Objectives:
At the conclusion of this presentation, participants should be able to:

• Discuss the major characteristics of MODY and list the 3 most common types.
• State 3 patient features that may be suspicious for a diagnosis of MODY.
• Analyze case studies and determine if MODY testing should be considered.

*I have no conflicts of interest to disclose

Maturity-Onset Diabetes of the Young (MODY) – What is it??

• Rare monogenic form of diabetes
• Accounts for 2-5% of all diabetes cases
• Frequently misdiagnosed as Type 1 (T1) or Type 2 diabetes mellitus (T2 DM)
• At least 13 different gene mutations may result in MODY

History of MODY

• First reported in 1974 by Tattersall, et al
• Recognized a familial form of non-insulin dependent diabetes distinct from T1 and T2 DM
• Noted an autosomal dominant pattern of inheritance usually presenting by age 25
• Labeled “MODY” reflecting terms in use at that time for presentation as “juvenile or maturity onset” diabetes

MODY diagnosis may impact treatment
- Some MODY types can be treated with oral sulfonylureas
- Surveillance for complications differs based on MODY type
- Some MODY types have similar risks as T1 and T2 DM, some do not

Importance of Correct Diagnosis – Why Does it Matter?

• Ability to screen at risk family members
• Ability to perform genetic counseling
Brief Review of T1 and T2 DM

- Multi-factorial inheritance
- Polygenic

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 DM</td>
<td>Autoimmune destruction pancreatic beta cells</td>
<td>Absolute insulin deficiency</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>Insulin resistance and relative beta cell deficiency</td>
<td>Typically occurs in the setting of obesity</td>
</tr>
</tbody>
</table>

GENETICS OF T1 & T2

Multi-Factorial/Polygenic Inheritance

- Multiple genetic factors combine with environmental factors
- Tend to see clustering in families
- Clinical genetic testing is typically not looking for polygenic risk factors because most play an extremely small role
MULTI-FACTORIAL/POLYGENIC INHERITANCE

- Various genetic defects are simply risk factors
- Other environmental factors add in
- It takes a while for all of the “marbles” to add up
- At some point, the jar fills up and disease manifests

Quick Genetics Review

- Each chromosome is made up of one large DNA molecule
- A gene is a segment of DNA that encodes a protein product
- A protein is a complex compound made up of hundreds to thousands of amino acids (building blocks of proteins)

The Basics

- Many genetic conditions are caused by mutations in genes that affect the structure and/or function of a protein
- Mutation = an abnormality in how a gene is sequenced
- By definition, a mutation must cause a problem in the corresponding protein
Maturity-Onset Diabetes of the Young (MODY)

Monogenic Disease

- Caused by one defect in a single gene present in all cells of the body
- Function of the affected gene determines the nature of the respective disease
- Requires genetic testing for definitive diagnosis
- Monogenic diseases are rare, but affect millions world-wide
- Estimated that 10,000 human diseases are known to be monogenic


CHARACTERISTICS OF MODY

<table>
<thead>
<tr>
<th>Dominant pattern of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>- hx of diabetes in one or two consecutive generations</td>
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</tbody>
</table>

- Usual onset in childhood, adolescence, or young adulthood -typically before age 25

- Risk of micro and macrovascular complications differ based on MODY type

- Treatment differs based on MODY type

INDEX OF SUSPICION

NEW OR PREVIOUSLY DIAGNOSED INDIVIDUAL WITH ATYPICAL FEATURES:
- Absence of pancreatic auto-antibodies
- Evidence of endogenous insulin production beyond typical honeymoon
- T2 diagnosis in young individual not significantly overweight or without signs of insulin resistance
- Diabetes in 2 or more consecutive generations

MODY GENE MUTATIONS

- At least 13 disease causing mutations have been identified
- Novel mutations continue to occur and more will likely be recognized
- Affected genes are responsible for beta cell development, function and regulation
- Gene defects result in disordered glucose sensing and insulin secretion

Testing Strategies

Sequencing Tests: 3 Basic Strategies

- Single gene → stepwise
  (Sanger Sequencing Method)

- Multiple gene panel
  (Next Generation Sequencing)

- Whole exome or whole genome sequencing

Slide borrowed with permission from Laura Baker, MGC, LCGC, NNASCN

Step-Wise Approach

- Screening of the most common MODY genes with Sanger Sequencing (SS) method
- Often leaves less common MODY genes un-tested → possible missed diagnosis
- Time consuming & ultimately more costly than Next Generation Sequencing (NGS)
- Recent studies show MODY mutations identified by NGS in patients with previous negative testing by SS

