Diabetes Masqueraders: Elevated Blood Glucose Not Due to Classic Type 1 or Type 2 Diabetes

David R. Repaske, PhD, MD
Professor of Pediatrics
Director, Division of Endocrinology and Diabetes
University of Virginia Children’s Hospital
Charlottesville, VA

Disclosure
David R Repaske, PhD, MD
• Nothing to disclose

What Can Cause Elevated Blood Glucose?
• Type 1 diabetes and Type 2 diabetes
• MODY
• LADA
• Medications
• Pancreas Disease
• Critical Illness
• Rare: Neonatal DM, Wolfram, MIDD, IPEX
Case AA

- 19 yo Indian-American male college student
- Father and Paternal Grandfather have “Type 2 Diabetes” treated with sulfonylurea.
- He is pre-med student and was playing with his father’s glucometer and discovered his own fasting BG = 132. Came to diabetes clinic
- Healthy appearing, slender (as was his father who attended clinic with him), no symptoms of polyuria or polydipsia.

Case AA

- A1c = 6.6%
- Considered early DM1, or DM2, but sent home with BG and PRN ketone monitoring
- Islet antibodies negative
- MODY panel detected mutation in glucokinase gene, MODY2

MODY

MONogentic Diabetes of the Young

Autosomal dominant
Mutations in genes (now 13 identified) that affect functioning or formation of beta cells
Non-autoimmune insulin deficiency
MODY

Presentation:
Can resemble DM1 or DM2, but:
- Family history of diabetes in AD pattern
- Onset generally less than 25 yo
- Unlike DM1:
  - Negative antibodies
  - Gradual, insidious onset, no ketones, no DKA
  - Insulin and c-peptide still present 5 years after onset
- Unlike DM2:
  - Overweight not necessary
  - No acanthosis present

Prevalence is high:

- Estimates that there are as many as 500,000 MODY patients in US (most being undiagnosed MODY2)
  (Compare with 2,000,000 DM1 patients in US)
- Thirteen MODY genes identified so far, and still finding more
- Majority of MODY is MODY2 or MODY3
- Rare MODY1, MODY4 and MODY5
- Others are very rare, some only a few families

MODY2

- Case AA has MODY2:
- Mutation in GK gene (150 different mutations described)
- Decreases activity of GK in beta cells and in liver
- In beta cell, decreased GK activity fools the beta cell into thinking that there is less glucose in the blood
- Otherwise normal beta cell mass, normal ability to respond to rises in glucose, but the blood glucose set point is raised.
- In AA, the beta cells carefully regulate BG at 132 rather than 95.
- Typically BG is regulated at 110 to 145 depending on the specific mutation and the residual activity of GK
- Hyperglycemia is congenital and non-progressive
MODY2

GLK also has lower activity in the liver
In the liver, it is the first step in glucose metabolism (both for glycogen synthesis and for glycolysis)
So, glucose is metabolized more slowly in the liver
Can lead to abnormal OGTT, and to hyperglycemia after high carb meal

Therapy:
Avoid high carb meals
No medical therapy
A1c is regulated at 7.5 or less. In fact, same A1c with or without insulin
Complications:
No microvascular complications (retinopathy, nephropathy)

Does not protect from DM2, so with weight gain, it is possible to develop DM2 on top of MODY2

MODY2: Effect on pregnancy

If mother has MODY2 and fetus does not (50% chance):
Baby sees elevated BG and secretes fetal insulin leading to macrosomia. No effective therapy, but may need early delivery.

If mother has MODY2 and fetus does too (50% chance):
Baby has elevated BG but senses it as normal and does not secrete excessive insulin and has normal growth.
MODY3: The other common MODY

Mutation in HNF1A, a transcription factor involved in fetal pancreas development and in beta cell differentiation and function

Many (150) described mutations

Generally develop slowly rising BG that progresses to diabetes in teens or 20’s.

Most have normal beta cell mass, but develop defects in beta cell function, with normal insulin release at modestly elevated glucose but insulin plateau so unable to control a large glucose load

Generally have normal fasting glucose initially, but impaired OGTT A1c will rise with progressive beta cell dysfunction

Microvascular complications can occur.

Therapy:

Low dose sulfonylurea: glyburide 1.25 mg qday

MODY3

• HNF1A also in renal tubules and regulates expression of glucose transporter, SGLT2.

• MODY3 patients have glucosuria at reduced level of serum glucose.

