Are you confident your patients have the correct diagnosis?

Maggie Shepherd

Misdiagnosis of monogenic diabetes is common and can lead to years of unnecessary insulin treatment. Aids to diagnosis are available and can differentiate between maturity onset diabetes of the young and type 1 diabetes; however, these are seldom used routinely in clinical practice. This article provides details of these aids and illustrates their use in ensuring the correct diagnosis in a case study, highlighting their importance in terms of both appropriate treatment and follow-up of family members.

Ensuring that the correct type of diabetes is diagnosed is not always simple. Although type 1 and type 2 diabetes account for the vast majority of diabetes cases, there are many other types that are frequently misclassified, leading to inappropriate treatment and management (Royal College of General Practitioners and NHS Diabetes, 2011). The proportion of diabetes classifications that are incorrect has been estimated to range from 5% in an audit of five GP practices (Royal College of General Practitioners and NHS Diabetes, 2011) to 14.5% in an audit of 100 UK-wide practices (de Lusignan et al, 2010). However, work conducted by the author and colleagues suggest that these figures may be underestimates, as 37% of patients within south-west GP practices classified as type 1 were still producing insulin 5 years post-diagnosis and 10% classified as type 2 were insulin-deficient, at least raising the question of whether the diagnosis was correct (Shields, unpublished).

Maturity onset diabetes of the young (MODY) is estimated to account for 1% of diabetes equating to approximately 26 000 cases predicted in the UK; however, recognition of monogenic diabetes varies widely (Shields et al, 2010). Misclassification is extremely common with around 80% of those with monogenic diabetes initially misdiagnosed as having type 1 or young onset type 2 diabetes (Shields et al, 2010). In the molecular genetics laboratory at the Royal Devon and Exeter NHS Foundation Trust, 140 (35.5%) of 405 patients referred for genetic testing and subsequently identified with HNF1-alpha MODY were initially misdiagnosed with type 1 diabetes and inappropriately treated with insulin (Besser et al, 2011). This suggests widespread unfamiliarity with the condition and a failure to identify the majority of cases. The minimum UK prevalence is reported as approximately 6000 cases, but the exact prevalence will remain unknown until population-based studies are performed (Shields et al, 2010). With genetic

Article points

1. The misdiagnosis of maturity onset diabetes of the young (MODY) is common and can lead to unnecessary insulin treatment.
2. This paper highlights three aids to differentiate between MODY and type 1 diabetes: the online MODY probability calculator, urinary C-peptide creatinine ratio and pancreatic antibody testing.
3. The author concludes that using a series of simple and low-cost steps can highlight those most likely to have a monogenic cause of diabetes and benefit from genetic testing.

Key words

- Diagnosis
- Genetic testing
- Maturity onset diabetes of the young
- Monogenic diabetes

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diagnosis confirming 2570 cases of MODY in the UK to date, the majority of cases still remain misdiagnosed or undiagnosed. Misclassification leads to inappropriate clinical management, potential negative psychological effects and sub-optimal use of resources, as well as the unnecessary use of insulin treatment and inappropriate family follow-up (Shepherd et al, 2010; Stone et al, 2010).

Diagnosing the specific type of diabetes can be complex, especially in young people, and genetic testing is expensive so it is important to assess which patients should be tested (Shields et al, 2012). This article aims to outline three strategies to aid differential diagnosis and increase the identification of individuals with monogenic diabetes.

Characteristics of MODY

MODY is characterised by three key features:

- A young age of onset (less than 25 years in at least one family member).
- Autosomal dominant family history (with diabetes present in a parent).
- Non-insulin dependent diabetes (Stride and Hattersley, 2002; although often these patients are mistakenly treated with insulin from diagnosis so this feature may be overlooked).

There are additional characteristics associated with the different genes causing MODY which can also be helpful in identifying a likely genetic cause. Those with HNF1-alpha MODY are sensitive to low doses of sulphonylureas and also have a low renal threshold for glucose (Pearson et al, 2003; Stride et al, 2005). Those with glucokinase MODY have mild stable hyperglycaemia with a fasting glucose of typically 5.5–8 mmol/L (Froguel et al, 1993; Page et al, 1995; Stride et al, 2002), and HbA_{1c} levels at between 40 mmol/mol (5.8%) and 60 mmol/mol (7.6%); they do not require treatment (Stride and Hattersley, 2002). People with HNF4-alpha MODY may be born with neonatal hypoglycaemia and macrosomia, and people with HNF1-beta MODY often have renal cysts in addition to diabetes (Bingham and Hattersley, 2004; Pearson et al, 2007).

