65 yo M w/type 1 diabetes presents w/frequent hypoglycemia

Jess Hwang
4/4/13
HPI

- Diagnosed with diabetes at the age of 14 – presented with symptoms of polydypsia
- No neuropathy, retinopathy or nephropathy
- On Orinase (SU) for 15 years, then insulin
- Started on an insulin pump 2002
- Exercises 3 times per week
- Diet is fairly healthy
- Nocturnal hypoglycemia 3 times per week
PMH
- Dyslipidemia
- Diabetes
- Mildly elevated PSA

Social history
- Engineer/consultant
- Lives with wife
- No tobacco, EtOH

Family history: pending

Medications
- Lovastatin
- Ergocalciferol 1000
- Medtronic insulin pump
  - Basal (24h = 10.63U)
  - Carb ratio 10-11
  - ISF 40
  - Target 95-110
Pedigree

Diabetic Died at 30

Dx 20s SU

Dx 23 Insulin

Dx 37 Pills

Dx 12 Insulin

Dx 24 Insulin

Dx 14

Dx ? age

--- Per redcap survey data and medical chart ---
Physical exam

Vitals: 140/74  75  6’5”  188lb (85kg)  BMI 23.5
HEENT: PERRLA, EOMI
Neck: no thyromegaly, no nodules
CV: RRR, no murmurs
Lung: CTA bilaterally
Abdomen: soft, nontender, non-obese
Skin: no acanthosis nigricans
Extremities: no edema, good pulses
<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-peptide</td>
<td>0.12</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.5%</td>
</tr>
<tr>
<td>GAD65</td>
<td>neg</td>
</tr>
<tr>
<td>Lipid: HDL</td>
<td>65</td>
</tr>
<tr>
<td>Lipid: LDL</td>
<td>80</td>
</tr>
<tr>
<td>Lipid: TG</td>
<td>96</td>
</tr>
</tbody>
</table>
Genetic testing

\[ HNF1A: \text{c.526C}>CT, \ p.176Q>QX \]

- Premature stop codon in exon 2 of \( HNF1A \)
- Previously reported nonsense mutation
- Associated with Maturity-onset Diabetes of the Young (MODY) Type 3
<table>
<thead>
<tr>
<th></th>
<th>Prior to transition</th>
<th>+6 months</th>
<th>+2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td>Insulin pump</td>
<td>Glyburide 2.5 BID</td>
<td>Glyburide 1.25 TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin pump</td>
<td>Januvia 100 mg Insulin pump</td>
</tr>
<tr>
<td><strong>Avg BG (mg/dL)</strong></td>
<td>135 ± 46</td>
<td>135 ± 54</td>
<td>141 ± 58</td>
</tr>
<tr>
<td><strong>Sensor BG (mg/dL)</strong></td>
<td>128 ± 41</td>
<td>127 ± 43</td>
<td>125 ± 45</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>6.1</td>
<td>6.1</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Insulin TDD (U)</strong></td>
<td>33.3 ± 5</td>
<td>14.3 ± 4.2</td>
<td>11.3 ± 2.9</td>
</tr>
</tbody>
</table>
Insulin Total Daily Dose

![Insulin Total Daily Dose Chart]

- Insulin
- Insulin + Glyburide
- Insulin + Glyburide + Januvia

Insulin TDD (U)
**Insulin pump alone**

**4 months after adding sulfonylurea**
*Insulin pump + glyburide 2.5 mg twice a day*

**2 months after adding DPP-IV inhibitor**
*Insulin pump + glyburide 1.25 mg three times a day + sitagliptin 100 mg daily*
Clinical Questions

• When to consider testing for MODY?
• Pathophysiology of *HNF1A*-MODY?
• Pharmacotherapy in *HNF1A*-MODY?
  – Efficacy vs Metformin
  – Hyperexcitability to SUs
• Incretin-based therapy as alternative or adjunct to SU?
Criteria for considering testing