Next Generation Sequencing

- Newer targeted NGS allows for sensitive, quicker, and more cost-effective genetic analysis
- Allows for parallel sequencing of many sections of DNA simultaneously
- Checks all coding exons of all genes on the panel
- Enables testing of all genes on the panel at the same cost as testing only a few of the more common mutations

Whole Exome Sequencing – sequencing the exons, coding regions of all possible genes at once

Common MODY Types

- Hepatocyte Nuclear Factor 4Alpha (HNF4A/MODY 1)
  - Third most common type
  - Similar characteristics to MODY 3
  - Accounts for ~15% of all MODY cases
- Glucokinase (GCK/MODY 2)
  - Second most common type
  - Accounts for ~30% of all MODY cases
- Hepatocyte Nuclear Factor 1Alpha (HNF1A/MODY 3)
  - Most common type
  - Accounts for ~50% of all MODY cases
- Hepatocyte Nuclear Factor 1Beta (HNF1B)
  - Fourth most common type
  - Has a lot of extra-pancreatic features
  - Accounts for ~1% of all MODY cases
- Defects in PDX1, NEUROD1, KFL11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11 account for less than 1% of all MODY cases
MODY 1 (HNF4A)

**GENE**
- Heterozygous mutation in gene encoding transcription factor HNF4A

**Mutation Effects**
- Alters gene expression for proteins responsible for glucose transport/metabolism
- ↓ beta cell proliferation, ↑ apoptosis

**Pathophysiology**
- Beta cell defect with progressive deterioration in glucose tolerance

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MODY 1 (HNF4A) - continued

**Complication Rate**
- Micro/macrovacular complications frequent
- Similar rates to Type 1 and Type 2 DM

**Treatment**
- Sulfonylurea sensitive
- May progress to insulin

**Special Features**
- Uncommon cause of diazoxide responsive hyperinsulinism in infancy

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MODY 2 (GCK)

**GENE**
- Heterozygous inactivating mutation of GCK gene

**Mutation Effects**
- Encodes glucose sensing enzyme glucokinase
- Compromised glycemic threshold for appropriate insulin release

**Pathophysiology**
- Glucose sensing defect with non-progressive fasting hyperglycemia
**MODY 2 (GCK) - continued**

- **Complication Rate**
  - Rare incidence of micro/macro vascular complications given mild hyperglycemia

- **Treatment**
  - Medication is not usually required
  - Healthy diet and exercise

- **Special Features**
  - Occasional cause of persistently impaired glucose tolerance after gestational diabetes

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**MODY 3 (HNF1A)**

- **Gene**
  - Heterozygous mutation in gene encoding transcription factor HNF1A
  - High penetrance (~80% of individuals with this mutation develop DM by age 35)

- **Mutation Effects**
  - Alters gene expression for proteins responsible for glucose transport and metabolism
  - ↓ beta cell proliferation, ↑ apoptosis

- **Pathophysiology**
  - Beta cell defect with progressive deterioration in glucose tolerance

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**MODY 3 (HNF1A) - continued**

- **Complication Rate**
  - Micro/macrovacular complications frequent
  - Similar rates to Type 1 and Type 2 DM

- **Treatment**
  - Sulfonylurea sensitive
  - May progress to insulin

- **Special Features**
  - Uncommon cause of diazoxide responsive hyperinsulinism in infancy

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References:

MODY 5 (HNF1B)

**GENE**
- Heterozygous mutation in gene encoding hepatic transcription factor 2 (TCF2)

**Mutation Effects**
- HNF1B expressed in early embryonic development in pancreas, kidney, liver and GU tract

**Pathophysiology**
- Beta cell defect with progressive deterioration in glucose tolerance
- Insulin resistance is an additional feature

**Complication Rate**
- Micro/macrovascular complications frequent
- Approximately 50% develop end stage renal disease before age 45

**Treatment**
- Early treatment with insulin
- Not sulfonylurea sensitive

**Special Features**
- Predominant extra-pancreatic feature is renal disease
- Most common renal malformation is renal cysts


**TREATMENT STRATEGIES**
TREATMENT

- Many forms of MODY require treatment with insulin similar to T1 DM
- Insulin needs are often less compared to individuals with T1 DM
- MODY 1 & 3 are sulfonylurea sensitive
- ~30% of those with MODY 1 & 3 later progress to needing insulin therapy


Sulfonylureas: Mechanism of Action

- Lower blood sugar by stimulating the pancreas to release more insulin
- Increase tissue sensitivity to insulin
- Only effective when some pancreatic beta cell activity is present
- Work by blocking ATP sensitive potassium channels

