CASE REPORT

A case of hepatocyte nuclear factor-1β (TCF2) maturity onset diabetes of the young misdiagnosed as type 1 diabetes and treated unnecessarily with insulin

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Introduction

Maturity onset diabetes of the young (MODY) is a heterogeneous group of monogenic diabetes subtypes characterized by onset before 25 years of age, residual β-cell function, and autosomal dominant inheritance. In addition to diabetes, hepatocyte nuclear factor (HNF) 1β MODY (formerly MODY5) exhibits a phenotype of structural renal abnormalities, abnormal liver function tests, hyperuricemia, and abnormalities of the pancreas, genital tract, and gastrointestinal system.1,2 In contrast with HNF-1α and HNF-4α MODY patients, who are sensitive to sulfonylureas, patients with HNF-1β MODY usually require insulin.3 There is no report of the successful use of metformin or insulin sensitizers in this setting.

Case report

A 21-year-old pregnant Caucasian woman was diagnosed with type 1 diabetes at 16 years of age after presenting with diabetic ketoacidosis (DKA). She was treated with insulin; however, she reported several week periods of insulin omission, without developing ketoacidosis. Prior imaging incidentally revealed multiple renal cysts and “half a pancreas”. The patient’s two siblings and father also had renal cysts and her father had type 2 diabetes (see Fig. S1, available as Supplementary Material to this paper). After premature rupture of membranes, the patient delivered at 30 weeks. The newborn had renal cysts and transient neonatal hyperglycemia requiring insulin for the first 16 days of life.

At 23 weeks gestation, the patient’s HbA1c was 5.7% (normal range 4%–6%) and C-peptide was 0.99 nmol/L (normal range 0.26–1.32 nmol/L; Table 1). The patient was negative for glutamic acid decarboxylase 65 and islet antigen-2 (IA-2) autoantibodies. She had normal renal function (calculated glomerular filtration rate >60 mL/min per 1.73 m²) and liver function. Her diabetes had been poorly controlled prior to pregnancy (HbA1c 8.9% at 7 weeks gestation), but with continuous insulin use her HbA1c was 7.5% by 11 weeks gestation. Genetic testing (Ambry Genetics, Aliso Viejo, CA, USA; Fig. S2) revealed a novel truncation mutation in exon 3 of the transcription factor-2 (TCF2) gene (c.727C>T, p.Q243X), confirming a diagnosis of HNF-1β MODY.

At 2 weeks postpartum, metformin therapy was added to insulin. Two weeks later, insulin was discontinued. Blood glucose control remained excellent for a follow-up period of 1 year (Table 1). The patient had one modestly elevated HbA1c value at 6 months postpartum (7.4%), after she had decreased the metformin dose on her own, but her glycemic variability remained very low (15.4 mg/mL 1,5-anhydroglucitol; Table 1). Reduced glycemic variability after the transition from insulin to metformin was also demonstrated by similar mean blood glucose levels with reduced standard deviations on glucometer downloads (Fig. 1), as well as very stable glucose values on 3-day continuous glucose monitor (CGM) tracings (Fig. 2). By 1 year postpartum, after increasing the metformin dose, the patient’s HbA1c was back down to <7%.

Discussion

A MODY diagnosis was initially considered in this patient because of her periods of insulin independence and a two-generation family history of diabetes (the index case and her father). Renal cysts and pancreatic agenesis raised the suspicion of HNF-1β MODY. The patient’s initial presentation with DKA had led to a misdiagnosis of type 1 diabetes. However, diabetes autoantibodies were negative and she had intact β-cell function, with a C-peptide level of 0.99 nmol/L more than 5 years after her diagnosis. Type 2 diabetes was
Misdiagnosed case of HNF-1β MODY

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Table 1 Glucose control on different therapies

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>11 weeks gestation</th>
<th>23 weeks gestation</th>
<th>2 weeks postpartum</th>
<th>1 month postpartum</th>
<th>6 months postpartum*</th>
<th>1 year postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin + metformin</td>
<td>Metformin alone</td>
<td>Metformin alone</td>
<td>Metformin alone</td>
</tr>
<tr>
<td>Insulin (units/kg per day)</td>
<td>0.39</td>
<td>ND</td>
<td>0.38</td>
<td>–</td>
<td>500 mg am/</td>
<td>500 mg</td>
</tr>
<tr>
<td>Metformin</td>
<td>–</td>
<td>–</td>
<td>500 mg</td>
<td>1000 mg pm</td>
<td>twice daily</td>
<td>twice daily</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.4</td>
<td>5.7</td>
<td>5.9</td>
<td>5.7</td>
<td>7.4</td>
<td>6.8</td>
</tr>
<tr>
<td>C-Peptide (nmol/L)</td>
<td>ND</td>
<td>0.99</td>
<td>0.37</td>
<td>0.53</td>
<td>0.83</td>
<td>0.76</td>
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<tr>
<td>Random glucose (mmol/L)</td>
<td>6.05</td>
<td>6.38</td>
<td>5.83</td>
<td>5.33</td>
<td>10.61</td>
<td>7.97</td>
</tr>
<tr>
<td>1,5-AG (mcg/mL)</td>
<td>ND</td>
<td>ND</td>
<td>9.9</td>
<td>12.4</td>
<td>15.4</td>
<td>ND</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36.3</td>
<td>36.7</td>
<td>36.3</td>
<td>35.3</td>
<td>32.4</td>
<td>ND</td>
</tr>
</tbody>
</table>

