Maturity onset diabetes of the young

Key facts

- Maturity onset diabetes of the young (MODY) is an autosomal dominant condition, and a form of monogenic diabetes.
- It is estimated to cause between 2% and 4% of all cases of diabetes in those younger than 30 years old at diagnosis.
- Most individuals with MODY are misclassified as having type 1 and type 2 diabetes for many years before receiving a definitive genetic diagnosis.
- It is important to diagnose MODY, as treatment depends on the gene affected and is different to the standard care provided to those with other diabetes types.
- The genetic basis of MODY has been identified for approximately 87% of cases.

Clinical features

HNF1A-MODY (Hepatocyte nuclear factor 1 alpha) and *HNF4A*-MODY (Hepatocyte nuclear factor 4 alpha)

- Variants in the *HNF1A* gene account for between 30% and 70% of all MODY cases; variants in the *HNF4A* gene account for between 5% and 10% of all cases.
- The condition typically presents in adolescence or early adulthood.
- Sensitivity to sulphonylureas, which may result in hypoglycaemia. However, this makes low doses of sulphonylureas an excellent first line therapy for those affected.
- With time, some individuals will eventually require insulin therapy.
- As in cases of type 1 and type 2 diabetes, people with *HNF1A*- or *HNF4A*-MODY are at risk of microvascular and macrovascular complications.
- History of macrosomia at birth, and neonatal hypoglycaemia in individuals with *HNF4A*-MODY.

GCK-MODY (Glucokinase gene)

- *GCK*-MODY is a genetic cause of hyperglycaemia that seldom requires treatment.
- Complications are rare, even when no treatment is given. This has led to the suggestion that people with *GCK*-MODY be 'declassified' as having diabetes.
- Variants inactivating the GCK enzyme raise the threshold for glucose-stimulated insulin secretion, but insulin secretion remains regulated.
- Typically, affected individuals have lifelong, stable fasting hyperglycaemia (fasting plasma glucose 5.5-8 mmol/L) and develop virtually no complications.
- *GCK*-MODY is often detected incidentally, for example, in pregnant women who appear to have gestational diabetes on oral glucose tolerance testing (characteristically fasting hyperglycaemia, but a small two hour increment).
- As *GCK*-MODY is asymptomatic, there may be no known family history of diabetes, even though it is autosomal dominantly inherited.

- Pregnant women with *GCK*-MODY may require treatment to reduce blood glucose levels if fetal macrosomia is detected.

HNF1B-MODY (Hepatocyte nuclear factor 1 beta)

- Also known as renal cysts and diabetes syndrome, *HNF1B*-MODY results in diabetes with multisystem features, and accounts for between 5% and 10% of MODY cases.
- Clinical features include malformations of the genitourinary system (renal cysts are common, but other renal developmental abnormalities can present), pancreatic exocrine failure, hypomagnesaemia, elevated serum aminotransferases and genital abnormalities. Learning difficulties are characteristically present with whole gene deletions.
- There is a 50% rate of a de novo variant (arising for the first time in the affected individual, having not been present in the parents), often with whole gene deletions. Therefore, a family history may not always be present.
- Affected individuals are not sensitive to sulfonylureas and usually require insulin, as diabetes results from pancreatic atrophy or structural defects.

Diagnosis

- The typical clinical features that were first used to identify MODY have remained largely unchanged, although supplementing with biomarker tests provides the greatest sensitivity to detect cases.
- Common features include:
  - young age of onset (younger than 45 years; frequently younger than 25 years);
  - autosomal dominant family history of diabetes;
  - absence of pancreatic auto-antibodies (GAD-65, IA-2 and ZnT8 antibodies negative);
  - preserved C-peptide measurement (marker of endogenous beta-cell function);
  - atypical features for type 2 diabetes (for example, relatively lean body mass); and
  - atypical features for type 1 diabetes (for example, managed off insulin initially).
- Those with suspected MODY can be stratified further by using an online probability calculator, however this has not been validated for use in those diagnosed above 35 years of age, or in those of non-white ethnicity. MODY should not be discounted in any ethnicity, and cases have been detected in virtually all ethnic groups, although the segregation of MODY from young onset type 2 diabetes in some ethnic groups may prove challenging.

Genetic basis and genetic testing

- People with suspected MODY should be referred to a diabetes specialist team or a genetic diabetes nurse who can take informed consent and carry out a simple blood test from which DNA can be extracted.
- In the UK, all genetic testing for MODY is carried out in a centralised molecular genetics laboratory in Exeter.
- In cases with a very strong and clear clinical phenotype, an individual gene can be selected for testing. When the phenotype is unclear or mixed, it may be more effective to select a panel of genes for testing, which may uncover less common MODY types.

Clinical management

- Optimal management depends on the subtype of MODY, as described above, making the genetic test particularly important in ensuring affected individuals receive the most effective treatment.
- In people with a genetic diagnosis of MODY (usually made via a family history) and without a current diagnosis of diabetes, an annual blood test (HbA1c or fasting glucose) is recommended to detect the onset of diabetes, as individuals may be asymptomatic in the early stages.

Direction to further reading and guidelines

- Shields BM, Shepherd M, Hudson M, McDonald TJ, Colclough K, Peters J, et al. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. Diabetes Care. 2017 Aug;40(8):1017–25.
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- Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. Diabetologia. 2012;55(5):1265–72.
- Ellard S, Lango Allen H, De Franco E, Flanagan SE, Hysenaj G, Colclough K, et al. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. Diabetologia. Heidelberg; 2013 15;56(9):1958–63.
- Misra S & Owen K. Genetics of monogenic diabetes: present clinical challeneges. Current diabetes reports. 2018;18:141

This information is intended for educational use and was current in September 2019. For clinical management, it is recommended that local guidelines and protocols are used.

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