Antibody Negative Diabetes: A Case of MODY

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PENS 2017

Disclosures

- No relevant disclosures

Objectives

- Understand how MODY differs from other types of diabetes
- Identify which patients should be tested for MODY
- Distinguish MODY 5 from other forms of MODY
Case: JM

- 8/26/13: PCP for PE at age 16 11/12
- u/a showed glycosuria
- 8/27/13: Referred to Pediatric Endocrinology and Diabetes at Children’s Hospital at Montefiore
- JM denied polyuria, polydipsia, polyphagia, weight loss

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Case: JM

<table>
<thead>
<tr>
<th>Vital Signs</th>
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<tbody>
<tr>
<td>- Weight 56.5 kg (20%)</td>
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<tr>
<td>- Height 173.2 cm (30%)</td>
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<tr>
<td>- BMI 18.83 (10%)</td>
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<tr>
<td>- Pulse 79 bpm</td>
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<tr>
<td>- BP 109/73</td>
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<table>
<thead>
<tr>
<th>Allergies</th>
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<tbody>
<tr>
<td>- PCN</td>
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<table>
<thead>
<tr>
<th>Medications</th>
</tr>
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<tbody>
<tr>
<td>- none</td>
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<table>
<thead>
<tr>
<th>Birth history:</th>
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</thead>
<tbody>
<tr>
<td>- Full term, NSVD</td>
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<tr>
<td>- No prenatal or newborn complications</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Medical history:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Learning disability</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Father T2DM age 47yrs</td>
</tr>
<tr>
<td>- MFG T2DM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical history:</th>
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</thead>
<tbody>
<tr>
<td>- none</td>
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Case: JM

- Review of Systems: Non-contributory
- Denies polyuria, polydipsia, polyphagia, weight loss
- Physical Exam: Unremarkable
- General-well appearing, no acute distress
- Mouth-MMM
- Skin-no acanthosis noted
- Genitalia-normal male genitalia, testes descended bilaterally, tanner stage 4 pubic hair, testes 20cc
Case: JM

Visit on 8/27/13 in pediatric diabetes clinic:
- POCT in pediatric diabetes clinic
  - Glucose: 308 mg/dL (70-115 mg/dL)
  - HbA1c: 11.3% (4.7-6.4%)
- Urinalysis
  - Leukocytes: negative (negative)
  - Nitrite: negative (negative)
  - Urobilinogen: 0.2 (0.2-1.0)
  - Protein: negative (negative)
  - pH: 5.5 (5.0-7.0)
  - Blood: negative (negative)
  - Spec. Gravity: 1.020 (1.000-1.030)
  - Ketone: trace (5) (negative)
  - Bilirubin: negative (negative)
  - Glucose: >=1000 (negative)

Case: JM

What would you do?

Case: JM

- More Labs
- 75 gram OGTT
  - Glucose, Fasting: 338 (H) (70-95) mg/dL
  - Glucose, 2 hour: 590 (H) (70-200) mg/dL
Case: JM

- Insulin Autoantibody:
  - < 0.4 (0.4-4.0)
- GAD Autoantibody:
  - < 1.0 (< 1.1) U/mL
- Islet Cell Autoantibody:
  - < 1.2 (1.2-2.0)
- IA-2 Autoantibody:
  - NOT DONE AT THIS TIME
- Zinc Transporter 8 Autoantibody:
  - NOT DONE AT THIS TIME
- Hemoglobin A1C:
  - 6.1 (4.7-6.4)
- Celiac screen: negative
- Immunoglobulin A (IgA), Quantitative:
  - 267 (68-423) mg/dL
- Thyroglobulin Antibody:
  - < 1.0 (< 10.1) IU/mL
- Thyroid Peroxidase Antibody:
  - 0.0 (0-5.1) IU/mL
- Zinc Transporter 8 Antibody:
  - 0.0 (0-5.1) IU/mL

Case: JM

- Next step
  - JM was referred for diabetes education with the diabetes team (RN, CDE, RD, Social Worker)
  - Started insulin pump therapy 10/01/13

Case: JM

- Follow up
  - 12/23/13: JM’s blood sugars upon awakening are usually less than 100mg/dL and he is usually low after school, below 60mg/dL
  - 3/31/14: “A1C in normal range but at cost of hypoglycemia often”
  - 4/6/15: “Patient is rarely bolusing and mostly living off of basal and still keeping A1c below 6%. Pt using 0.4 units/kg/day”
  - 1/11/16: “Basal:bolus 90%/10% and 3 days without bolusing in past 12 days”
  - C-peptide drawn at 1/11/16 visit
  - IA 2 and Zn Transporter 8 antibody drawn 5/19/16
Case: JM

HbA1c (%)