MODY1, MODY4, MODY6

• Also due to mutations in pancreas transcription factors

• All quite similar to MODY3
Case MC

• MC is a 17 y 4 m female considered to have type 1 diabetes since February 2003.
• She has maintained meticulous metabolic control with all her HbA1Cs in < 7% range:
  – September 2008: 6%.
  – March 2009: 5.8%.

Case MC

• Her total daily insulin has varied from a low of 46 to a high of 62 units (0.5-0.7 units/kg/day). She takes a total daily basal of 35 units via pump (55-60% of daily total).
• She uses an insulin-to-carbohydrate ratio of 1 unit for every 9 g of carbohydrate all day.
• Her sensitivity is 1 unit for every 40 mg of glucose.
• Her target is 85 mg/dl.

Case MC

• In general, her health is excellent.
• Normal systolic and diastolic blood pressures, and normal physical exam findings, except weight at 90th percentile and height at 50th percentile, BMI 95-97th percentile.
• When last checked in September 2008, her thyroid function was normal and total cholesterol was normal at 154 mg/dL.
Case MC

Because of positive "dipstick" urine for protein, she had an overnight urine collection in June 2005 which showed an albumin excretion of 156.8ug/min (Normal up to 20 ug/min)

In August 2005, a "split" day/night urine collection showed:
- Alb/Cr ratios (normal up to 30 mg/g)
  - Day 1254.4 mg/g
  - Night 87.6 mg/g

Findings consistent with daytime macroalbuminuria and nighttime microalbuminuria.

Case MC

The early development of albuminuria within 3 years of diagnosis, despite excellent metabolic control as judged by consistent HbA1c values of less than 6.5%, led to suspicion of MODY5 and the discovery of a novel change in intron 2 of the HNF1B gene, at a location that likely alters a splice site resulting in an altered protein product.

MODY5

- HNF1B is present in both pancreas and in kidney and in GU system
- Associated with renal cysts and Mullerian structure dysplasia
- MODY5 has reduced beta cell mass, so lose insulin secretion ability more quickly, and need to use insulin
MODY8

- Mutation in CEL (carboxyl ester lipase), a major pancreatic fluid digestive enzyme
- Pancreatic insufficiency in childhood
- Diabetes at 30-40 yo
- Therapy: Insulin

Take Home: MODY

Can resemble DM1 or DM2, but:
- Family history of diabetes in AD pattern
- Unlike DM1:
  - Negative antibodies
  - Insidious onset, no ketones, no DKA
  - Insulin and c-peptide present 5 years after onset
- Unlike DM2:
  - Overweight not necessary
  - No acanthosis present
- Definite diagnosis is gene sequencing

Take Home: MODY

- It is important to diagnose MODY, and the type of MODY, to provide the correct therapy
- The best therapy may not be insulin
- Some MODY is associated with other abnormalities such as renal cysts (MODY5), glucouria (MODY3), exocrine pancreatic insufficiency (MODY 8)
**MODY Types and Therapy**

<table>
<thead>
<tr>
<th>MODY</th>
<th>Gene</th>
<th>Frequency</th>
<th>Associated</th>
<th>Therapy</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>HNF4A</td>
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<td>S-U</td>
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<td>GCK</td>
<td>common</td>
<td></td>
<td>Diet</td>
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<td>HNF1A</td>
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<td>Glucosuria</td>
<td>S-U</td>
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<td>S-U</td>
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<td>HNF1B</td>
<td>rare</td>
<td>Renal cysts</td>
<td>S-U → Insulin</td>
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<td>S-U</td>
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<td>8</td>
<td>CEL</td>
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<td>Panc insuff</td>
<td>Insulin</td>
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<td>10</td>
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<tr>
<td>14</td>
<td>APPL1</td>
<td>very rare</td>
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</tbody>
</table>

**Case KR**

- 35 year old male pre-surgery evaluation for arthroscopy right knee.
- Lean and athletic
- Blood glucose 150. Repeated fasting 140 and A1c 6.2
- No polyuria, polydipsia, or weight change
- Islet cell Ab’s: only GAD65 positive

**Case KR**

- A1c already at goal, so no therapy
- Followed A1c every 3 months:
  - 6.2 @ baseline
  - 6.8 @ 3 months. Added metformin
  - 7.5 @ 6 months. Added liraglutide
  - 8.3 @ 9 months. Added insulin
  - 6.6 @ 12 months
LADA: Latent Autoimmune Diabetes in Adults

- Some 5% of adult patients with new onset indolent (so seems to be Type 2) diabetes in adults have LADA:
  - >30 years old
  - GAD65 Ab positive
  - Don’t require insulin initially
  - Do require insulin after 6-60 months

What is LADA?

