MONOGENIC DIABETES
WHAT AM I LOOKING FOR?

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WHAT IS MODY AND WHAT DIFFERENCE DOES A DIAGNOSIS MAKE?

- MODY is most often autosomal dominant with 50% inheritance.
- 1-2% of patients with diabetes have MODY and many of these are misdiagnosed as having Type 1 or Type 2 diabetes.
- Can present over lifetime, though generally appears through childhood or early adulthood.
- In some cases, treatment may need to change.
- Other family members might be identified.

SOME OF THE SUBTYPES OF DIABETES

- Type 1
- Type 2
- Neonatal
- HNF1A/4A
- GCK
- MIDD
SO, WHO CAN I EXCLUDE?

- No family history of diabetes or solid history of Type 2 diabetes with obesity and insulin resistance
- People who “fit the mold” of Type 2: Obesity, insulin resistance, acanthosis nigricans, etc.
- Antibody positive:
  Consider testing GAD, IA-2 and ZnTransport-8 antibodies, especially if new diagnosis.

GAD AND IA2 VERY UNLIKELY IN MODY

- At least one positive antibody has 99% sensitivity and 82% specificity for DM1 versus MODY
- Probability of MODY is 1 in 8200 with one positive antibody and less than 1 in 3 million with 2 positive antibodies.
DOES ZNT8 IMPROVE DIAGNOSIS ACCURACY?

- ZnT8 prevalence 87/131 x 100 = 66%
- 26 additional patients were Znt8 positive = 10.2%
- No MODY patients were antibody positive

WHO SHOULD RAISE MY SUSPICIONS?

Detectable C-Peptide/UCPCR more than 5 years after diagnosis of DM1
Diabetes that appears strongly genetic-even if various “diabetes types” in family history (any Monogenic Diabetes)
“Doesn’t look like your typical Type 2” (GCK)
Non-progressive diabetes (GCK)
Type 1 but can go without insulin without having DKA (HNF1a, HNF1b, HNF4a)
Renal cysts/kidney or uterine malformations co-occurring with diabetes (HNF1b)
High birthweight and hypoglycemia at birth (HNF4a)
Diagnosis under age 35 and unsure of type of diabetes (HNF1a, HNF4a, HNF1b, GCK)
SU sensitive or history of hypoglycemia with SU use (HNF1a, HNF4a)
Low renal threshold for glucose (HNF4a)
Hearing loss also strong in family history (MIDD)
Diabetes as a child that went away and came back again
Syndromic diabetes (hemochromatosis, cooccurring seizure disorder, small stature, odd features)
Review of Genetics

- Typical Inheritance with no defect
- All children have “TT” or no defect
Review of Genetics

- One parent has defect, the other is unaffected.
- Typical Mody inheritance pattern
- Now 50% of the children are unaffected “TT” and 50% of the children are affected “Tt.”

GCK MODY

- Non-progressive hyperglycemia since birth
- Diabetes diagnosed after routine lab work or misdiagnosed as GDM
- A1c may slightly increase with age but generally is not expected to ever rise above 8%
There is an increase in glycemia in GCK-MODY

GCK MODY

- Non-progressive hyperglycemia since birth
- Diabetes diagnosed after routine lab work or misdiagnosed as GDM
- A1c may slightly increase with age but generally is not expected to ever rise above 8%
- No treatment needed, if on treatment, stop treatment
GCK AND PREGNANCY

- If BMI is less than 25 and FBG >99mg/dL consider testing for GCK
- If known GCK:
  - Check fetal growth during 3rd trimester and treat with insulin if abdominal circumference percentile is high, or, latest studies suggest no treatment at all and gestational size simply corresponds to whether the baby is GCK+ (smaller) or GCK- (larger)

Fetuses that inherit GCK-MODY are normal weight despite maternal hyperglycaemia

Fetus | no mutation | mutation
--- | --- | ---
Percentile | 85% | 47%

Spyer et al. Diabetic Medicine 2009
Mean birth weight centile for pregnancies of a parent with a GCK mutation

If both parents have GCK MODY and both contribute the GCK MODY gene, the baby will have permanent neonatal diabetes.
Review of Genetics

• In the unlikely event of 2 affected parents having offspring. Note the “tt” is now added.
• 25% unaffected “TT”
• 50% affected “Tt” - MODY
• 25% double affected “tt” Permanent diabetes from birth. No blood sugar sensing capability at all.