Three years later - results
- C-Peptide: 1.9 (1.3 - 4.2) ng/mL
- Hemoglobin A1C: 7.1 (H) (4.7 - 6.4) %
- IA-2 Autoantibody: <0.8 (<0.8) U/mL
- Zinc Transporter 8 Autoantibody: <10 (<15) U/mL

Insulin Autoantibody: <0.4 (<0.4)
GAD Autoantibody: <1.0 (<1.1) U/mL
Islet Cell Autoantibody: <1:2 (titer < 1:2)

Case: JM - Review of the data

C-peptide: 1.9 (1.3 - 4.2) ng/mL
Insulin Autoantibody: <0.4
GAD Autoantibody: <1.0
Islet Cell Autoantibody: <1:2
IA-2 Autoantibody: <0.8
Zinc Transporter 8 Autoantibody: <10
Case: JM

* MODY testing...

<table>
<thead>
<tr>
<th>Gene test</th>
<th>Technical result</th>
<th>Mutation Type</th>
<th>Inheritance</th>
<th>Clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1B</td>
<td>Exons deleted:</td>
<td>Heterozygous deletion</td>
<td>Autosomal dominant</td>
<td>Predicted pathogenic</td>
</tr>
</tbody>
</table>

WHAT DOES THAT EVEN MEAN?
MODY

- Maturity Onset Diabetes of the Young (MODY)
- Monogenic diabetes—a problem with 1 gene that causes beta cell dysfunction
- Occurs in about 1%–2% of people with diabetes
- Usually misdiagnosed as T1DM or T2DM
- First described in 1970’s to describe “inheritable” diabetes that was different from T1DM and T2DM
- In the 1990’s the molecular genetic basis was recognized

MODY

- Main characteristics
  - Diabetes develops before 30 years old
  - Diabetes runs in families
  - Diabetes may be treated with diet or pills
  - Absence of autoantibodies
    - About 4% of people with insulin dependent diabetes are autoantibody negative
  - Measurable C-peptide
  - No DKA

- Most common MODY genes
  - MODY 1 (HNF4A)—most common cause
  - MODY 2 (GCK)
  - MODY 3 (HNF1A)
  - MODY 5 (HNF1B) 1%–5% of cases of MODY in UK

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prevalence among those with MODY</th>
<th>Other characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1A</td>
<td>30%–50%*</td>
<td>Common mutation. Highly penetrant. Large (&gt;5 mmol/L) rise in 2-hour glucose levels on 75 g–OGTT. Progressive β-cell failure. Sensitivity to sulphonylureas.</td>
</tr>
<tr>
<td>GCK</td>
<td>30%–50%*</td>
<td>Common mutation. Raised fasting glucose levels, with small (&lt;3 mmol/L) rise in 2 hour glucose following 75 g–OGTT. Mild hyperglycemia; generally does not require treatment.</td>
</tr>
<tr>
<td>HNF4A</td>
<td>5%</td>
<td>Presents in similar manner to HNF1A mutations. Associated with higher birth weight and transient neonatal hypoglycemia. Progressive β-cell failure. Sensitivity to sulphonylureas.</td>
</tr>
<tr>
<td>HNF1B</td>
<td>5%</td>
<td>Characterized by renal disease. Urogenital tract abnormalities in females.</td>
</tr>
<tr>
<td>INS</td>
<td>&lt;1%</td>
<td>Wide clinical spectrum. Most present with neonatal diabetes, but may also present in early childhood and adulthood.</td>
</tr>
<tr>
<td>IPF1</td>
<td>&lt;1%</td>
<td>Average age of onset is 35 years. Regulates early pancreatic development. Pancreatic agenesis seen in homozygotes and compound heterozygotes.</td>
</tr>
<tr>
<td>NEUROD1</td>
<td>&lt;1%</td>
<td>(fewer than five families reported) Very rare, adult onset (mid-20s). Reduced insulin production (developmental β-cell dysfunction). Individuals may be overweight or obese, similar to type 2 diabetes.</td>
</tr>
<tr>
<td>CEL</td>
<td>&lt;1%</td>
<td>(fewer than five families reported) Very rare, adult onset (mean age 36 years). Exocrine pancreatic insufficiency (dysfunction of the mature acinar cell). Pathophysiology of endocrine dysfunction not clear.</td>
</tr>
<tr>
<td>PAX4</td>
<td>&lt;1%</td>
<td>(fewer than five families reported) Only two families described.</td>
</tr>
</tbody>
</table>

Abbreviations:
- HNF1A, hepatocyte nuclear factor 1 homeoboxA
- GCK, glucokinase
- HNF4A, hepatocyte nuclear factor 4 homeoboxA
- HNF1B, hepatocyte nuclear factor 1 homeoboxB
- IPF1, insulin promoter factor 1
- NEUROD1, neurogenic differentiation 1
- CEL, carboxyl ester lipase
- PAX4, paired box 4.
MODY 5-HNF1B

