

Making an aetiological diagnosis in diabetes: How and why?

Amanda Webster, Katharine Owen

As health professionals we are increasingly being exposed to diabetes being diagnosed in young adults – largely due to the well-documented rise in multifactorial type 2 diabetes. At the same time, there is also a greater understanding of rare inherited causes of diabetes, which also tend to arise in young adults. Healthcare professionals are often unfamiliar with the key characteristics of rare forms of diabetes so making a correct aetiological diagnosis can be difficult; but it is important to do so for optimal management and advice to family members (Shepherd et al, 2001; Hattersley and Pearson, 2006). The potential of stopping assumed lifelong insulin treatment is the most far-reaching of the possibilities associated with identifying cases of Maturity-Onset Diabetes of the Young (MODY). This article focuses on the features of MODY and how primary care health professionals may distinguish this from the more common forms of diabetes they see.

MODY is a heterogeneous group of autosomal dominantly inherited, young-onset β -cell disorders thought to affect 1–2% of people with diabetes (Shepherd et al, 2001). Using classic criteria, at least two generations are affected with a family member being diagnosed before 25 years of age (Owen and Hattersley, 2001). MODY was understood as a clinical entity for many years before the genes involved were discovered because patients presented with a young-onset, non insulin-requiring diabetes before type 2 diabetes became common in this age group (Tattersall, 1974). In the 1990s the major genes were identified, accounting for >80% of MODY cases (Owen and Hattersley, 2001).

There are two main types of MODY: those caused by mutations in the glucokinase gene and those due to mutations in transcription factors.

Glucokinase

Glucokinase (GCK) is the first enzyme in glycolysis and is termed the 'pancreatic glucose sensor' because it directly links glucose levels to initiation of insulin secretion. This made it an obvious candidate gene for diabetes and it was the first MODY gene to be described (Froguel et al, 1992; Hattersley et al, 1992).

People with GCK mutations have a lifelong, regulated, mild fasting hyperglycaemia in the range

5.5–8.5 mmol/l. The hyperglycaemia deteriorates only slightly with age and individuals are rarely symptomatic – often being diagnosed as part of routine screening. Importantly, insulin secretion remains regulated, but occurs at higher ambient blood glucose levels. Therefore those with GCK mutations do not experience large postprandial excursions in blood glucose. HbA_{1c} is almost always <8% and microvascular disease is not a reported feature (Owen and Hattersley, 2001). It is not known whether there is a higher risk of CVD because of the hyperglycaemia – this might be predicted if compared to those with impaired glucose tolerance, but as insulin resistance is not usually a feature of GCK-MODY this risk is likely to be lower than in multifactorial diabetes.

A large observational study has shown that HbA_{1c} in GCK-MODY is not altered by anti-hyperglycaemia therapy (Gill-Carey et al, 2007). HbA_{1c} was compared pre- and post-genetic diagnosis and according to treatment with insulin, oral hypoglycaemic agent or diet. No difference was observed between the three different treatments. In theory, blood glucose levels could be lowered by intensive insulin treatment but it seems doubtful that any slight improvement in HbA_{1c} would be worth the disadvantages that multiple daily injections are associated with (such as hypoglycaemia) except possibly in pregnancy.

Article points

1. MODY is a heterogeneous group of autosomal dominantly inherited, young-onset β -cell disorders.
2. There are two main types of MODY: those caused by mutations in the glucokinase gene and those due to mutations in transcription factors.
3. It may be possible to change treatment in those with MODY gene mutations to sulphonylureas or diet.
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
- Transcription factors
- Genetic tests

Amanda Webster is a Genetic Diabetes Nurse and Katharine Owen is a Clinical Lecturer, Oxford Centre for Diabetes, Endocrinology and Metabolism.

Page points

1. HbA_{1c} in GCK-MODY is not altered by hypoglycaemic treatment.
2. Individuals with GCK-MODY are frequently asymptomatic and detected during routine urinalysis.
3. Transcription factors switch other genes on and off and cause diabetes by affecting both pancreatic development and decreasing insulin secretion in the mature islet.
4. HNF-1 α is the most common form of MODY accounting for 65 % of cases in the UK.
5. HNF-4 α accounts for 5 % of MODY cases, with a similar phenotype to HNF-1 α .

