When to consider a diagnosis of MODY at the presentation of diabetes: aetiology matters for correct management

INTRODUCTION

A GP will often be the first health professional involved in making a diagnosis of diabetes. For adults who do not need immediate insulin treatment, a default diagnosis of type 2 diabetes is the most common outcome, but a small proportion of patients will actually have maturity-onset diabetes of the young (MODY; a type of monogenic diabetes).

MODY is inherited in an autosomal dominant pattern and estimated to account for 1–2% of all diabetes. It is estimated that around 80% of MODY patients are misdiagnosed as type 1 (T1DM) or type 2 diabetes (T2DM), and a delay of >10 years from presentation of diabetes to molecular diagnosis is frequently reported.

Two cases where genetic referral for MODY was arranged at presentation of diabetes are described.

CASE PRESENTATIONS

Case 1. An 18-year-old female presented to her GP with 2 kg weight loss, mild polydipsia, and polyuria but otherwise well. Her fasting blood glucose of 12 mmol/L was diagnostic of diabetes (normal range 3.9–5.5 mmol/L). Her mother had been diagnosed with T1DM at age 15 years and treated with insulin. Her paternal grandfather had diabetes diagnosed in his forties and was treated successfully with an oral agent for four decades.

Referral to the monogenic diabetes clinic was made for investigation. Her BMI was 17 kg/m² with no signs of insulin resistance. Her fasting blood glucose was 6.7 mmol/L, and her HbA1c was 49 mmol/mol (6.6%), and he had negative GAD antibodies. His BMI was 23 kg/m². His father had recently been diagnosed with diabetes at age 47; the diabetes was controlled with diet. The patient was referred to the monogenic diabetes clinic for consideration of MODY. A mutation in GCK was suspected and confirmed on genetic testing. The patient was reassured that he did not require any treatment and discharged. His father is waiting for genetic testing for the same mutation.

Case 2. A 24-year-old male presented to his GP with lethargy and no other symptoms. His fasting glucose was 6.7 mmol/L, his HbA1c was 49 mmol/mol (6.6%), and he had negative GAD antibodies. His BMI was 23 kg/m². His father had recently been diagnosed with diabetes at age 47; the diabetes was controlled with diet. The patient was referred to the monogenic diabetes clinic for consideration of MODY. A mutation in GCK was suspected and confirmed on genetic testing. The patient was reassured that he did not require any treatment and discharged. His father is waiting for genetic testing for the same mutation.

DIAGNOSIS

A typical patient with MODY presents with diabetes in the second to fourth decade of life and does not fit the clinical features of either T1DM or T2DM (Table 1). Patients with MODY have a subacute or incidental presentation without ketosis, unlike in T1DM. They are usually non-obese without features of insulin resistance such as dyslipidaemia, hypertension, or fatty liver, so do not resemble type 2 diabetes. Frequently, diabetes is present in at least two consecutive generations, although this is not a good discriminator from young T2DM.

HNF1A-MODY and HNF4A-MODY have very similar clinical features and result in a...


**Figure 1.** The family tree of the patient with HNF4A-MODY. The proband is marked with an arrow. Family members with diabetes are in blue: the darkest shade used for T1DM; pale blue for IGT; and stripes for HNF4A mutation carrier. DM = diabetes mellitus. IGT = impaired glucose tolerance. T1DM = type 1 diabetes mellitus.

progressive beta-cell dysfunction. Affected individuals are normoglycaemic in childhood, but develop diabetes as young adults. Patients with HNF1A-MODY have decreased renal glucose threshold, resulting in glycosuria often before diagnosis of diabetes, whereas HNF4A-MODY have hyperinsulinaemia in utero with macrosomia at birth (>4 kg) and transient neonatal hypoglycaemia. Hypoglycaemia on normal starting doses of sulphonylureas (SUs) suggests HNF1A/4A-MODY. GCK mutations cause a resetting of the glucose threshold for insulin secretion, leading to mild hyperglycaemia without a significant postprandial glucose increment. The hyperglycaemia in GCK-MODY is present throughout life, but is usually asymptomatic and detected when blood glucose is measured incidentally (for example, during pregnancy). In some cases other clinical features in combination with diabetes should prompt consideration of a unifying diagnosis, for example, HNF1B mutations are associated with renal cysts and genitourinary abnormalities and mitochondrial diabetes with deafness.