Aids to differential diagnosis

People diagnosed under the age of 25 years who are slim and present with "typical symptoms" are often assumed to have type 1 diabetes and commence insulin treatment. The ability to determine which patients should be considered for genetic testing is important for diagnosis, management and family screening. The aids below can be used to identify those most likely to benefit from genetic testing.

MODY probability calculator

An online clinical prediction model (or "MODY probability calculator") is now available and can be used to calculate an individual's probability of having MODY (Shields et al, 2012). It uses a weighted combination of factors (age at diagnosis, BMI, HbA_{1c}, sex, family history, current age and insulin or oral hypoglycaemic treatment) to differentiate between type 1, type 2 and MODY (Shields et al, 2012).

The model provides a more reliable prediction of MODY compared with predictions based on traditional clinical criteria alone, such as age of onset, family history and non-insulin dependence. The model is accessible to all via the website www.diabetesgenes.org and is simple to use, requiring only eight fields of basic clinical information to be completed for a probability of MODY to be calculated. It is advisable that the model be used in all Caucasian patients diagnosed with diabetes under the age of 35 years when considering differential diagnosis (Shields et al, 2012). Optional data can also be added if the results of the urinary C-peptide creatinine ratio (UCPCR) and pancreatic antibodies are available.

Urinary C-peptide creatinine ratio

The vast majority of people with type 1 diabetes will become insulin-deficient within the first few years of developing the condition, although insulin production is not routinely measured (Palmer et al, 2004). A urine test, incorporating the measurement of C-peptide, an indicator of endogenous insulin

Page points

1. In the case study presented, Tom was diagnosed with "type 1" diabetes at the age of 17 years and started on a basal–bolus regimen.
2. Six years later, Tom's original diagnosis was questioned by his new diabetes team owing to his family history.
3. Upon further investigation, Tom was predicted to have a 1 in 13.9 or 7.2% chance chance of having maturity onset diabetes of the young (MODY), as indicated by the MODY probability calculator.

production, is considered both practical and affordable, at £10 per test. UCPCR is a convenient single-sample test of beta cell function, which is stable for 3 days in boric acid preservative, allowing samples to be posted (McDonald et al, 2009). UCPCR can detect patients with possible monogenic diabetes as it shows discrimination between HNF1-alpha or HNF4-alpha MODY and type 1 diabetes of more than 5 years' duration (Besser et al, 2011). Postprandial UCPCR is markedly lower in individuals with type 1 diabetes than those with HNF1-alpha or HNF4-alpha MODY, and a cut-off UCPCR of >0.2 nmol/mmol discriminates HNF1-alpha or HNF4-alpha MODY from type 1 diabetes with 97% sensitivity and 96% specificity (Besser et al, 2011).

Finding a UCPCR >0.2 nmol/mmol outside the "honeymoon period" would suggest that further investigation concerning the cause of diabetes may be appropriate. However, this test is less useful closer to diagnosis as C-peptide is likely to persist in those with type 1 diabetes for the first few months and occasionally years after diagnosis (Palmer et al, 2004). In cases where there is an affected parent, UCPCR testing could therefore be performed in this parent if the child has only recently been diagnosed.

Pancreatic autoantibodies

The measurement of pancreatic autoantibodies can also be used to aid differential diagnosis (McDonald et al, 2011). Type 1 diabetes is characterised by the presence of pancreatic islet autoantibodies in approximately 80% of adults and 96% of children close to diagnosis indicating an autoimmune cause of the condition (Sabbah et al, 2000). In contrast, the prevalence of glutamic acid decarboxylase (GAD) or insulinoma antigen 2 (IA2) antibodies, or both, in those with MODY is the same as for control participants at <1% (McDonald et al, 2011). Autoantibodies may be the most helpful test close to diagnosis to differentiate between type 1 and MODY but can still be present even after many years (Borg et al, 2000). Testing for GAD and IA2 antibodies is available via the laboratory at the Royal Devon and Exeter NHS Foundation Trust for £20, making this an easily affordable test, which increases the accuracy of diagnosis in those with a condition requiring lifelong treatment.

Case study

Tom was diagnosed at the age of 17 years with "typical" symptoms of polyuria, polydipsia and lethargy. He presented with a blood glucose of 21 mmol/L, ketonuria and an HbA_{1c} of 86 mmol/mol (10%). He was of normal weight with a BMI of 23 kg/m^2. A diagnosis of type 1 diabetes was presumed and he was immediately started on a basal–bolus insulin regimen.