Following a confirmed genetic diagnosis, the authors would recommend an annual HbA_{1c} and follow-up in primary care as the only monitoring required for GCK-MODY. It has also been successfully argued that those with GCK-MODY should not have the usual weighting applied to them by insurance companies as other kinds of diabetes (Andrew Hattersley, personal communication).

A note of caution: those with GCK mutations are not protected from developing type 2 diabetes with age and obesity (Owen and Hattersley, 2001). If HbA_{1c} rises, treatment with metformin may be required.

Identifying GCK-MODY

Individuals with GCK-MODY are frequently asymptomatic and detected during routine urinalysis. Undiagnosed family cases can mask the autosomal dominant pattern of inheritance. Fasting blood glucose is the best simple screening test as this is rarely observed to be below 5.5 mmol/l. This finding is much more likely to represent a genetic cause in younger individuals (Feigerlová E et al, 2006). Those with GCK mutations can be categorised as having one of the following: normoglycaemia; gestational diabetes; impaired fasting glucose; impaired glucose tolerance; or type 2 diabetes depending on the timing and test performed.

Transcription factor MODY

Transcription factors switch other genes on and off and can cause diabetes by affecting both pancreatic development and decreasing insulin secretion in the mature islet. Hepatocyte nuclear factors (HNF) 1 α and 4 α have their major clinical effects on the pancreatic islet, while HNF-1 β causes the development of renal anomalies as well as diabetes due to pancreatic atrophy.

HNF-1 α

HNF-1 α is the most common form of MODY accounting for 65 % of cases in the UK (Shepherd et al, 2001). These individuals have a normal fasting glucose in childhood but show increasing hyperglycaemia between the second and fourth decades of life. They present with symptomatic diabetes with progressive β -cell dysfunction and treatment requirements. Unlike people with GCK-MODY, those with HNF-1 α MODY frequently develop microvascular complications and large vessel disease (Owen and Hattersley, 2001).

A particular feature of HNF-1 α - (and HNF-4 α -) MODY is the sensitivity observed to the hypoglycaemic action of sulphonylureas. This was suspected from anecdotal reports, but was shown in a randomised

controlled trial in 2003 (Pearson et al, 2003). Those with HNF-1 α MODY had a 4-fold greater fall in fasting glucose with gliclazide than matched people with type 2 diabetes and a 5.2-fold greater response compared to metformin. The prandial glucose regulators repaglinide and nateglinide probably have a similar effect (Tuomi et al, 2006).

This suggested that people with HNF-1 α MODY placed directly on insulin at diagnosis could be transferred to a sulphonylurea. This was shown in a small case series to be possible even after many years and is now standard practice (Shepherd et al, 2003). However the progressive β -cell dysfunction that characterises HNF-1 α means that insulin is often required at some point, in some earlier than others (Shepherd et al, 2001). For those who have already progressed through standard treatment modalities, insulin withdrawal should not be attempted.

Those with HNF-1 α MODY also have a low renal threshold for glucose and glycosuria is observed following a carbohydrate load, often prior to formal development of diabetes (Stride et al, 2005). This feature can be usefully employed in screening of family members, particularly children.

HNF-4 α

HNF-4 α accounts for 5 % of MODY cases, with a similar phenotype to HNF-1 α (Pearson et al, 2005). Recently a case of neonatal hypoglycaemia was noted in a family with HNF-4 α and further investigation showed that paradoxically those with HNF-4 α have intra-uterine and neonatal hyperinsulinism, macrosomia and neonatal hypoglycaemia, resolving within the first few months of life (Pearson et al, 2007). Pregnancies where the foetus may be affected by HNF-4 α should be carefully monitored for these complications. Subsequently, mutation carriers develop typical MODY diabetes. The mechanism of this is as yet unknown, but it provides a useful method of differentiating between HNF-1 α and HNF-4 α , otherwise both genes need to be screened to exclude a diagnosis of transcription factor MODY.

