Making an aetiological diagnosis in diabetes: Case examples

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Article points

1. GPs and practice nurses providing diabetes care in the community should be aware of the features of MODY and other rare forms of diabetes.
2. Patients are often understandably nervous about stopping treatment after they have been diagnosed with of type 1 diabetes.
3. HNF-1α should be considered in those with young age of onset of type 2, negative antibodies and no evidence of metabolic syndrome, with sensitivity to sulphonylureas providing support.
4. The first-degree relatives of an individual with confirmed MODY have a 50 % chance of having inherited the abnormal gene.

Key words
- MODY
- Glucokinase
- Trancription factors
- Genetic tests

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In the last issue of the journal, our article focused on the features of maturity-onset diabetes of the young (MODY) and how primary care health professionals may distinguish this from the more common forms of diabetes they see. Here we present four cases in order to illustrate some exemplar patients who were misdiagnosed with atypical type 1 or 2 diabetes, but had some form of MODY.

The following case studies describe people with the most common forms of MODY (maturity-onset of diabeets of the young) caused by mutations in the HNF-1α or glucokinase genes. Initially, all cases had been assumed to have either type 1 or type 2 diabetes. Genetic testing was arranged after their clinicians noted atypical features for their diagnostic label.

Figures 1 and *2* illustrate the impact on a family, of making a genetic diagnosis. This large family (reported in Selwood & Owen, 2008) was investigated after the finding of an HNF-1α mutation in an individual previously assumed to have type 1 diabetes.

Figure 3 suggests a diagnostic pathway for identifying which patients to refer for genetic investigation. As MODY shares some features with type 1 diabetes (age of onset in the teen years or twenties, lack of insulin resistance) and others with type 2 (non-insulin dependent, frequent parental diabetes), differentiation from each of these types of diabetes must be considered separately.

There is little doubt that making a firm genetic diagnosis of MODY has benefits for individuals with the condition and their families. GPs and practice nurses providing diabetes care in the community should be aware of the features of MODY and other rare forms of diabetes and refer those not fitting neatly in the type 1 or type 2 diabetes 'boxes' for aetiological investigation.

Case Studies

Case 1

Eric, aged 27 years. Atypical type 1

Eric, originally from Germany, had been diagnosed with type 1 diabetes at the age of 20 years, on the basis of incidental glycosuria and a fasting blood glucose of 7.2mmol/l. He had no symptoms and glutamic acid decarboxylase antibodies were negative at diagnosis. He had always been treated with low dose insulin and was on 8 units of a basal insulin od (0.12U/kg) when reviewed in our clinic. HbA_{1c} was 6.7% with no hypoglycaemia. An OGTT showed a fasting plasma glucose of 6.5mmol/l and a 2-hour plasma glucose of 7.2mmol/l.

Genetic testing confirmed the diagnosis of glucokinase MODY after which his insulin was stopped. At his request he was treated with gliclazide for a few months and then treatment was discontinued. HbA_{1c} ranged from 6.5% to 6.8% regardless of treatment and his average capillary monitored readings also did not alter. His mother was subsequently found to have fasting hyperglycaemia.

The incidental finding of diabetes, negative antibodies and evidence of fasting hyperglycaemia with a small increment at 2 hours on OGTT made glucokinase MODY the most likely diagnosis. Typically, HbA_{1c} did not alter with treatment. The case also illustrates that patients are often understandably nervous about stopping treatment after they have been given a diagnosis of type 1.

Case 2

Andrew, aged 31 years. Atypical type 2

Andrew was diagnosed with diabetes at the age of 27 after presenting with thrush. Fasting blood glucose was 7.4mmol/l. BMI was 26kg/m^2 and he was normotensive with a normal lipid profile. He had no family history of diabetes and glutamic acid decarboxylase and islet cell antibodies were both negative at diagnosis.

He was commenced on glibenclamide 2.5mg daily and immediately experienced severe hypoglycaemic episodes. He continued to take glibenclamide intermittently, with HbA_{1c} of 6.4–6.9%. Later, due to hypoglycaemia, he switched to metformin, with a deterioration in HbA_{1c} to 8.4%. After 4 years of diabetes he was reviewed in secondary care and HNF-1α testing was arranged. This confirmed a diagnosis of HNF-1α MODY, presumably arising *de novo* in this patient.

Subsequently his treatment was switched to 1.25mg glibenclamide, with an HbA_{1c} of 7.3% and a reduction in reported hypoglycaemic events.

This case illustrates that HNF-1α should be considered in those with young age of onset of type 2, negative antibodies and no evidence of metabolic syndrome, with sensitivity to sulphonylureas providing support. Control typically deteriorates on metformin.