Six years later, Tom moved to a new area and the original diagnosis was questioned by his new diabetes team. Tom was being treated with 0.4 unit/kg/day of insulin and achieving HbA_{1c} levels of 48–68 mmol/mol despite admitting to omitting his insulin on a number of occasions. He had an autosomal dominant family history of diabetes with a father who had been diagnosed at 48 years with "type 2" diabetes and treated with metformin. His father was of normal weight with a BMI of 24 kg/m^2. Tom's paternal grandmother, now deceased, had been diagnosed with diabetes in her 60s and was treated with a combination of insulin and oral agents (see *Figure 1*). Tom's diabetes team entered his details into the online MODY probability calculator, which predicted a 1 in 13.9 or 7.2% chance of him having MODY (see *Figure 2*). As the team were aware that Tom had missed a number of his insulin injections without an obvious decline in glycaemic control and that there was evidence of an autosomal dominant inheritance with a slim parent diagnosed at a relatively early age with "type 2 diabetes", they felt he warranted further investigation. As a positive diagnosis would have implications for his treatment and other family members, the team decided to organise a postprandial UCPCR sample to decide if further testing would be appropriate. This indicated endogenous insulin production 6 years post-diagnosis with a UCPCR of

1.7 nmol/mmol. Consequently, pancreatic antibodies were taken for GAD and IA2, which were both negative. Adding this piece of data to the probability calculator recalculated his probability of having MODY as 1 in 1.9 or 53%. A sample was then sent for molecular genetic testing, which confirmed HNF1-alpha MODY. Tom was subsequently able to stop his insulin injections and was transferred to just 40 mg of gliclazide once a day, achieving excellent control on this treatment (HbA_{1c}, 48 mmol/mol [6.5%]).

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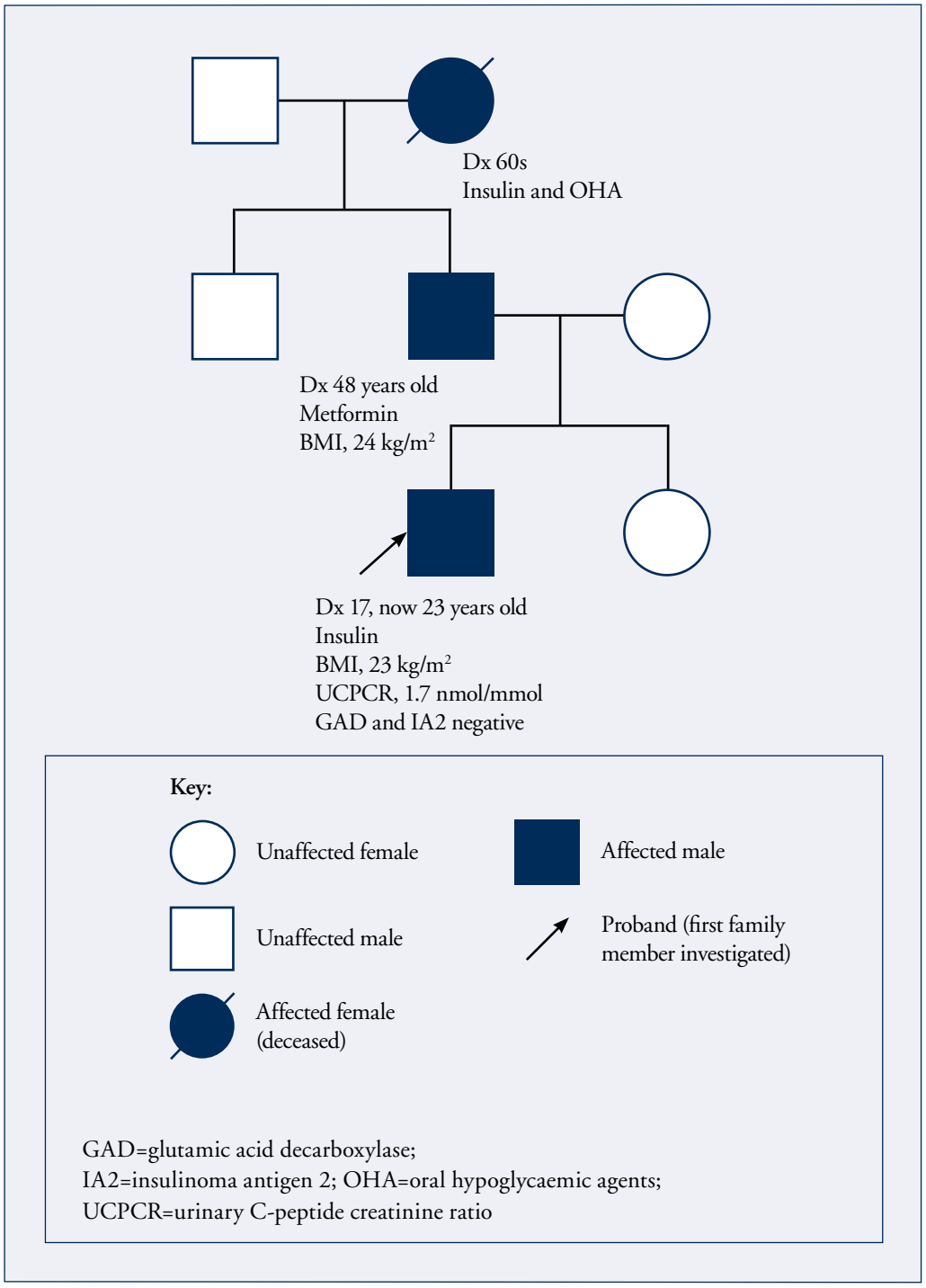