Identifying HNF-1 α or 4 α

Many of these families represent the classically described MODY phenotype of an autosomal dominant family history and onset of non-insulin requiring diabetes ≤ 25 years. Such typical MODY pedigrees are relatively easy to identify and would now have diagnostic testing arranged if seen in secondary care.

However, a significant proportion of individuals are misdiagnosed initially. Those presenting with

osmotic symptoms in the second or third decade of life can seem to be an early presentation of type 1 and are treated with insulin from diagnosis, while later age of presentation would be assumed to be type 2. Approximately one-third of cases of HNF-1 α present from 25–45 years of age, so the diagnosis needs to be considered in the 10–15% of people with type 2 diabetes who also present in this age group (Shepherd et al, 2001).

Differentiating from type 1 diabetes

Where the differential diagnosis is type 1 diabetes, it is most important not to delay insulin treatment in someone with a risk of metabolic decompensation – if in doubt treat as type 1 diabetes and re-examine the diagnosis later. In people with moderate hyperglycaemia (<15mmol/l), mild symptoms and no ketones a trial of sulphonylurea therapy is probably warranted with close follow-up. If this is very effective – causing hypoglycaemia – then a diagnosis of MODY seems likely. In other cases, negative β -cell antibodies at diagnosis, a parental history of diabetes or evidence of circulating C-peptide outside the ‘honeymoon period’ (see later) are all triggers to consider a diagnosis of MODY.

Differentiating from type 2 diabetes

This requires a different approach. It has been shown previously that in those diagnosed between 25 and 45 years of age, absence of insulin resistance features is the best discriminator (Owen et al, 2002). Parental history of diabetes is poorly specific as many with young-onset type 2 diabetes have a strong family history. The authors suggest that diagnosis of MODY is considered in those with onset of type 2 diabetes under 45 years of age, negative β -cell antibodies and absence of the metabolic syndrome. In one study, 2 cases out of 15 screened were found to have an HNF-1 α based on these criteria (Owen et al, 2003).

Differentiating from GCK-MODY

Although these 2 forms of MODY would seem to have a quite different phenotype, distinguishing can be difficult, particularly in the early years of HNF-1 α MODY if control is good. The pattern of diabetes in other family members can be a clue, and the OGTT can be very useful in this respect: those with transcription factor MODY can have normal fasting glucose, but will have a large 2-hour increment (5mmol/l), while those with GCK-MODY always demonstrate fasting hyperglycaemia (>5.5mmol/l), but have a low 2-hour increment (\leq 4mmol/l; Stride et al, 2002).

HNF 1 β

HNF-1 β mutations are relatively uncommon. These individuals are not sensitive to sulphonylureas and require insulin as β -cell function deteriorates (Pearson et al, 2004). HNF-1 β mutations should be suspected when there is history of non-diabetic (cystic) renal disease or other structural anomalies and young-adult diabetes.

Other MODY genes

Mutations in the transcription factors Insulin Promotor Factor-1 and NeuroD1 (Stride and Hattersley, 2002) and the enzyme CEL (Raeder et al, 2006) have also been found to cause MODY, but these have been in a very limited number of families so far. They are not offered for routine diagnostic testing.

Of those families who fit MODY criteria, 10–15% do not have mutations of the known MODY genes. Finding these additional genes is an area of active research.

The diagnostic armoury

Two of the most useful tests are not genetic at all, but are helpful in distinguishing those who are likely to have autoimmune diabetes. β -cell antibodies are a marker for autoimmune diabetes. Although they are not invariably present, if positive, they confirm this diagnosis. Glutamic acid decarboxylase (GAD) antibodies are the most useful, although others may be available according to the testing centre. They are most likely to be present close to diagnosis and, as they are a relatively cheap test, should be performed at diagnosis in those diagnosed \leq 45 years. Apart from excluding a diagnosis of MODY, if present they also identify a group with apparent type 2 diabetes who progress rapidly to insulin treatment (Turner et al, 1997).

C-peptide is secreted along with insulin and is thus a marker for endogenous insulin production that can be measured even in those taking insulin. In those assumed to have type 1 diabetes, continued presence of C-peptide is a sign that this initial diagnosis may have been incorrect. While this could be measured systematically in all those with apparent type 1 diabetes, clinical indicators that endogenous insulin could be present include; an unusually low replacement dose of insulin (<0.5 unit/kg), periods of omitting insulin treatment (without metabolic decompensation occurring) or extended periods of normal HbA_{1c} (without hypoglycaemia).

