early development of breast tissue&lt;br&gt;- Typically presents in the toddler&lt;br&gt;- May be asymmetric&lt;br&gt;- About 2/3 of cases regress in 18 months&lt;br&gt;- Workup – bone age and ultrasensitive LH, +/- pelvic ultrasound to assess uterine volume&lt;br&gt;- Normal bone age and no elevated ultrasensitive LH (&lt;0.03)&lt;br&gt;- DDx – idiopathic precocious puberty, peripheral precocious puberty</td>
</tr>
<tr>
<td><strong>Premature Adrenarche (Girls and Boys)</strong></td>
<td>- Early development of pubic hair (&lt;8 years for girls or &lt;9 years for boys)&lt;br&gt;- More common in girls than boys&lt;br&gt;- No thelarche or other pubertal signs&lt;br&gt;- Workup – bone age, DHEA-S, ultrasensitive LH, AM 17 hydroxyprogesterone&lt;br&gt;- Normal bone age, LH, 17-OHP&lt;br&gt;- DHEA-S may be slightly elevated&lt;br&gt;- DDx – Late onset CAH, precocious puberty, early PCOS</td>
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</table>
Precocious Puberty – Pathologic Causes

• You should be concerned with:
  – Advanced bone ages
  – Elevated gonadotropins
  – Elevated sex steroid levels
  – Contra-sexual puberty (puberty discordant with the patient’s sex) suggests peripheral tumor

• Central precocious puberty
  – Sex steroid and gonadotropins should be elevated
  – Always evaluate the CNS with MRI in boys; most girls do not have a CNS lesion – check MRI if CNS symptoms

• Peripheral precocious puberty
  – McCune-Albright – Café au lait spots that don’t cross with midline with jagged border
  – Typically gonadotropins are suppressed
Delayed Puberty – Definitions and Differential

- No breast tissue by 13 in girls
  - Constitutional growth delay
  - Gonadotropin deficiency (Kallman syndrome)
  - Turner syndrome
- No testicular enlargement by 14 in boys
  - Constitutional growth delay
  - Gonadotropin deficiency (Kallman syndrome)
Turner Syndrome

• With delayed puberty/short stature in a females, **always** check a karyotype
• Signs of puberty do not necessarily rule out this syndrome
  – 1/3 of girls may undergo thelarche
  – <10% may have spontaneous menarche
• Physical exam findings (may be very subtle especially in mosaic patients; **don’t assume you can identify a Turner’s patient based on clinical exam**):
  – Prominent auricles
  – pigmented nevi
  – webbed neck
  – low hairline
  – cubitus valgus – abnormal carrying angle
  – Madelung deformity – dorsal bowing of radius
  – Short 4th metacarpal
  – Lymphedema – most commonly seen in neonate
  – Aortic arch anomalies (including bicuspid valve and aortic root dilatation).**
Diabetes
How common is diabetes in kids?

Prevalence Data on Diabetes in Children

Pettitt Diabetes Care 2014
Diabetes

1. fasting glucose >125 or
2. 2 hour glucose of >200 on OGTT
3. A1C>6.5%
4. Random (serum) glucose >200 with signs of hyperglycemia

Type 1 Diabetes

Type 2 Diabetes

Other
- CF Diabetes
- Drugs
- Mitochondrial

* = frequent urination, thirst, weight loss
Other Technical Terms

• Impaired fasting glucose – fasting glucose values between 100 and 125
• Impaired glucose tolerance – a 2 hour glucose between 140-200 on an oral glucose tolerance test
• Hemoglobin A1C – an approximation of the average glucose level over the past 3 months.
Diabetes

- Insulin Resistance
- Insulin Deficiency
Type 1 Diabetes

Insulin Resistance

Insulin Deficiency
Type 2 Diabetes

Insulin Resistance

Insulin Deficiency
Classical Distinction Between Type 1 and Type 2 Diabetes

Type 1
1. Thin
2. Caucasian
3. Insulin deficient
4. No family history of diabetes

Type 2
1. Obese
2. Caucasian or African-American or Hispanic
3. Insulin resistant
4. Positive family history of diabetes
Model of Progression to Type 1 Diabetes

**

100 %

Time

Beta cell function

- Genetic risk
- Antibody positivity
- Altered glucose metabolism

Clinical symptoms & Diagnosis

20%
Lifestyle and Type 2 Diabetes

Visceral (inflammatory) vs. Subcutaneous fat (non-inflammatory)

Increased resistance to insulin in:
- Liver
- Muscle
- Adipose Tissue
Pediatric Obesity Rates 2013
How do children present with diabetes? **

- Unexplained weight loss
- Polyuria
- Polydipsia
- Polyphagia
- Poor growth
- Altered mental status
- Fruity breath
- Hyperpnea

Suggests DKA
Initial work-up

**Symptomatic**
1. Urine for glucose and ketones or fingerstick glucose (fingerstick over 200 with symptoms makes the diagnosis)
2. Contact your nearest pediatric diabetes center to discuss the case
3. Initial lab workup in the hospital includes:
   1. Insulin/C-peptide
   2. GAD/IA2/insulin/ZnT8 antibodies
   3. TTG Ab and total IgA
   4. Thyroid studies and antibodies
   5. CBC/Chemistries
   6. Venous blood gas

**Asymptomatic**
1. Fasting glucose and HbA1C +/- oral glucose tolerance test
2. A fasting glucose >125 or a 2 hour glucose >200 **that is confirmed on repeat testing** makes the diagnosis
Management Pearls - DKA