Case 3

Amy, aged 30 years. Atypical type 1

Amy was diagnosed with type 1 diabetes at the age of 20 years after developing high blood glucose levels (>15mmol/l) during an intercurrent illness following a holiday abroad. A subsequent fasting blood glucose was 9.2mmol/l. She had no family history of diabetes and was slim and

Figure 1. Pedigree of a family with HNF-1α MODY diagnosed in the authors' clinic last year

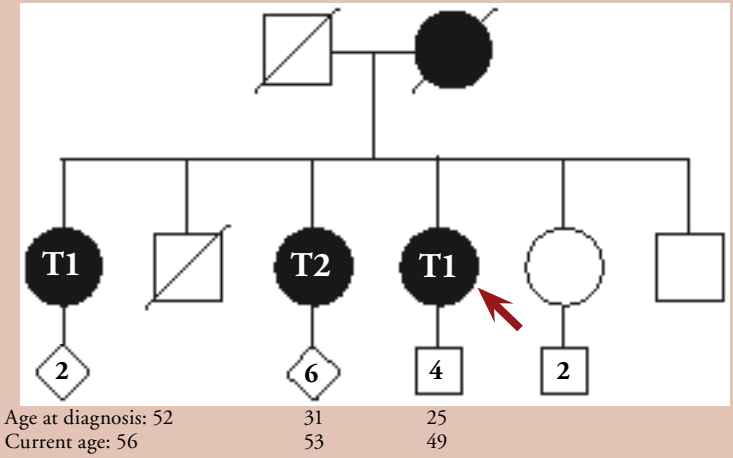


Figure 2. Pedigree of the family in *Figure 1* following genetic diagnosis

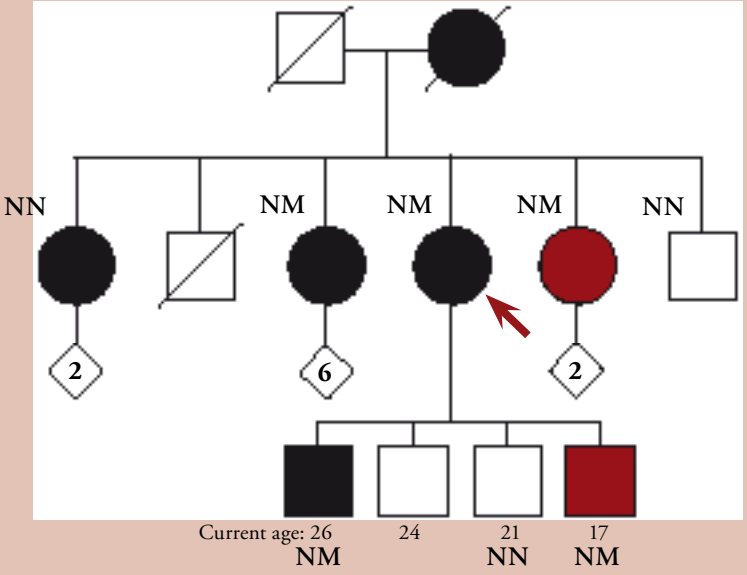
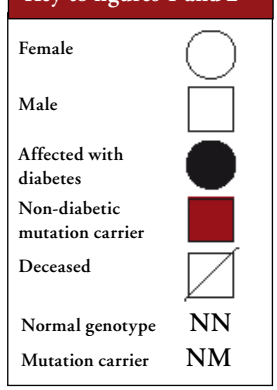


Figure 1. Before genetic diagnosis: the proband (indicated with an arrow) had been diagnosed with type 1 aged 25 and had 2 older sisters diagnosed with Type 2 aged 31 and 52.

Figure 2. Following genetic diagnosis: After identifying an HNF-1a mutation in the proband, all her siblings and 3 of her 4 sons chose to have a genetic test. HNF-1a mutations were found in one of her affected sisters, her younger unaffected sister and 2 of her sons. In addition, her eldest son was found to have unsuspected diabetes. The children of her sisters have yet to be investigated. Note that her eldest sister, who was diagnosed at a significantly older age and had other features of insulin resistance, did not carry the HNF-1a mutation. Other types of diabetes can commonly be seen in large HNF-1a pedigrees.

Key to figures 1 and 2



normotensive with no dyslipidaemia. Antibody tests were not carried out and she was treated with insulin from diagnosis.

Ten years later, she was well controlled on a relatively low dose basal–bolus regimen of 0.4U/kg with HbA_{1c} 6.3% and no hypoglycaemia. Fasting C-peptide was found to be 0.4nmol/l (normal range is 0.2–0.5nmol/l) and HNF-1α testing was requested. This confirmed a diagnosis of HNF-1α MODY and she was able to stop insulin and maintain the same HbA_{1c} on gliclazide 80mg od.

In this case the low dose of insulin with excellent control prompted C-peptide measurement. Presence of a normal C-peptide well outside the usual honeymoon period for type 1 then lead to MODY testing. The relatively high blood glucose levels at diagnosis were more in keeping with HNF-1α than glucokinase MODY, although if uncertain an OGTT could have been performed.

Case 4

Richard aged 17 years.