HNF1A + HNF4A

• 2-3 generations of diabetes diagnosed at a young age
  • May appear to be a combination of DM1 and DM2
• Often dx before age 30
  • Early teens most common
• Misdiagnosed as DM1
• Polyuria, polydipsia, weight loss
• Negative antibodies and positive C-peptide
• No history of DKA
• Do well on low dose sulfonylurea. Might even get hypoglycemic from sulfonylurea.
MECHANISM FOR EXCELLENT RESPONSE TO SULFONYLUREAS IN HNF1A

Pearson et al, Lancet 2003

HNF1A + HNF4A

- Often dx before age 30
- Onset often in early teens
- Misdiagnosed as DM1
- Polyuria, polydipsia, weight loss
- Negative antibodies and positive C-peptide
- 2-3 generations of diabetes diagnosed at a young age
  - May appear to be a combination of DM1 and DM2
- Do well on low dose sulfonylurea. Might even get hypoglycemic from sulfonylurea.
- Years from diagnosis tends to be predictive of how well they well they will do off of insulin.
DURATION OF DIABETES AT GENETIC TEST PREDICTS TREATMENT AT 2 YEAR FOLLOW UP IN HNF1/4A

<table>
<thead>
<tr>
<th>Duration of diabetes at genetic diagnosis</th>
<th>% off insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 yrs</td>
<td>33%</td>
</tr>
<tr>
<td>10.1-20 yrs</td>
<td>23%</td>
</tr>
<tr>
<td>&gt;20 yrs</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

27/38 (71%) off insulin

HNF1A
- Low renal threshold for glucose
- Early MI
- Associated with liver adenoma

HNF4A
- Often a higher birth weight in babies who are affected.
- Neonatal hypoglycemia
Case Study

Susan diagnosed at 20 years, presented with thirst and polyuria, Random BG 254mg/dL, trace ketones, BMI 28, HbA1c 8.8%

What’s the most likely diagnosis?
What other information would be helpful?

Father diagnosed at 35 years with Type 1 diabetes and paternal grandfather Type 2 diagnosed at 65yrs (now deceased), BMIs not known.

Susan is antibody negative.

Now 3 months post diagnosis on insulin 0.3u/kg/day (about 20 units)
Would you advise genetic testing?
Case Study (continued)

Probability calculator score = 1 in 8 chance of this being MODY
Susan’s C-peptide is 2.0,
Father’s C-peptide is 1.2 and he is antibody negative

What’s the diagnosis?

HNF1A MODY

What treatment / advice would you recommend?

Transfer from insulin to low dose sulphonylurea, offer genetic testing to father and consider treatment change for him. Note higher chance of early MI.

HNF1B/RCAD
(RENAL CYSTS AND DIABETES)

- Tend to be in their early to mid 20s at diagnosis, but can range
- Like most other forms of MODY, 50% inheritance, however spontaneous mutations are also common
- 2 or 3 generations of diabetes and/or the following
  - Renal cysts (variable severity)
  - Renal/uterine/genital tract malformations or structural problems (small kidney, no kidney misshaped kidney, “bright” kidneys on prenatal ultrasound)
  - Small pancreas or pancreatic tail on ultrasound
  - Uterus might be bicornuate, horseshoe or otherwise malformed
HNF1B/RCAD
(RENAL CYSTS AND DIABETES)

- Elevated LFTs in this case are **unlikely** to cause disease
- Dyslipidemia
- Not responsive to SUs
- Insulin dependent after diagnosis, and some degree of insulin resistance
MIDD (MATERNALLY INHERITED DIABETES AND DEAFNESS)

- Peak age of onset is 25-40 years
- Family history of deafness/hearing loss and/or diabetes
  - Deafness might not be complete, hearing loss counts!
  - Hearing loss of high frequency versus low frequency
- Tend to be short statured
- Cardiomyopathy
- Pigmented retinopathy in some
- Maternally inherited so males may get the disorder from mom but they would not pass it on.
- Often need insulin within one year, can have DKA
- Might have muscle symptoms with metformin

MIDD IN LARGE PEDIGREE
NEONATAL DIABETES

- Diagnosis of diabetes under the age of 6 months is rare but really worth looking into. Often diagnosed as DM1, but if <6months, there is a better chance of one of these:
- KCNJ11 and ABCC8 are strong contributors
- Both are permanent but can be treated with SUs
- KCNJ11 seems to have a neurological component, with developmental delay which improves with SUs if started early
- There are other causes for diabetes at such an early age, these are insulin requiring.

WHERE CAN I LEARN MORE?

- Future Learn: Genomic Medicine
- University of Exeter: www.diabetesgenes.org
  This site has the very nice MODY probability calculator
- University of Chicago: Kovler Diabetes Center
REFERENCES

QUESTIONS?