- Slowly progressive autoimmune type 1 diabetes that is manifest early due to co-existent type 2 pathology of insulin resistance

LADA

- Genetics
  - Like Type 1: HLA-DQB1, PTPN22, Insulin gene, CTLA4 polymorphisms
  - Like Type 2: TCF7L2 polymorphism

- Immunology
  - Like Type 1: GAD65 autoantibody positive
  - ~Like Type 2: often only single Ab positive
LADA

• If lean and athletic, more type 1-ish
  – Tend to need insulin sooner
• If overweight and metabolic syndrome, more type 2-ish
  – Tend to need insulin later

LADA

• Typical Type 2 diabetes without islet cell antibody, 14% are on insulin at 6 years after diagnosis
• LADA patients with positive GAD65 antibody, 94% are on insulin at 6 years

LADA: Why is it important to recognize?

• Will need to be on insulin sooner
• Some day immunotherapy may work on LADA

• If 5% of all adult diabetes is LADA, it may be nearly as common as typical type 1 diabetes!
Case KT

- 4 mo male presented to ED in DKA
- No family history of diabetes
- In hospital: Started on insulin IV then maintained on insulin sub cu
- A1c at diagnosis 9.1%
- A1c after 3 months on insulin therapy 8.0%

Case KT

- Due to young age of onset of DM, genetic evaluation for neonatal monogenic diabetes was performed and he was found to have mutation in ABCC8 gene that encodes SUR1, the sulfonylurea receptor in beta cell

Neonatal Diabetes

- DM typically beginning by 6 weeks, but some up to 6-12 mo
- Caused by new mutation in gene encoding a beta cell protein (SUR, Kir, GK, Insulin, PDX1)
- Antibody negative insulin deficiency
- Beta cell contains lots of insulin but does not release it
- Typically IUGR (as insulin is growth factor)
- Rare: 1 in 250,000 births
Treatment of Neonatal Diabetes

More than 50% of neonatal DM is due to SUR1 or Kir6.2 (ATP-regulated K channel components)
90% of these respond to sulfonylurea
And, control with sulfonylurea is better than with insulin
Case KT

- At 15 mo, admitted to attempt transition from sub cu insulin to oral glyburide
- Started glyburide and weaned off insulin over 4 days.
- Has not needed insulin since
- A1c was 8.0% on insulin. Two months after glyburide: 5.8%. Eight months later: 5.3%.

Case 4: KT

Continuous Glucose Monitor (CGM) tracing for patient 1 on days 1 and 4 of sulfonylurea therapy.
Kir6.2 and SUR1 in brain

- The same K channel complex that regulates insulin secretion in the beta cell also regulates electrical activity in some neurons in the brain.
- Mutations that alter the K channel in the pancreas also alter the K channel in the brain and can cause DEND Syndrome (Developmental Delay, Epilepsy, and Neonatal Diabetes) that can be mild or severe.
- The neurological phenotype may also improve (but rarely resolves) with sulfonylurea therapy.

Take Home: Neonatal Diabetes

- DM that presents at less than 6 mo (and even up to 12 mo) is very likely monogenic neonatal diabetes, not type 1.
- Diagnosis is genetic analysis.
- Optimal treatment is often with sulfonylurea, not insulin.
- Many adults diagnosed “type 1” at young age (before we knew about Neonatal DM) could be treated with sulfonylurea.
- Some with neurological manifestations improve on sulfonylureas.

Case JS

- 18 yo girl with polycystic kidney disease and renal insufficiency.
- Received kidney transplant.
- Immunosuppression with prednisone and tacrolimus.
- Two weeks later: Found fasting BG 140 and A1c 6.9%.
Medication-Induced DM

<table>
<thead>
<tr>
<th>Insulin Resistance and Deficiency</th>
<th>Insulin Deficiency</th>
<th>Insulin Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics</td>
<td>Beta blockers</td>
<td>Beta-adrenergic agonists</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Calcineurin inhibitors</td>
<td>Growth hormone</td>
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<tr>
<td>Nicotinic acid</td>
<td>Diazoxide</td>
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<td>L-asparaginase</td>
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<td></td>
<td>Pentamidine</td>
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<td></td>
<td>Thiazide diuretics</td>
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</tbody>
</table>

Medication-Induced Diabetes

- Like type 1: Insulin deficiency
- Like type 2: Insulin resistance
- Like both: Insulin deficiency AND Insulin resistance