Reference ranges are as follows: HbA1c 4–5.6%; C-peptide 0.26–1.32 nmol/L; and 1,5-anhydroglucitol (1,5-AG) 10.7–32.0 μg/mL.

*The patient decreased the metformin dose on her own.

ND, no data; BMI, body mass index.

Figure 1 Glycemic profiles from glucometer downloads on various therapies. Data show mean ± SD blood glucose levels, showcasing decreased glucose variability on metformin alone while maintaining similar mean blood glucose.

Figure 2 Twenty-four hour glucose values, as assessed by continuous glucose monitoring, on metformin.

considered unlikely because the patient did not have examination findings of insulin resistance or obesity. Genetic testing revealed a previously unreported truncation mutation in exon 3 of the TCF2 gene (c.727C>T). Because her newborn had transient neonatal diabetes requiring insulin therapy in addition to renal cysts seen on antepartum ultrasound, he also underwent genetic testing and was found to have the same TCF2 mutation.

Most patients with HNF-1α and HNF-4α MODY subtypes show marked sensitivity to low-dose sulfonylureas and demonstrate improved glycemic control after transitioning from insulin to sulfonylureas, even decades after the diagnosis. Patients with HNF-1β MODY typically require insulin, attributed to a more rapid deterioration of β-cell function, as well as reduced β-cell mass due to reduced fetal development. A meta-analysis showed that insulin therapy was used to treat 77.0% (57/74) of HNF-1β MODY patients and the interval between diabetes diagnosis and insulin initiation was <3 years in 78% of patients. Twenty-three percent of patients were treated with oral hypoglycemic drugs or diet, but the exact agent and success of therapy was not described. Another study reported a kindred in which several family members with HNF-1β MODY were treated with sulfonylureas for up to 42 years before requiring insulin.

Patients with HNF-1β MODY also have evidence of hepatic insulin resistance, with higher fasting insulin levels and reduced insulin sensitivity, as measured by Homeostatic Model Assessment (HOMA), compared with patients with HNF-1α MODY and control subjects. Altered HNF-1β-mediated regulation of the key gluconeogenic enzymes glucose-6-phosphatase or phosphoenolpyruvate carboxykinase has been proposed as a possible mechanism. Despite this, there are no...
reports to our knowledge specifically addressing successful treatment with metformin or other insulin sensitizers in patients with HNF-1β MODY.

Based on the role of hepatic insulin resistance in patients with this MODY subtype and intact β-cell function in our patient, we predicted that she would not require insulin therapy and elected to transition her from insulin to metformin. Her blood glucose control after discontinuing insulin was excellent. Furthermore, the degree of glycemic variability improved, as indicated by the increase in the patients’ 1,5-anhydroglucitol levels, with the transition from insulin to metformin. When blood glucose rises above 180 mg/dL, serum 1,5-anhydroglucitol levels fall rapidly due to inhibition of renal reabsorption; therefore, 1,5-anhydroglucitol more accurately predicts rapid changes in glycemia than HbA1c. The patient remained off insulin at last contact (2 years postpartum).

In conclusion, monogenic forms of diabetes should be suspected in patients with “atypical” manifestations or treatment requirements for diabetes. HNF-1β MODY should be suspected in patients with diabetes and renal cysts, particularly when the family history is also contributory. Genetic testing can prevent misdiagnoses with type 1 or 2 diabetes and, in turn, guide appropriate treatment. In addition, genetic testing provides the opportunity for genetic counseling for the patient, family members, and offspring. Although most patients with HNF-1β MODY require insulin, the patient described herein achieved good blood glucose control on metformin alone, even 5 years after her diagnosis. This emphasizes the value of considering metformin or insulin sensitizers in these patients if there is evidence of residual β-cell function.

Disclosure
The authors have no conflicts of interest to declare.

References

Supporting information
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Figure S1 Family tree of patient.
Figure S2 Oligonucleotide primers used in genetic sequencing.
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</tbody>
</table>
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