Blood for C-peptide needs to be taken at the hospital phlebotomy department as it is unstable in prolonged transport. This is also relatively cheap, although it is

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not widely used in primary care. However, there is no point performing C-peptide at diagnosis because some degree of residual β -cell function remains for 1–3 years post-onset of type 1 diabetes ('honeymoon period').

Absence of β -cell antibodies and continued presence of C-peptide in a patient thought to have type 1 diabetes helps narrow down those who should have formal genetic testing. Formal genetic testing for MODY is available for GCK, HNF-1 α , HNF-4 α and HNF-1 β . The cost of this testing usually means that it is arranged through secondary care services. The diagnostic testing lab will also advise on which test is appropriate.

Keeping it in the family

One change from usual practice in diabetes is the need to consider screening and testing of family members. The first-degree relatives of an individual with confirmed MODY have a 50% chance of having inherited the abnormal gene. For those who already have diabetes, the genetic change can be easily (and cheaply) confirmed by the diagnostic testing lab. First-degree relatives without known diabetes should initially be offered a diabetes test.

In GCK-MODY, fasting blood glucose will usually indicate whether they are affected. As the hyperglycaemia observed is lifelong, testing should only have to be performed once and a genetic test offered to all those with fasting glucose >5.5 mmol/l.

The situation is more complicated in transcription factor MODY, as β -cell function declines with time. In addition, fasting glucose may remain normal while post-challenge levels reach diagnostic criteria and so an annual OGTT is the preferred test. Appropriate testing also needs to be considered in children, at least from the age of 10, which will often require input from the paediatric department. In younger children from HNF-1 α families, the presence of postprandial glycosuria is an extremely useful non-invasive test which, if positive, can then be followed by formal blood sugar testing (Stride et al, 2005). This can also be useful in older children and adults in between formal OGTT.

Some at-risk individuals prefer to progress straight to a genetic test to see if they carry the abnormal gene (predictive test). This requires careful consideration and counselling (Shepherd et al, 2001) and for those with less experience in this area, we would recommend clinical genetics input or the use of a Genetic Diabetes Nurse. In particular this is a problem area in children who might later regret a decision influenced by parents. However, for older adults such testing can obviate the need for annual

diabetes checks. Unaffected mutation carriers can only be advised that they are likely (>98%) to develop diabetes in their lifetime, 95% by age 45, and they continue to require an annual OGTT.

Genetic diabetes nurses

This is an initiative from the Peninsula Medical School (www.diabetesgenes.org). Experienced DSNs, each based within a different region in the UK, receive training about monogenic diabetes and genetic testing and aid their local diabetes teams in identifying and following up MODY families. Regular study days ensure that skills are maintained and case histories and management experience are shared with the group. A selection of case studies to illustrate the diagnoses will be published in the next issue of the journal.

Who to refer to secondary care for testing

We are entering an era where the emphasis on diabetes care, particularly of type 2 diabetes, but also of well controlled type 1 diabetes is being concentrated in primary care. This means it is important to identify which individuals would benefit from a secondary care assessment and follow-up. In the next issue of the journal a flow chart will be presented showing a suggested investigation pathway for young adults with diabetes, using β -cell antibodies and C-peptide as simple investigations prior to genetic referral. The first stage is always to look for additional clinical features associated with diabetes as these could suggest a different genetic or syndromic diabetes (ADA, 2004).

We recommend that those suspected of having genetic diabetes should have secondary care contact to ensure that appropriate diagnostic testing, management and screening of family members is arranged. For those with GCK-MODY, once a positive genetic test has been confirmed, long-term secondary care follow-up is not required. However the progressive nature of transcription factor MODY and the need for close attention to family members means we recommend that these individuals are followed up in secondary care.

Conclusion

There is little doubt that making a firm genetic diagnosis of MODY has benefits for both 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. ■

The next issue of the journal will contain exemplar case studies showing misdiagnoses of type 1 and 2 diabetes as well as an investigation pathway.