1° Effects on Pancreas

Calcineurin Inhibitors
- L-Asparaginase
- β-blockers
- Didanosine
- Diphenhydantoin
- Diazoxide
- Pentamidine
- Gatifloxacin

Pancreas → Insulin
1° Effects on Insulin Action

- Megesterol
- β-agonists
- Epinephrine/NE
- Growth Hormone

Multiple 1° Effects

- Glucocorticoids
- Antipsychotics
- Protease Inhibitors
- Thiazides
- Statins
- Nicotinic Acid

Glucocorticoids: Mechanisms

Insulin resistance

1. Decreased peripheral glucose uptake into
   • Muscle
   • Adipose
2. Decreased suppression of hepatic gluconeogenesis

Pagano, J Clin Invest, Vol 72, p1814, 1983
**Glucocorticoids: Mechanisms**

β-cell dysfunction:

2 hours after prednisolone dose
- OGTT shows
  - Hyperglycemia
  - Without any increase in insulin release

van Raalert, DH, Eur J Endo, Vol 162, p729 2010

**Glucocorticoid DM: Therapy**

- Glucocorticoid acts like a combination of Type 1 and Type 2 diabetes: decreased insulin production and decreased insulin action.
- Treatment:
  - Reduce the glucocorticoid, if possible
  - Metformin, as if treating type 2
  - Other medications (oral or injection) for treating type 2 might be useful (but have not been tested in pediatrics)
  - Insulin, as if treating type 1

**Calcineurin Inhibitors**

- Tacrolimus: macrolide antibiotic
- Cyclosporin A: cyclic polypeptide
- Inhibit calcineurin (serine phosphatase) to block NF-AT activation of IL-2 production in lymphocytes
Tacrolimus

Kasiske: Renal transplant patients 1996-2000
- n=11,659.
- High risk of DM 3-6m
- Continuing over 3 years
- More DM with Tacrolimus


Cyclosporin: Mechanism of DM

- Hjelmesaeth: Study of cyclosporin in dialysis patients awaiting transplant. n=9
- No glucocorticoid!
- Hyperglycemic clamp: before and after 2 weeks of cyclosporin.
- Found reduced insulin release in the subjects treated with cyclosporin

Atypical Antipsychotics

- Typical antipsychotics inhibit D2 receptors; atypicals inhibit a spectrum of other receptors: D2 and 5-HT2a, plus a mix of 5-HT1a, 5-HT2c, α1, M1, M3, H1
- Started being used 1989
- Case reports began soon after re: weight gain and DM (and even DKA). Some DM was before weight gain.


Atypical Antipsychotics in Peds: Epidemiology

- Bobo: Tennessee Medicaid children 6-24yo
- n=28,858 initiating atypical antipsychotic therapy
- n=14,429 controls, very carefully matched, initiating some other psych med (lithium, antidepressant, clonidine, stimulant, etc.)

Bobo, WV, JAMA Psychiatry, Vol 70, p1067, 2013
Atypical Antipsychotic DM: Mechanisms

- Stowell: Prospective study of insulin resistance and β-cell function
- Normal volunteers n=48 who where randomized to 15-17d course of:
  - Risperidone
  - Olanzapine
  - Placebo
- Hyperglycemic clamp before and after therapy


Atypical Antipsychotic DM: Mechanisms

- Stowell:
  - No significant decrease in beta cell insulin production
  - Increase in insulin resistance, BUT all accounted for by weight gain (averaged 3kg in 2-1/2 weeks!)
- But some patients have DM/DKA before weight gain, so something additional must be going on


Antipsychotic DM: Additional Mechanisms

- L. Best: Insulin secretion from rat β-cells
- At high [glucose = 256 mg/dL] clozapine hyperpolarized and decreased insulin release

Best, L, J Psychopharm, Vol 19, p 597, 2005
Antipsychotic DM: Mechanisms II

- Johnson: Insulin secretion from rat islets
- Used more physiologic glucose (126 mg/dl) plus 10 µM carbachol
- Carbachol is M3 agonist: mimics vagus nerve-stimulation of β-cells, or neural release of insulin.

Antipsychotic DM: Mechanisms II

- Olanzapine and clozapine antagonize M3 receptor → Block carbachol ("neural-stimulated") insulin secretion
**Take Home Messages**

- Lots of medications have DM as a potential side effect
- Diabetes can result from decreased insulin secretion and/or decreased insulin action (and/or decreased insulin-like direct neural effects)
- Therapy for medication-related DM:
  - Discontinue or switch the medication, if possible.
  - Treat like DM1 for insulinopenia or DM2 for insulin resistance, so knowledge of mechanism may be valuable to optimize therapy.