• Diabetes in 2+ generations (AD pattern)
• Diagnosis < 25 years of age
• Non-obese
• Non-insulin dependent (or on low doses)
• Type 1 like- with negative antibodies, detectable c-peptide years after diagnosis

Fajans SS, Bell GI. Diab Care 2011;34:1878-1883
**HNF1A-MODY**

- Most common cause of MODY in the UK
- Autosomal dominant inheritance
- Highly penetrant
- At risk for micro/macrovascular complications
- ?Phenotype:
  - Low renal threshold for glucose
  - Decreased hsCRP
Pathophysiology of \textit{HNF1A-MODY}

- Progressive beta cell dysfunction
- Reduced insulin secretion to glucose
- Beta cell apoptosis

- \textit{HNF1a} \(-/-\) mice had decreased mRNA levels of proteins involved in glucose uptake and glycolysis (GLUT2, L-pyruvate kinase)
Pathophysiology of HNF1A-MODY

Clinical implications

• Observational study
• Aim: Investigate clinical course of patients transitioning from insulin→SU after *HNF1A* diabetes is confirmed.
• N = 43 patients
• Success: HbA1c < 7.5% or improvement of pre-transition HbA1c of >1%

Finding HNF1A mutation does influence physicians’ treatment decision. Transferring from insulin to SUs is successful in a majority of patients.

Sulfonylurea
Hyperexcitability

Suspected diabetic or IGT
Hypoglycemia with SU
HNF1A diagnosis

Tolbutamide-modified IVGTT


IV Glucagon test

HNF1A

2x ↑ to IV glucose

2.5x ↑ to IV tolbutamide

HNF1A

4x ↑ to glucagon
Metformin vs SU in *HNF1A-MODY*

- Randomized crossover trial (1 week washout)
- N = 36 patients
- Primary outcome = response of fasting plasma glucose
- Secondary outcomes = fructosamine, episodes of hypoglycemia
Metformin vs SU in HNF1A-MODY

Change in fasting plasma glucose (mmol/L)

Gliclazide

Metformin

Type 2 diabetes

HNF-1α diabetes

p = 0.002

p = 0.45
Metformin vs SU in HNF1A-MODY

![Bar chart showing the change in fasting plasma glucose (mmol/L) for Gliclazide and Metformin in Type 2 diabetes and HNF-1α diabetes. The p-values are p=0.002 for HNF-1α diabetes and p=0.45 for Type 2 diabetes.](chart)
Low dose of nateglinide prevents acute postprandial rise in glucose more efficiently and causes less hypoglycemia than glibenclamide

Incretin-based therapy in MODY

• Not well-defined… yet
• In the last 3 years, isolated case reports
• Ideal treatment would directly address the primary defect of declining beta cell function
• GLP-1 RA/DPP-4 inhibitors have a number of protective effects on beta cells including a reduction in apoptosis and beta cell preservation
Take Home Points

• Criteria for considering genetic testing
• Mechanism for the increased glycemic response to SUs seen in HNF1A-MODY
  – increased insulin secretory responses to SUs
  – increased insulin sensitivity
• Rapid onset, short-acting SUs (glinides) are good alternatives to long-acting SUs
• Incretin-based therapy needs to explored
References

- Fajans SS, Bell GI. MODY: History, genetics, pathophysiology and clinical decision making. Diab Care 2011;34:1878-1883.
- Bacon S, Kythar MP, Schmid J, Rizvi SR, Bonner C, Graf R, Prehn JHM, Byrne MM. Serum levels of pancreatic stone protein (PSP)/reg1A as an indicator of beta-cell apoptosis suggest an increased apoptosis rate in HNF1A-MODY carriers from the 3rd decade of life onward.
SAVE THE DATE

2013 Monogenic Diabetes Forum

July 17-20, 2013
Chicago, IL

We are excited to announce our second conference for families & individuals with monogenic diabetes.

Please join us for this interactive & educational opportunity to connect with others whose lives have been affected by genetic forms of diabetes.

More details to be announced in January 2013.