**Investigation of young adults**

Initial blood tests should include glucose, HbA1c, and beta-cell antibodies, for example, GAD antibodies, if available [Figure 2]. If glucose is >15 mmol/L, capillary ketones ought to be checked but are usually negative in MODY. C-peptide is a helpful test in those on insulin, as it indicates endogenous insulin secretion that becomes negative in T1DM after the honeymoon period (the first 1–3 years post-diagnosis). In MODY C-peptide remains in the normal range and beta-cell antibodies are negative. The lipid profile is normal. Patients with HNF1B-MODY may have elevated liver enzymes or abnormal renal function. Very low C-reactive protein (CRP) of <0.5 mg/dL is characteristic for HNF1A-MODY. Mild fasting hyperglycaemia and HbA1c <7.5% point towards GCK-MODY.

**Table 1. Comparison of main types of monogenic diabetes with type 1 and type 2 diabetes**

<table>
<thead>
<tr>
<th>Feature</th>
<th>HNF1A-/4A-MODY</th>
<th>HNF1B-MODY</th>
<th>GCK-MODY</th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age at diagnosis</td>
<td>10–45 years</td>
<td>10–45 years</td>
<td>Birth onwards</td>
<td>1–30 years</td>
<td>After 25 years</td>
</tr>
<tr>
<td>Ketonaemia/diabetic ketoacidosis</td>
<td>Very rare</td>
<td>Very rare</td>
<td>Would not be predicted to occur</td>
<td>Common</td>
<td>Rare except in ketosis-prone subtype</td>
</tr>
<tr>
<td>First-degree relative with DM</td>
<td>Reported in 50–60%</td>
<td>Around 50% [high rate of spontaneous mutations]</td>
<td>Often undiagnosed or reported as IGT/GDM</td>
<td>2–4%</td>
<td>Around 50%</td>
</tr>
<tr>
<td>Insulin resistance/obesity</td>
<td>Same as non-diabetic population</td>
<td>Same as non-diabetic population</td>
<td>Same as non-diabetic population</td>
<td>Same as non-diabetic population</td>
<td>Common</td>
</tr>
<tr>
<td>Beta-cell antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive at diagnosis in 86–93%</td>
<td>Negative</td>
</tr>
<tr>
<td>C-peptide after 3 years from diagnosis</td>
<td>Normal range</td>
<td>Normal range</td>
<td>Normal range</td>
<td>Low or undetectable in majority</td>
<td>High normal</td>
</tr>
<tr>
<td>First-line drug treatment</td>
<td>Low-dose sulphonylurea</td>
<td>Metformin if renal function allows</td>
<td>None</td>
<td>Insulin</td>
<td>Metformin</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus. GCK = glucokinase. GDM = gestational diabetes mellitus. IGT = impaired glucose tolerance. MODY = maturity-onset diabetes of the young. T1DM = type 1 diabetes. T2DM = type 2 diabetes mellitus.
Observational studies have shown that those with GCK-MODY do not develop diabetic complications and HbA1c does not change with pharmacological treatment. In any type of MODY, diabetic relatives should be offered genetic testing for the same mutation as they could also benefit from treatment changes. Unaffected first-degree family members should be offered diabetes screening. In the UK, the network of genetic diabetes nurses/monogenic diabetes clinics can offer assistance with screening of family members (www.diabetesgenes.org).

CONCLUSION
It is important to consider monogenic diabetes in young patients with non-acute presentation of diabetes, absence of beta-cell autoimmunity, and no signs of insulin resistance. Careful monitoring and rapid referral for genetic testing can establish optimal treatment and avoid insulin use.

Patient consent
The patients gave their consent for publication of this article.

Funding
A Juszczak is a Diabetes UK George Alberti Clinical Fellow. KR Owen receives funding from the Oxford NIHR Biomedical Research Centre.

Provenance
Freely submitted; externally peer reviewed.

Competing interests
The authors have declared no competing interests.

Acknowledgements
The authors would like to thank both patients for their consent.

Discuss this article
Contribute and read comments about this article: bjgp.org/letters