Collaborate ➢ Cultivate ➢Educate

Flatbush diabetes

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- 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

	1-2013	4-2013 CV	7-2013 CV	10-2013 CV	1-2014 CV	
A1c	10	6.2	5.2	5.2	6.0	
Ketones	+				Off insulin	
Na	130*					
K	3.5					
Cl	87*					
CO2	31*					
pH	7.36					
C pep (0.8-3.1)	0.88					
GAD In AB	<1.0			<0.02 0		
Mg	1.6*					
Cholesterol TG	131 308			NL 63		

@ Dx thyroid AB, function, & celiac normal

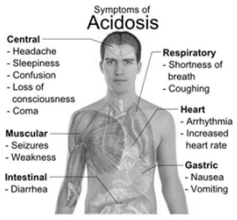
Summary post diagnosis

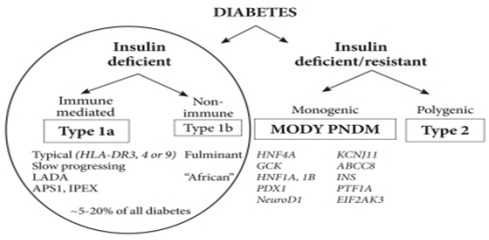
- At 10 month after Dx: type 1 diabetes
- Daily numbers great on 1.1 u/kg/day
- GAD, Insulin-auto, Islet cell 512 antibodies all negative.
- Due to lows, and most numbers in range, reduced doses
- Told to send numbers weekly for evaluation & adjustment

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
    - AA is lean and athletic
    - adopted thus family Hx unknown;
- Type 2 diabetes:
  - Often in family, environment turns it "on"
- Idiopathic
- LADA latent autoimmune
  - (immune negative with a quick onset),
- MODY, maturity onset diabetes of the young,
  - monogenic gene causes the diabetes;
  - Slower onset
  - often familial pattern of ancestors on low dose insulin for a long time;
- Atypical diabetes mellitus (ADM)
  - Many AA with T1d w/o evidence of autoimmunity have atypical diabetes mellitus ADM or Flatbush diabetes
  - Abrupt onset, recovery, with period of returned function of insulin secretion





Current classification of diabetes.
APS1, autoimmune poly endocrine syndromes 1; IPEX, immunodeficiency, poly endocrinopathy, enteropathy, X-linked syndrome; MODY, maturity-onset diabetes of the young
Rewers, M. Dibetes Metabolism Journal. 2012 April: 36(2): 90-97

Types of diabetes in youth

type	type 1	ADM	MODY	type 2
age at onset	through out childhood	pubertal	pubertal	pubertal
predominant race	All	AA*	Caucasian	Hisp, AA, NA
onset	acute-severe	acute severe	subtle	subtle to severe
islet autoimmunity	present	absent	absent	unusual
insulin secretion	very low	Moderate/Low	variable	variable
insulin sensitivity	NL	NL	NL	decreased
Ketosis, DKA at onset	up to 40%	common	rare	up to 33%
obesity	as in population	as in population	uncommon	>90%
portion of pop. diabetes	70-80%	<10%	5%	20-25%
mode of inheritance	Not, sporadic	Auto. Dom.	Auto. Dom.	strong familial

classification of children with diabetes. Ushitz, f, page 59

The rest of the story

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

- Off insulin for 5 months,
- Now 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

	1-2013	4-2013 CV	7-2013 CV	10-2013 CV	1-2014 CV	Crash 3-2014	4-2014	
A1c	10.0	6.2	5.2	5.2	6.0	BG 673 DKA	12.7 BG 352 Pneu-monia	
Ketones					Off Insu-lin	DKA Restart insulin	DKA #2	
Na	130*					128**	137	
K	3.5					4.1	4.4	
Cl	87*					93**	95*	
CO2	31*					27	31	
pH	7.36							
C pep (0.8-3.1)	0.88							

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 w/reduced expression & insulin stimulated threoine-308 phosphorylation of Akt2 in skeletal muscle
- Severe gluco-toxic **blunting** of an intracellular pathway which leads to insulin secretion may contribute to reversible B cell dysfunction

- This is characteristic of KPD:
  - AB neg, 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

- Vaibhav, Mathai, & Gorman, 2013

	1-2013	4-2013 CV	7-2013 CV	10-2013 CV	1-2014 CV	Crash 3-2014	4-2014	5- 2014	7-2014-	10-2014	12-2014	1-2015
A1c	10.0	6.2	5.2	5.2	6.0	BG 673 DKA	12.7 BG 352 Pneu-monia	12.7	8.7	8.0	9.1	9.1 BG 438
Ketones					Off insulin	DKA restart	DKA #2				none	
Na	130*					128**	137				134	134
K	3.5					4.1	4.4				3.5	4.2
Cl	87*					93**	95*				95	98
CO2	31*					27	31				32	30
pH	7.36											
C pep (0.8-3.1)	0.88											
GAD in AB	<1.0			<0.02 0								
Mg	1.6*											
Cholesterol TG	131 308			NL 63								158 87

Flatbush Diabetes

- Common in Africa
- Named after New York area where first described
- Other names:
  - atypical,
  - type 1B,
  - idiopathic,
  - type 1,
  - ketosis prone 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 w/ **acute, severe defects in insulin secretion** w/o islet cell auto-antibodies
  - Following treatment, insulin secretion is recovered and keto-acidosis generally does not occur
  - If not obese, normal insulin sensitivity is not uncommon
  - A1c of 12-14 are not uncommon

- Flatbush diabetes seems to be somewhere between type 1 and type 2.
- Primarily in non white persons, especially those of sub-Saharan African descent,
  - but Asians, Hispanics and Caucasians can be diagnosed.
- Onset through childhood, rare past age 40 ,
- Not associated with HLA typing,
- No antibodies against the beta cells;
- May be overweight
- Male prominence (Vaibhav et. Al)
- May have some insulin resistance

- Are not at risk for increased CV like insulin resistant persons (T2d) have
- Differences in visceral, not subcutaneous adipose tissue volume, seem to determine insulin sensitivity
- Can have spontaneous remission and long term insulin independence
- Management:
- Acute: Usual DKA protocol
  - Test for AB
  - Treat with MDI
- Chronic
  - Even if off insulin, may relapse and need insulin
  - May respond to metformin or low dose sulphonylurea

Other features

- Major distinguishing feature:
  - when very high sugars are brought down with insulin, some do quite well on oral meds and/or lifestyle choices.
- Some Flatbush relapse and have other 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% if 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 lipo toxicity (Banerji, 2004)

Other

- There may be several sub types 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 life long 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 [illegible]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

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