Unaffected family member

Richard's mother had been found to have an HNF-1α mutation after 26 years of diabetes which had been assumed to be type 1. She had multiple complications including end-stage renal failure. Her frequent ill-health had been a feature of Richard's teenage years. Diabetes testing (with OGTT) was arranged for Richard and he also decided to have a predictive genetic test after discussion with a clinical geneticist.

His OGTT was normal. (fasting plasman glucose 4.9mmol/l, 2-hour 7.1mmol/l and no glycosuria). However, he was found to be a carrier of the HNF-1α mutation. He has been advised of the risks of developing diabetes (65% by age 25 years, 95% by age 45 years, and 99% for his lifetime) and an annual OGTT, supplemented with intermittent postprandial urinalysis has been recommended. He also has been counselled that he has a 50% risk of passing the gene to his own children.

This case illustrates the issues that need to be considered in unaffected first-degree relatives – diabetes testing, genetic testing and the use of clinical genetics services. ■

Selwood MP, Owen KR (2008) Keeping Diabetes in the Family. *European Journal of Diabetes Nursing.* In press

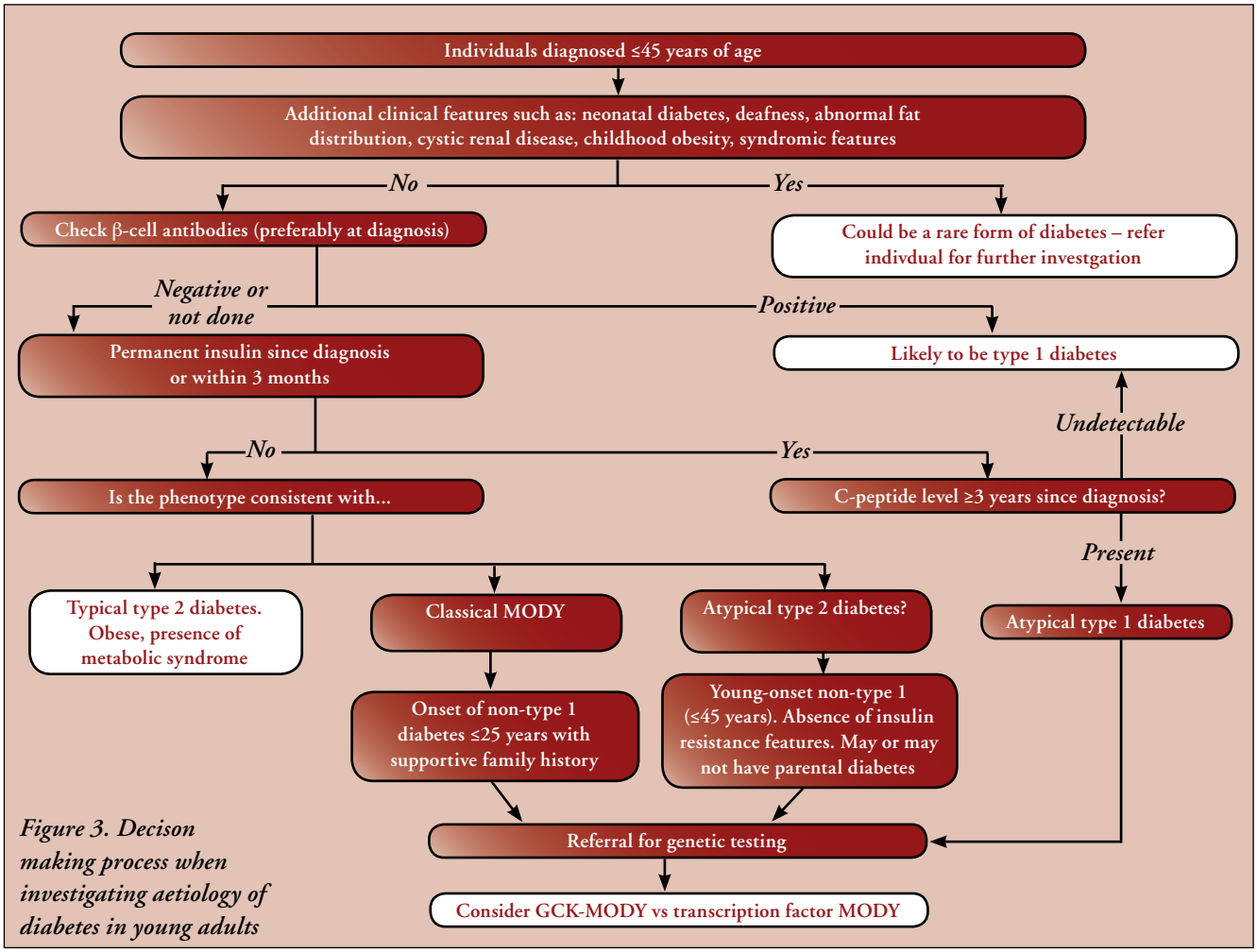


Figure 3. Decison making process when investigating aetiology of diabetes in young adults