HOW SULFONYLUREAS WORK

Ionic Control of Insulin Secretion

SULFONYLUREA DOSAGE FORMS

- Amaryl® (Glimperide) 
  - 1mg - 2mg once daily. Max 8mg daily
- Glynase® (Glyburide) 
  - Conventional tablets: initially 2.5-5mg daily. Max 20mg daily 
  - Micronized tablets: initially 1.5-3mg daily. Max 12mg daily
- Glucotrol® (Glipizide) 
  - Immediate release: initially 2.5-5mg daily. Max 15mg daily 
  - Extended release: initially 5mg daily. Max 20mg daily 
  - Dose adjusted based on blood sugar patterns, A1C levels and avoidance of hypoglycemia.

Patient Instructions

- Administer once daily with breakfast or 1st meal of the day
- Don’t skip meals – sulfonylureas work to ↑ insulin production throughout the day, so ↑ risk of hypoglycemia if meal skipped

SIDE EFFECTS:
- Hypoglycemia most common 
- GI upset 
- Skin reactions (including Stevens-Johnson Syndrome) 
- ↑ sun sensitivity

CONTRAINDICATIONS

- Hypersensitivity to sulfonylureas or any component of the formulation 
- History of allergic reaction to sulfonamide derivatives 
- Pediatric safety/efficacy not established 
- Pregnancy Category C 
- Breastfeeding: depends on the specific drug. Some are excreted in breastmilk with subsequent risk for hypoglycemia
Drug Interactions

Beta Blockers
- May ↑ hypoglycemic effect
- Cardio selective beta blockers (ex: Atenolol) may be safer
- All beta blockers seem to mask tachycardia as a symptom of hypoglycemia

Somatropin
- May diminish hypoglycemic effect of anti-diabetic agents

Ranitidine
- May ↑ serum concentration of sulfonylureas
- Monitor therapy for potential ↑ in hypoglycemia effects

TAKE AWAYS:

Source: DIABETease
CHARACTERISTICS OF MODY

Dominant pattern of inheritance
-hx of diabetes in one or two consecutive generations

Usual onset in childhood, adolescence, or young adulthood
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Risk of micro and macrovascular complications differ based on MODY type

Treatment differs based on MODY type

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3 MOST COMMON MODY TYPES

- Hepatocyte Nuclear Factor 1 Alpha (HNF1A/MODY 3): 50-60%
- Glucokinase (GCK/MODY 2): 15-30%
- Hepatocyte Nuclear Factor 4 Alpha (HNF4A/MODY 1): <30%
Case Study #1:

“Brian” is a 15 year old Caucasian male with ADHD and no other significant past medical history. He presented to his PCP with complaints of fatigue, sudden worsening of school performance, and recently failing his eye test for his driver’s license. No polyuria, polydipsia or weight loss.

Weight 68.3kg (76%tile), Height 175.6cm (64%tile). BMI 22.15kg/m².

Initial baseline labs performed by PCP showed elevation of fasting glucose at 144mg/dl. Follow up lab studies done as outlined below. He was referred to Endocrinology.

<table>
<thead>
<tr>
<th>PCP FOLLOW UP LABS</th>
<th>BASELINE NEW ONSET LABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>Result</td>
</tr>
<tr>
<td>Fasting Blood glucose</td>
<td>Reference</td>
</tr>
<tr>
<td>122</td>
<td>65-95 mg/dl</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>negative</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>negative</td>
</tr>
<tr>
<td>HbgA1c 7.1%</td>
<td>3.0-5.5%</td>
</tr>
<tr>
<td>Insulin Not drawn</td>
<td></td>
</tr>
<tr>
<td>GAD 65</td>
<td>0.00 &lt;=0.02nmol/L</td>
</tr>
<tr>
<td>IA-2 Ab &lt;0.8</td>
<td>&lt;0.8U/ml</td>
</tr>
<tr>
<td>Insulin Ab 0.00</td>
<td>0.00-0.02 nmol/L</td>
</tr>
<tr>
<td>ZNT8 Ab &lt;10.0</td>
<td>0-10 U/mL</td>
</tr>
<tr>
<td>C-Peptide 1.7</td>
<td>1.1-4.4 ng/mL</td>
</tr>
</tbody>
</table>

Case Study #1 (cont’d)

FAMILY HISTORY:
• Father healthy, and with no history of DM. + T2 DM in PGGF (obese).
• Mother diagnosed with T1 DM age 18. On insulin for 20 years. Last A1c 5.8% on very small insulin doses.
• Younger sister (age 12 years) just diagnosed with T1 DM 2 weeks ago. Also with negative autoimmune markers for T1 DM. She is currently insulin treated.

