Flatbush diabetes
• Shari Liesch APN, CDE
• Conflict of interest
• None

Objectives
1. Discuss presenting symptoms
2. Differential diagnosis
   1. Type 1 diabetes, type 2
   2. LADA
   3. MODY
   4. other
3. Explore Flatbush Diabetes: Atypical diabetes mellitus (ADM) or ketosis prone diabetes, (KPD)
A New admission: Diagnostic criteria

- Late teen
- Thirst, weight loss, severe DKA
- Appeared at a local ED in full DKA, A1c 10, vomiting, very sick.
- After recovery of the DKA started on MDI
- Went into honeymoon!!
- A1c @ goal for several visits (<6)

ADA diagnostic criteria for diabetes:
- Symptoms + casual glucose >200
- Fasting >126
- 2 hr glucose >200 with OGTT

Impaired:
- Impaired 2hr post 140-200
- Impaired fasting 100-125

<table>
<thead>
<tr>
<th>Date</th>
<th>Hgb</th>
<th>A1c</th>
<th>Weight</th>
<th>BP</th>
<th>Notes</th>
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<tr>
<td>4/12</td>
<td>6.5</td>
<td>5.2</td>
<td>4.2</td>
<td>6.0</td>
<td>OFF insulin</td>
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<tr>
<td>4/14</td>
<td>6.5</td>
<td>5.5</td>
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<td>4/17</td>
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<td>6.5</td>
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<td>4/20</td>
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<tr>
<td>4/23</td>
<td>6.5</td>
<td>6.5</td>
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</tbody>
</table>

@ Dr thyroid AB, function & cell normal

Summary post diagnosis

- At 10 month after Dx: type 1 diabetes
- Daily numbers great on 1.1 u/kg/day
- GAD, insulin-auto, islet cell 522 antibodies all negative.
- Due to lows, and most numbers in range, reduced doses
- Told to send numbers weekly for evaluation & adjustment

At next visit: Jan. 2014
- 1 year post diagnosis,
- totally off insulin,
- with a normal A1c (<6),
- he stopped all insulin 3 months earlier,
- stated he was going low from Bb, (but did not call for help).
**Differential Diagnosis**

- **Type 1 diabetes:**
  - Immune-mediated, HLA specific
  - Insulin production stops
  - Onset before age 30

- **Type 2 diabetes:**
  - Often insulin-resistant
  - Onset with weight gain
  - Usually arises later in life

- **Type 2 diabetes:**
  - Often in family, environment turns it "on"

- **Idiopathic:**
  - Many clinical situations
  - Erroneously negative HLA

- **Atypical diabetes mellitus (ADM):**
  - Many non-HLA positive with typical ADM

**Legend classification of diabetes**

- APS1, autoimmune polyendocrine syndromes 1
- IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome
- MODY, maturity onset diabetes of the young

**Types of diabetes in youth**

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1</th>
<th>ADM</th>
<th>MODY</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>onset age</td>
<td>through childhood</td>
<td>pedi</td>
<td>pedi</td>
<td>potential</td>
</tr>
<tr>
<td>insensitivity of insulin</td>
<td>&quot;0&quot;</td>
<td>nil</td>
<td>nil</td>
<td>potential</td>
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<tr>
<td>acute</td>
<td>acute onset</td>
<td>acute onset</td>
<td>acute onset</td>
<td>acute onset</td>
</tr>
<tr>
<td>chronic</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
</tr>
<tr>
<td>ketosis</td>
<td>up to 40%</td>
<td>common</td>
<td>rare</td>
<td>nil</td>
</tr>
<tr>
<td>obesity</td>
<td>&gt;90%</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>5%</td>
</tr>
<tr>
<td>mode of inheritance</td>
<td>Not familial</td>
<td>Auto.</td>
<td>Auto.</td>
<td>strong familial</td>
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- APS1: Autoimmune Polyendocrine Syndrome Type 1
- IPEX: Immunodeficiency, Polyendocrinopathy, Enteropathy, X-Linked Syndrome
- MODY: Maturity Onset Diabetes of the Young
- ADM: Atypical Diabetes Mellitus

**Collaborate, Cultivate, Educate**

**Epidemiology of Acute Diabetic Acidosis**

- Central: Nausea, confusion, loss of consciousness
- Respiratory: Drowsiness, bradycardia
- Cardiovascular: Hypotension, shock
- Gastrointestinal: Vomiting, diarrhea


**Current classification of diabetes.**

- APS1, autoimmune polyendocrine syndrome 1
- IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome
- MODY, maturity onset diabetes of the young

**Types of diabetes in youth**

- Type 1
  - Pediat. onset
  - Childhood pubertal pubertal pubertal
  - All AA, Caucasian, Hispanic, AA, NA
  - Acute-severe, subclinical to severe
  - Autoimmunity present, absent, absent, unusual
  - Insulin secretion very low, moderate-low, variable, variable
  - Insulin sensitivity normal, normal, normal, decreased
  - Ketosis at onset up to 40%, common, rare, nil
  - Obesity as in population, rare, nil, <10%
  - Mode of inheritance: Not familial, Auto., Auto., strong familial

- Type 2
  - Through childhood
  - Normal pubertal pubertal pubertal
  - Nil, rare, <10%, 20-25%
  - Auto., Auto., strong familial

- MODY
  - Maternal onset
  - Pubertal pubertal pubertal
  - AA, Caucasian, Hispanic, Asian
  - Potential, potential, potential

- ADM
  - Acute-onset
  - Pubertal pubertal pubertal
  - AA, Caucasian, Hispanic, Asian
  - Potential, potential, potential
The rest of the story

Spring 2014: had DKA with co-morbidity of pneumonia.