Figure 1. Tom's family tree, including treatment prior to the genetic test.

"Although the type of diabetes an individual has at diagnosis may not always be clear, the possibility of monogenic diabetes should be considered in those diagnosed below the age of 25 years who have an affected parent."

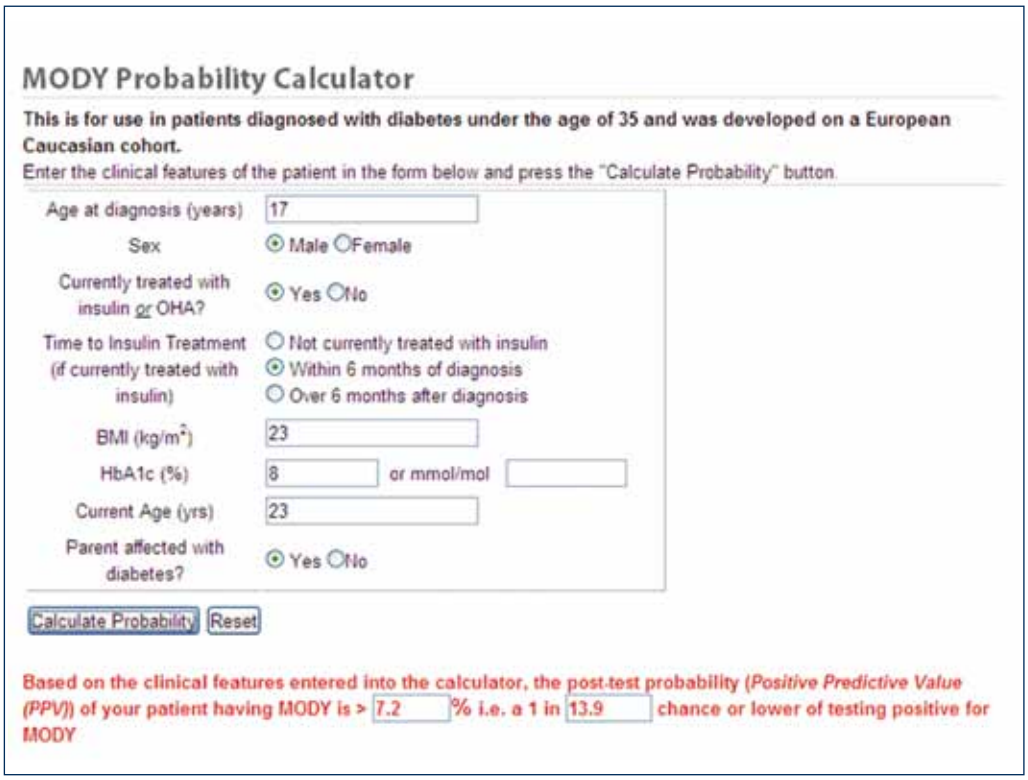

Figure 2. The online MODY probability calculator complete with Tom's details.

Tom was delighted to be able to stop his insulin injections and achieve better control on oral agents. His father was also tested and HNF1-alpha MODY confirmed, he transferred from metformin to gliclazide 80 mg twice daily with a good outcome. Identifying HNF1-alpha MODY allowed appropriate follow-up of other family members and the possibility of predictive genetic testing was discussed with Tom's sister and paternal uncle.

Conclusion

Although the type of diabetes an individual has at diagnosis may not always be clear, the possibility of monogenic diabetes should be considered in those diagnosed below the age of 25 years who have an affected parent. Genetic testing is expensive and is only appropriate for individuals meeting the criteria for testing. Being aware of the key characteristics of MODY (an early age of diagnosis, less than 25 years in at least one family member; diabetes in a parent; and non-insulin dependence or continued insulin production) may raise the possibility of an alternative diagnosis. In these cases, using a series of simple and low-cost steps can highlight those most likely to have a monogenic cause of diabetes and benefit from genetic testing. Further information on monogenic diabetes, the MODY probability calculator, UCPCR and pancreatic antibody testing can be found on www.diabetesgenes.org. ■

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