INITIAL TREATMENT:
• No insulin therapy prescribed at this point.
• Instructions to monitor blood sugars closely and call if persistently above 180.
• Advised to call if any abdominal pain, nausea or vomiting + ED eval to rule out DKA.
• Genetic testing for MODY ordered.

CLINICAL IMPLICATION:
• DM of unclear etiology
  - Type 1 DM with negative autoimmune markers in honeymoon?
  - MODY?

Case Study #1 (cont’d)

MODY TESTING RESULTS:
• Positive for a pathogenic mutation in the HNF1A. Heterozygous frame shift designated c.872: 1 bp duplication of C: Codon:291.
• Autosomal dominant pattern of inheritance – family members are at risk for possessing or inheriting this mutation.

So – What now?

Mother and sister tested
-Mother and sister tested positive for the same mutation
-Sister was taken off of insulin and prescribed sulfonylurea medication.
-Mother had incorrect diagnosis since teen years.
Case Study #1 (cont’d)
OUTCOME:
• Approximately 2 months out from diagnosis, we saw Brian back in clinic for follow up. HNF1A/MODY 3 mutation discussed.
  • A1c was 6.5% on no treatment.
  • Glimpiride 1mg daily was started. A1c remained 6.1-6.3% for the next year.
  • Discussed importance of monitoring blood sugars and for signs of hypoglycemia. Plan to adjust dosage based on BG trends, A1c and hypoglycemia patterns.
  • Discussed risk of micro/macrovacular complications similar to T1 DM.
  • Remaining sibling screened (twin of sister with same mutation) – normal A1c, negative for HNF1A mutation.

Case Study #2:
"Tiffany" is a 14 year old Caucasian female with no significant past medical history. She presented to her PCP with a 3-4 month history of abdominal pain, dyspepsia and dysphagia. Weight 66.9 kg (86%ile), Ht. 166.1 cm (71.8%ile), BMI 24.25kg/m².

She was referred to Gastroenterology where she additionally complained of polydipsia and polyphagia. Baseline labs revealed elevated fasting blood sugar (221mg/dl) and glucosuria on urinalysis, but no ketones.

<table>
<thead>
<tr>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35 (7.31-7.41)</td>
</tr>
<tr>
<td>pCO₂</td>
<td>51 (42-55mmHG)</td>
</tr>
<tr>
<td>PO₂</td>
<td>49 (30-50mmHG)</td>
</tr>
<tr>
<td>Glucose</td>
<td>247 (65-95 mg/dl)</td>
</tr>
<tr>
<td>HCO₃</td>
<td>27 (22-29 mmol/L)</td>
</tr>
</tbody>
</table>

Case Study #2 (cont’d)
FAMILY HISTORY:
• No family history of DM on maternal side
• Father: Non-obese and reports “borderline” high blood sugars on past several screenings.
• Paternal GF’s sister and brother both non-obese and with history of DM. Undear historical information on diabetes type and treatment.

INITIAL TREATMENT:
• Initially started on traditional basal/bolus regimen. Lower blood sugars necessitated repeated decreases in insulin dosage.
• 6 weeks post diagnosis in clinic: A1c 6.5% (down from 7.5% at diagnosis) on 0.2u/kg/d of insulin.

CLINICAL IMPRESSION:
• DM of unclear etiology
  - Type 1 DM with negative autoimmune markers in honeymoon?
  - MODY?
MODY Testing results:
- Heterozygous in the HNF4A gene for a sequence variant designated c.733C>T in exon 7. Predicted to result in amino acid substitution p.Arg 245 Cys.
- Based on this information – it is classified as a variant of unknown clinical significance.

So – What now?

Parent of origin testing
- Dad tested positive for the same mutation

OUTCOME:
- 4 months out from initial diagnosis, we finally had all of Tiffany’s MODY testing results as well as parent of origin results.
- A1c was 5.9% on 0.2u/kg/d.
- Decided to trial her on a sulfonylurea:
  - Glimepiride 1mg daily
  - Cut insulin dose in half (already only 9% of body wt. in kg)
  - Counseled to monitor for ketones if ↑ blood sugars as well as for any hypoglycemia.
- Within 2 months, Tiffany was off of all insulin and A1c was 5.5%.
- She is now almost year out from initial diagnosis with an A1c of 5.4% on Glimepiride only regimen.
- Genetic counseling was done and siblings are being tested.

Questions??

Thank you for your attention!
References:


• Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®. Hudson, Ohio: Lexi-Comp, Inc February 5, 2017