- Caused by a mutation in the HNF1-beta gene (hepatocyte nuclear factor-1 beta)
- On chromosome 17q12
- Responsible for normal development of beta cells, kidneys, genitourinary organs
  - Critical role in early embryogenesis of pancreatic beta cells
  - HNF1B expression is predominantly in kidneys
- Autosomal dominant: an affected person’s child has a 50% risk of inheriting the mutation/developing diabetes
- Female:Male is 1:1
- Also called RCAD (Renal Cysts And Diabetes)

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>% Of affected subjects (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cysts</td>
<td>66% (36/55)</td>
</tr>
<tr>
<td>Renal histology</td>
<td>4% (2/55)</td>
</tr>
<tr>
<td>Cystic renal dysplasia</td>
<td>4% (2/55)</td>
</tr>
<tr>
<td>Oligomeganephronia</td>
<td>7% (4/55)</td>
</tr>
<tr>
<td>Glomerocystic kidney disease</td>
<td>4% (2/55)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>4% (2/55)</td>
</tr>
<tr>
<td>Morphological renal abnormalities</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Single kidney</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Renal function</td>
<td>86% (47/55)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>15% (8/55)</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>6% (3/55)</td>
</tr>
</tbody>
</table>

MODY 5

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>% Of affected subjects (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>58% (32/55)</td>
</tr>
<tr>
<td>Mean age of diagnosis: 25.8 years</td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance, aged 17 and 30 years</td>
<td></td>
</tr>
<tr>
<td>Uterine malformations</td>
<td>14% (5/36)</td>
</tr>
<tr>
<td>Male genital tract malformations</td>
<td>5% (1/19)</td>
</tr>
<tr>
<td>Hepatocentesis</td>
<td>1% (1/15)</td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>13% (1/3)</td>
</tr>
<tr>
<td>Other features</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Prognathism</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Ligament laxity</td>
<td>2% (1/55)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2% (1/55)</td>
</tr>
</tbody>
</table>
MODY 5

- The Bad News...
  - Patients can develop:
    - Renal cysts
    - Renal dysplasia
    - Renal tract malformations
    - Hypoplastic glomerulocystic kidney disease
    - Pancreatic atrophy
    - Genital tract abnormalities (epididymal cysts, atresia of vas deferens, bicornuate uterus)
    - Abnormal liver levels
    - Hypomagnesemia
    - Diabetes
    - Learning disabilities
  - Renal disease can be progressive through adulthood in the absence of diabetic nephropathy

MODY 5 and diabetes (RCAD)

- Diabetes typically presents after renal disease
- Diabetes in 58% of reported HNF1-beta mutation carriers
- Impaired glucose tolerance in 4% of patients
- The pathophysiology of the diabetes likely due to reduced insulin secretion due to beta cell dysfunction possibly caused by pancreatic atrophy
- Pts with HNF1B mutations with diabetes are not sulphonylurea sensitive and usually require insulin, although not dependent on insulin
- Birth weight can be reduced by about 800 grams due to reduced insulin secretion in utero

MODY

- Who should get tested for MODY?
  - Strong family history
  - Absence of autoantibodies
    - About 4% of people with diabetes can be autoantibody negative
  - Evidence of endogenous insulin secretion (c peptide, low insulin requirement)
  - Lack of DKA
  - Lack of obesity
  - Absence of acanthosis nigricans
  - Normal triglycerides and normal HDL
MODY 5

- Who should get tested for MODY 5?
  - 2 or 3 generations of diabetes
  - Family history of renal cysts
  - Family history of structural problems of uterus or kidneys
  - No history of DKA
  - De novo mutations can occur (30%-50%) so testing should be encouraged even in the absence of a family history of diabetes or renal disease

Case: JM

- Renal Ultrasound 12/27/16
  - Liver demonstrates normal and homogenous echotexture
  - No solid or cystic lesions
  - Portal vein: Normal without thrombosis
  - Intrahepatic and extrahepatic bile ducts not dilated
  - Gallbladder: Normal
  - Pancreas: Head and body appear normal: tail obscured by bowel gas
  - Spleen: Normal
  - Kidneys: Right kidney- 11.1cm in length, mild hydronephrosis of unknown etiology, left kidney- 10.6cm in length
  - Aorta/inferior vena cava: appear normal
  - Ascites: None
  - Pleural Effusion: None
- Pt scheduled to see Renal

Case: JM

- Good news...
  - No need to check for thyroid antibodies or celiac disease annually because this is not an autoimmune process
Key Points

- Consider MODY when there is a patient with antibody negative diabetes who does not fit the criteria for T1DM or T2DM
- From a provider perspective:
  - Do not take every diagnosis at face value
  - Take time to review and re-evaluate the entire chart

References