**Case DS**

- 15 yo girl admitted with persistent severe abdominal pain, like a knife digging through upper abdomen. Never had an episode like this before.
- Lipase 6,621 mg/dL and amylase 601 mg/dL ➔ Pancreatitis
- Lab results were remarkable for blood glucose 180. Hemoglobin A1c 5.5%

**Hyperglycemia in Pancreatitis**

- Common: 25-50% of children with acute, acute recurrent, or chronic (anatomic changes) pancreatitis have hyperglycemia during episode.
- About 5% of pancreatitis patients will have persistent diabetes
  - These tend to be with overweight, family history of diabetes, and most severe pancreatitis.

*Raman, J Pediatr, Vol 158, p 612, 2011*
Pancreatitis

- Not clear if it’s due to:
  - Injury to beta cells
  - Hormone dysregulation from inflammation
  - Cytokines, adrenaline, cortisol, etc., from severe pain and illness
  - Combination of all of the above
  - Pancreas cancer also presents with hyperglycemia in 50%: Some evidence it’s a soluble factor from the cancer. Resolves with resection

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Case CG

- 60 yo with inflammatory bowel disease develops fever and hypotension and is admitted to ICU with concern for sepsis.
- Blood cultures are positive for Staph aureus.
- Blood glucose is 265 mg/dL.
- Treated with IV antibiotic and survives
- At discharge fasting blood glucose is 92

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Hyperglycemia during Illness

- “Stress Hyperglycemia” is temporary diabetes: meets the definition of DM but resolves after illness resolves
- Common with severe illness (up to 50% in the ICU). Can be seen with milder illness (UTI, influenza).
Stress Hyperglycemia

- Counter regulatory hormones (glucagon, catecholamines, growth hormone, cortisol)
- Cytokines (TNFα, IL-1, IL-2)
- Beta cell failure
- Medication effects
- Family history
- Higher BMI

Stress Hyperglycemia

- Stress hyperglycemia that resolved predicts a 3-fold increase in subsequent development of diabetes
- Appears that a person who is on path to diabetes, e.g:
  - reduced beta cell mass, and/or
  - insulin resistance
  is more likely to develop stress hyperglycemia

Case JK

- 19 yo blind man developed DM at 7 yo.
  Had normal vision until 10 when progressive loss of vision began, first color then peripheral. Now nearly blind. Low frequency hearing loss since birth. Also had had polyuria treated with DDAVP since 10 yo
Wolfram Syndrome, or DIDMOAD

- Diabetes Insipidus Diabetes Mellitus Optic Atrophy Deafness, a neurodegenerative disease of CNS, peripheral nerves and neuroendocrine tissues (such as beta cells).
- Autosomal recessive, so generally no family history
- Due to WFS-1 mutation on chromosome 4p16. Transmembrane endoplasmic reticulum protein involved with calcium regulation in the ER
- Heterozygotes have increased incidence of bipolar disorder

Diabetes mellitus is first symptom at 6-8 yo. (Beta cells atrophy: Antibody negative)
Optic atrophy at 10-15 yo
Later:
- Neuronal deafness
- Diabetes insipidus
- Ataxia
- Peripheral neuropathy
- Psychiatric illness

Represents about 0.7% of all youth-onset diabetes!

THM: Wolfram

- It presents like type 1 diabetes, but consider Wolfram for:
  - Insulin deficiency diabetes
  - Develops at 6-8 years old
  - Negative antibodies
  - No family history
  - Later development of optic atrophy and other neurologic abnormalities
Case DG

- 17 yo boy with cystic fibrosis exacerbation admitted to hospital for “cleanout”. Random BG 210. A1c 6.2%

Cystic Fibrosis Related Diabetes (CFRD)

1:2500 have CF
by 5-9 yo, 10% have CFRD
by 10-20 yo, 25% have CFRD
by 30 yo, 50% have CFRD

Due to abnormal chloride channel that makes secretions thick and appears to block digestive enzymes from pancreas leading to autodigestion of pancreas

Destroys beta cells and the α-cells that produce glucagon

Get post-prandial hyperglycemia, then fasting hyperglycemia
Insulin deficiency, but do not get DKA due to absence of glucagon

A1c is not good indicator of CFRD. Gold standard is still OGTT.