- Off insulin for 5 months,
- New very ill
- A1c 10%
- Insulin re-started

Two weeks later: A1c 12.7%

- Played in ball tournament
- Had another episode of DKA needing IV fluids.
- But he did not test/correct as recommended
- He needed higher doses to fix the sugars, was very insulin resistant
- Activity caused stress made him more insulin resistant

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<th>Blood Sugar</th>
<th>IV Fluids</th>
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<td></td>
<td>12.7</td>
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The stress of activity

Umpierrez et al studied AA with phenotype A-, B+ KPD

- Studied obese AA patients
- Looked at the role of gluco & lipotoxicity in causing severe but partially reversible B cell function defect
- Hyperglycemia, not hyperlipidemia caused severe blunting to C peptide response to glucose stim.
- Chronic hyperglycemia was associated with reduced expression & insulin stimulated threonine-308 phosphorylation of Akt2 in skeletal muscle
- Severe glucotoxic blunting of an intracellular pathway which leads to insulin resistance may contribute to reversible B cell dysfunction
- This is characteristic of KPD:
  - Allergy, Beta cell + function, KPD
  - Hyperglycemia may be exacerbated by defects in skeletal muscle glucose uptake as a result of glucotoxic down regulation of skeletal muscle insulin signaling.
- One mechanism of this glucotoxic B cell dysfunction is from increased oxidant stress in the islet cells
- They feel KPD has a genetic susceptibility

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Flatbush Diabetes

- Common in Africa
- Named after New York area where first described
- Other names:
  - type RA
  - idiopathic
  - type 1L
  - A1C or type 2B.
- Banerji, 2004
- Rewers, 2012
- Vaibhav, Mathai, & Gorman 2013

- The hallmark for Flatbush:
  - Present with sudden onset, extremely high BG levels (DKA) levels of over 700
  - Patients insulin resistant or acute, severe defects in insulin secretion with islet cell auto-antibodies
  - Following treatment, insulin secretion is recovered and keto-acidosis generally does not occur
  - If not obese, insulin sensitivity is not uncommon.
  - A1C of 12-14 are not uncommon
  - A1C of 12-14 are not uncommon

- Other features
  - Major distinguishing feature:
    - when very high sugars are brought down with insulin, some do quite well on oral medications and/or lifestyle
  - Some Flatbush relapse and have 2 episodes of DKA.
  - After 10 years, about 60% need insulin for good control, which is close to the type 2 rate of insulin use.
  - Flatbush is becoming more common in Africa and the Americas, accounting for 50% of the cases among African Americans who first present with DKA.
  - No one knows the cause,
  - It appears they are sensitive to the temporary damage to the beta cells by glucotoxicity and lipotoxicity.
  - When these conditions are reversed, the beta cells are able to recover
  - Important for 2 reasons:
    - 30% of AA with BMI >30 kg/m2 are not insulin resistant (are insulin deficient): less CV risk
    - In T2d metabolic syndrome properties (increased CV risk, insulin resistance & declining insulin production)
  - Metabolic stability allows for critical recovery of B cell function and reversal of glucose or lipotoxicity (Banerji, 2004)
Other

• There may be several subtypes of Flatbush diabetes.
• Some need insulin for control.
• Poor control may be precipitated by an infection.
• Gretchen Becker, in Health Guide from 9-2008 suggests that absence of antibodies may be a clue if you suspect your patient may have Flatbush diabetes.
• If there are antibodies, they are probably type 1.
• Being aware of the other forms of diabetes helps us to spot cases, as correct diagnosis is important in the treatment plan design and prevention of future DKA episodes.

Flatbush characteristics

Underlying mechanism seems to be:
• A combination of insensitivity to insulin
• And transient loss of ability to release adequate amounts of insulin.

• T2d gradually lose insulin resistance
• Flatbush:
  • do not have antibodies of t1d
  • they have a recovery of insulin secretion (rising C peptide)
  • Long term: can maybe maintain w/o injections (orals)

Low vitamin D

• Vitamin D can enhance insulin release and insulin sensitivity
• Improved glucose once supplemented if low
Learning points (Vaibhav, et al)

- It is assumed children need lifelong insulin replacement, this may not be the case.
- Early Mgmt of AD similar to t1d
- Rapidly falling insulin needs over the first few weeks should alert to possibility of AD: pancreatic auto antibodies and function should be checked (predict in dependence)
- The natural history of AD or Flatbush is distinct from either t1d or t2d- being aware can facilitate dx and mgmt.
- Patients presenting in DKA with AD will have spontaneous resolution of diabetes within a few months: most will relapse within 2 years of dx and will require insulin and or oral agent

In summary

- It is important to look for risk factors
- Management w/o insulin can have employment implications
- Reduced risk of hypoglycemia
- Separate the high risk from t1d
- Non Caucasian
- Family history of T2d, of African descent
- (also Korean) may be in Asian descent (12%)
- Suspect if absence of GAD, Insulin and Tyrosine phosphatase AB
- As well as healthy or elevated C peptide levels
- Most cases of T1d do not involve multiple cases of DKA
- Howath 2015

References