- Defined as a pH <7.3 or a serum bicarbonate <15 with hyperglycemia and serum/urine ketones
- This is a **metabolic emergency** caused by **severe** insulin deficiency
- Treated with IV regular insulin (0.1U/kg/hr) and IV fluids
  - IVF include an initial bolus of 10-20cc/kg (may repeat if appears very volume depleted but no more than 30cc/kg in 4 hours) followed by normal saline with 40 meq KCL/L for 4 hours at 1.5 times maintenance then 1/2NS with 40 meq KCL/L given at 1.5 times maintenance
  - **Do not give too much fluid (risk of cerebral edema)**
  - IV insulin adheres to plastic and the first 30 mls wasted through the tubing – 0.1 units/kg/hour (can be lower for young kids – 0.05 unit/kg/hr (<5y))
  - **DO NOT BOLUS INSULIN**
  - **Consider holding insulin if glucose >600 – recheck glucose after fluid bolus**
Management Pearls - DKA

• Goal is to decrease glucose by 100 mg/dl per hour
• When glucose decreases to under 300, add D10 to the intravenous fluids
Management Pearls - DKA

- Follow glucomes every 1-2 hours and blood gases and Na/K/Cl/bicarb every 2-4 hours
  - You may need to give more K orally or intravenously
- Mental status changes should be sent to the ICU for monitoring
- Abnormal neurological exam should be treated immediately with mannitol or hypertonic saline
- Take off of IV insulin and IV fluids and move to sq insulin when pH>7.3 or bicarbonate >15 (give injection of short acting, discontinue IV insulin after 15-30 minutes)
Management

• If a patient is **not in DKA**, you have time to administer subcutaneous insulin – **there is no emergency**
• For patients who appear to be type 1 (thin, young (less than 10), symptomatic) start insulin
• For patients who you think have more of a type 2 picture, start insulin if:
  • They have ketones in the urine or blood
  • Their glucoses are over 300
  • If not, then metformin is 1st line therapy
  • Even if using oral agents, teach patients how to check glucoses
Management Pearls – SQ insulin

• The current “standard of care” is to use multiple daily injections of rapid acting insulin (lispro or aspart) and to use a long acting basal insulin (glargine or detemir).
• Rapid acting insulin is used to correct high blood sugar and to “cover” carbohydrates that are ingested.
• Initial doses are based on a total daily dose (0.5U/kg/day to 1U/kg/day).
  – The older the patient, the higher the total daily dose
Aspart/lispro

Aspart/lispro

Aspart/lispro

glargine
# Management (Insulins)

<table>
<thead>
<tr>
<th></th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Insulin</td>
<td>0.5-1</td>
<td>2.5-5</td>
<td>6-8</td>
</tr>
<tr>
<td>Lispro(Humalog®)</td>
<td>15-30 min</td>
<td>30-120 min</td>
<td>3-4</td>
</tr>
<tr>
<td>Aspart (Novalog®)</td>
<td>15-30 min</td>
<td>30-120 min</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, isophane suspension (NPH)</td>
<td>2-4</td>
<td>6-8</td>
<td>12-18</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus®)</td>
<td>3</td>
<td>none</td>
<td>24</td>
</tr>
</tbody>
</table>
Management Pearls – SQ insulin

1. Calculate the total daily dose – 0.5-1U/kg/day – use higher doses for older children.
2. Take 50% of the TDD as the glargine dose To figure out how much insulin for food, divide 500 by the TDD
   Figure out a target blood sugar (usually 120-150).
3. To figure out how to correct high blood sugars to the target, divide 1800 by the TDD)
4. Now put it all together...
Subcutaneous Insulin Management

- 14 year old male
- 50 kg
- Glucose 450 and typical symptoms
- pH is 7.45
- Urine (+) for ketones
Subcutaneous Insulin Management

50 kg @ 1 U/kg/day: 50 U = Total Daily Dose

25U of basal (glargine)

Rapid Acting:
Correcting high sugars
1800/50 = 1U for every 35 over a target of 150

Insulin for food
500/50 = 1U for every 10 grams of carbohydrates eaten

So if the patient eats 100 grams of carb and the Blood sugar is 250 the patient would receive: 10U (for carbs) and 2U (for correction) = **12U of rapid acting insulin**
Type 2 Management

• Do not try to manage patients without self blood glucose monitoring – even if on just oral agents
• Exercise, exercise, exercise
• Work with the family – get everyone involved with dietary changes
• Screen for lipid and urinary abnormalities
• Metformin is the first line agent but it causes stomach upset/diarrhea
  – Start with a low dose (500 mg/day) and increase doses slowly
  – Add insulin if HbA1c >9% despite max dose of metformin
  – Some studies support the use of thiazolidinediones (pioglitazone, etc.) in adolescents
Summary

- The most important determinant of pathologic growth problems is an abnormal growth velocity.
- Normal pubertal variants should not have elevated sex steroid or gonadotropin levels.
- The most common forms of pediatric diabetes have both components of insulin deficiency as well as insulin resistance.
- The preferred insulin management strategy in children with type 1 diabetes is to use multiple daily injections to simulate physiologic release of insulin.
References

• [http://www.cdc.gov/healthyyouth/obesity/obesity-youth.htm](http://www.cdc.gov/healthyyouth/obesity/obesity-youth.htm)