CFRD: Reasons to recognize

Therapy:

Insulin is best, although there is no DKA and no macrovascular (cardiovascular) complication in CFRD

Prognosis:

Early and aggressive insulin therapy improves nutritional status by keeping calories in the body. This is critical for longevity in CF.

Early and aggressive insulin therapy improves pulmonary function and immune function, both critical to longevity in CF

Family:

Autosomal recessive
Case BJ

- 4 month old boy. Born at term with normal length and weight
- 2 weeks old developed severe eczema that partially responded to hydrocortisone
- 4 weeks old persistent secretory diarrhea. Duodenal biopsy showed flattened mucosal membrane with villous atrophy and lymphocytes in lamina propria. TPN was started.
- About the same time, developed coombs positive hemolytic anemia and ITP.
- 2.5 months old diagnosed with diabetes with BG 200 and low serum insulin and c-peptide.
- Anti GAD and anti ICA-512 were positive

IPEX
(Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-linked)

- FOX P3 mutation
  - Expressed on Treg lymphocytes involved with dampening autoimmune attack
  - Develop DM as infant plus autoimmune enteropathy and many other autoimmune problems

Case BJ

- 4mo: Bone marrow transplant from HLA-identical sister who did not have FOX P3 mutation.
- Continued to have diabetes, but eczema, ITP and diarrhea resolved
Take Home: IPEX

• Antibody positive diabetes that presents in boys early in life with GI and skin manifestations and other autoimmune diseases is an atypical variant of DM1.

Case 5: LD

• 44 yo woman of normal weight (BMI = 22)
• 11 year history of DM, on insulin after brief glyburide Rx. A1c = 8.8%
• 7 year history of hearing loss
• Complains of poor recovery from exercise
• She has 6 sibs (43-53yo), 4 with DM and 5 with deafness
• Her mother died young without known diabetes or deafness

MIDD

• Maternally Inherited Diabetes and Sensorineural Deafness
• Deafness typically precedes diabetes.
• Diabetes typically develops in the 30’s, but can be from 15-70 yo.
MIDD

- Due to mitochondrial DNA mutation
- Mitochondria are always inherited from the mother's egg cytoplasm so MIDD is passed from affected mother to all children, but only girls will pass it on.
- Many mitochondria are present in egg, so will typically get a mix of normal and mutant mitochondria
- The mutation results in poor generation of ATP

MIDD

- Diabetes
  - Poor ATP generation in beta cell, so K channel is not closed: like neonatal diabetes
  - Sulfonylurea works for a while, but progresses so that insulin is required within 2-4 years of elevated BG

MIDD frequency

- IDDM with family history: 6% have MIDD
- NIDDM with family history: 2% have MIDD
- DM and deafness: 60% have MIDD
- DM and family MELAS*: 20% have MIDD
- LADA 10% actually have MIDD
- Adult DM2 1% actually have MIDD

*Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
MIDD: Why good to recognize

Treatment:
Sulfonylurea, then will need insulin
Some recommend treat with CoQ10

Prognosis:
If DM is first to present, can anticipate
deafness and perhaps other manifestations

Family:
All of affected woman’s children will be
affected, but none of her sons will pass it on

THM: MIDD

• It looks like type 1 diabetes, but consider
MIDD for:
  – Patient who has a mother with diabetes and
deafness

Case GF

• 10 yo previously healthy developed
difficulty walking that gradually worsened
and spread to arms and trunk.
• 15 yo started dysarthria
• 17 yo was diagnosed with hypertrophic
cardiomyopathy and heart block
• 20 yo was confined to wheelchair
• 20 yo fasting BG 160
Friedreich’s Ataxia

- Degenerative disorder of neurons and cardiomyocytes resulting from mitochondrial dysfunction
- 25% develop insulin deficiency, typically 10-15 years after development of neurological symptoms
- Acute presentation of insulin deficiency, sometimes in DKA
- Autosomal recessive. FRDA gene encodes frataxin. It has a GAA trinucleotide repeat, causing disease when it elongates leading to decreased expression.

Friedreich’s Ataxia

- Decreased beta cell function and decreased beta cell mass
- Studies indicate decreased insulin release (from ATP production deficit) and increased beta cell apoptosis
- Associated with insulin deficiency, so be prepared to avoid acute (DKA) presentation

What Can Cause Elevated Blood Glucose?

- Type 1 diabetes and Type 2 diabetes
- MODY
- LADA
- Medications
- Pancreas Disease
- Critical Illness
- Rare: Neonatal DM, Wolfram, MIDD, IPEX