Antibody Negative Diabetes: A Case of MODY

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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

Case: JM

- Vital Signs
  - Weight 56.5 kg (20%)
  - Height 173.2cm (39%)
  - BMI 18.83 (19%)
  - Pulse 79 bpm
  - BP 109/73
- Allergies
  - PCN
- Medications
  - none
- Birth history:
  - Full term, NSVD
  - No prenatal or newborn complications
- Medical history:
  - Learning disability
- Family history:
  - Father T2DM age 47yrs
  - MFG T2DM
- Surgical history:
  - none

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

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)
- **GAD Autoantibody:**
  - < 1.0 (< 1.1) U/mL
- **Islet Cell Autoantibody:**
  - <1:2 (titer < 1:2)
- **IA-2 Autoantibody:**
  - NOT DONE AT THIS TIME
- **Zinc Transporter 8 Autoantibody:**
  - NOT DONE AT THIS TIME
- **Hemoglobin A1C:**
  - **11.1 (H)** (4.7-6.4) %
- **Celiac screen: negative**
- **Immunoglobulin A (IgA), Quantitative:**
  - 157 (68-423) mg/dL
- **Thyroglobulin Antibody:**
  - < 1.0 (< 10.1) IU/mL
- **Thyroid Peroxidase Antibody:**
  - 0.0 (< 5.1) IU/mL

Case: JM

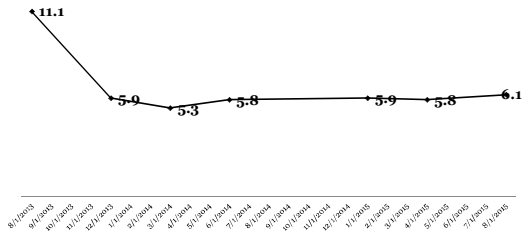
- **Next step**
  - JM was referred for diabetes education with the diabetes team (RN, CDE, RD, Social Worker)
  - Started insulin pump therapy 10/01/13

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"
  - 6/30/14: "Tired of doing 'this' and so sometimes slept without pump "
  - 9/15/14: "Hypoglycemia very frequent, consistently fasting and pre afternoon snack when he does not eat for long periods of time"
  - 4/6/15: "Patient is rarely bolusing and mostly living off of basal and still keeping A1c below 6%. Pt using 0.46units/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 (%)



Case: JM

- **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

Case: JM-Review of the data

- **C-peptide:**
  - 1.9 (1.3 - 4.2) ng/mL
- **Insulin Autoantibody**:
  - <0.4 (<0.4)
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Case: JM

- MODY testing…

Case: JM

- **MODY testing (Athena)**

	Gene test	Technical result	Mutation Type	Inheritance	Clinical relevance
Positive	HNF1B	Exons deleted: 1-9	Heterozygous deletion	Autosomal dominant	Predicted pathogenic

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
  - Measureable 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

MODY

Gene	Prevalence amongst those with MODY	Other clinical features
HNF1A	30%–50%[1–3]	Common mutation. Highly penetrant. Large (>5 mmol/L) rise in 2-hour glucose levels on 75 g–OGTT. Progressive β-cell failure. Sensitivity to sulphonylureas.
GCK	30%–50%[1–3]	Common mutation. Raised fasting glucose levels, with small (<3 mmol/L) rise in 2 hour glucose following 75 g–OGTT. Mild hyperglycemia; generally does not require treatment.
HNF4A	5%	Presents in similar manner to *HNF1A* mutations. Associated with higher birth weight and transient neonatal hypoglycemia. Progressive β-cell failure. Sensitivity to sulphonylureas.
HNF1B	5%	Characterized by renal disease. Urogenital tract abnormalities in females.
INS	<1%	Wide clinical spectrum. Most present with neonatal diabetes, but may also present in early childhood and adulthood.
IPF1	<1%	Average age of onset is 35 years. IPF1 regulates early pancreatic development. Pancreatic agenesis seen in homozygotes and compound heterozygotes.[83,84]
NEUROD1	<1% (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.
CEL	<1% (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.
PAX4	<1% (fewer than five families reported)	Only two families described.

Diabetes Metab Syndr Obes. 2012; 5: 101–108.

Abbreviations: *HNF1A*, hepatocyte nuclear factor 1 homeobox A; GCK, glucokinase; *HNF4A*, hepatocyte nuclear factor 4 homeobox A; *HNF1B*, hepatocyte nuclear factor 1 homeobox B; 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)

MODY 5
Renal phenotype summary for all reported subjects with HNF-1β mutations

Clinical feature	% Of affected subjects (number)
Renal cysts	66% (36/55)
Renal histology	2% Oligomeganephronia (1)
	4% Cystic renal dysplasia (2)
	7% Glomerulocystic kidney disease (4)
	4% Non-specific (2)
	83% Histology not examined (46)
Morphological renal	2% Horseshoe kidney (1)
abnormalities	2% Single kidney (1)
Renal function	86% Renal impairment (47)
	15% Dialysis/transplanted (8)
	6% Normal renal function (3)
	9% Not reported (5)

Nephrol Dial Transplant (2004) 19 (11): 2743–2748

MODY 5
Non-renal phenotype summary for all reported subjects with HNF-1β mutations

Clinical feature	% Of affected subjects (number)
Diabetes	58% (32/55)
	Mean age of diagnosis: 25.8 years
	2 Impaired glucose tolerance, aged 17 and 38 years
	12 Not examined
Uterine malformations	14% (5/36)
Male genital tract malformations	5% (1/19)
Hyperuricaemia	20% Reported (11)
Abnormal liver function tests	13% Reported (7)
Other features	2% Pyloric stenosis (1)
	4% Prognathism (2)
	2% Learning difficulties (1)
	2% Ligament laxity (1)
	2% Hearing loss (1)

Nephrol Dial Transplant (2004) 19 (11): 2743–2748

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

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