Monogenic diabetes

Does making the diagnosis matter?

CECILIA CHI MB BS, BSc(Med)Hons
JENNY E. GUNTON MB BS, FRACP, PhD

Monogenic diabetes – diabetes due to a single gene mutation – is often misdiagnosed as type 1 or type 2 diabetes. The significant differences in treatment needs and responses in patients with the various types of monogenic diabetes emphasise the need for an accurate diagnosis.

Key points

- **Monogenic diabetes (maturity onset diabetes in the young; MODY) should be considered as a diagnosis in the young person diagnosed with 'atypical' type 1 or type 2 diabetes.**
- **Insulin may be ceased in patients with certain types of MODY and be replaced by sulfonylurea monotherapy, often to the great relief of patients.**
- **Monogenic diabetes due to glucokinase (*GCK*) gene mutation usually remains mild and nonprogressive and, unless more significant glucose elevation develops (e.g. glucose levels greater than 11 mmol/L postprandially), may be controlled by lifestyle measures alone.**
- **Patients with gestational diabetes should be referred for specialist review as treatment of patients with diabetes due to *GCK* mutation may adversely affect the fetus if the fetus has inherited this mutation.**

ENDOCRINOLOGY TODAY 2016; 5(3): 32-35

Dr Chi is an Endocrinology Advanced Trainee in the Department of Endocrinology and Diabetes, Westmead Hospital. Professor Gunton is the Director of the Centre for Diabetes, Obesity and Endocrinology Research at the Westmead Institute for Medical Research, The University of Sydney, Sydney, NSW.

The incidence of diabetes is increasing in Australia, and diabetes is increasingly being detected in a younger population. Patients are typically classified as having type 1 or type 2 diabetes and the potential diagnosis of monogenic diabetes is often missed. Monogenic diabetes, often referred to as maturity onset diabetes of the young or MODY, is diabetes due to a single genetic mutation, mostly caused by heterozygous mutations. This is thought to account for 2 to 5% of all cases of diabetes.

Making the correct diagnosis of monogenic diabetes is important as it allows patients to be informed about the likely progression of their diabetes and to discuss risks for their children. Importantly, there are significant differences in treatment needs and responses for patients with different types of monogenic diabetes. Patients with monogenic diabetes who had been misdiagnosed as having type 1 diabetes (T1D) may sometimes be able to cease insulin therapy and their diabetes be successfully managed with oral hypoglycaemic agents alone.

Clues to monogenic diabetes

Monogenic diabetes occurs due to different genetic mutations (Table).[1-4] Patients with monogenic diabetes are usually, but not always, diagnosed with diabetes at a young age (i.e. under 25 years). They lack autoantibodies and may not require insulin until later in life.[5] Depending on the affected gene, patients may:

- have mild disease (e.g. glucokinase [*GCK*] gene mutation)
- have increased risk of microvascular and macrovascular complications (e.g. hepatocyte nuclear factor [HNF] 1-alpha gene [*HNF1A*] or HNF 4-alpha [*HNF4A*] mutations), or
- be at particular risk of renal problems (e.g. HNF 1-beta [*HNF1B*] mutation).

The six classic MODY genes all have autosomal dominant inheritance but incomplete penetrance, meaning that fewer than 100% of people who inherit the mutation display diabetes.

Features that suggest monogenic diabetes in patients misdiagnosed with T1D include:

- diabetes presenting before the age of 6 months; most people with onset before this age do not have T1D
- lack of islet cell autoantibodies (although this is more common in Asian ethnic groups with true T1D)
- continuing low insulin requirements and C-peptide positivity for many years after diagnosis
- a strong family history of diabetes across generations on one side of the family.

Features that suggest monogenic diabetes in patients misdiagnosed with type 2 diabetes (T2D) include:

- lack of obesity (presence of obesity does not exclude the diagnosis)
- lack of features of insulin resistance in the setting of high insulin doses
- a strong family history of diabetes across generations of the family, especially with early onset in some members
- high fasting glucose level with a small increment after a glucose/carbohydrate load (*GCK* mutation)
- diabetes diagnosed before 6 months of age (*GCK* mutation)
- inappropriate glycosuria when blood glucose has been well controlled over the same period (*HNF1A* mutation)
- renal cysts or renal or genital malformations (*HNF1B* mutation)
- persistent hypomagnesaemia (*HNF1B* mutation)
- history of neonatal hypoglycaemia (*HNF4A* mutation).

Common types of monogenic diabetes and implications for diagnosis and treatment

HNF1A mutation (MODY 3)

Overall, the most common cause of MODY is mutation in the *HNF1A* gene. *HNF1A* is a transactivator of the insulin gene in β-cells. In MODY 3, insulin secretion is reduced in response to a glucose load. The two-hour glucose level during a glucose tolerance test (GTT) is usually greater than 6 mmol/L higher than the fasting level. Patients with MODY 3 are at increased risk of microvascular and macrovascular complications of diabetes.

HNF1A mutations also cause a lower renal threshold for glucose loss. As a result, carriers of *HNF1A* mutations have detectable glycosuria in the setting of reasonable blood glucose levels (BGLs) or even before diabetes onset. Sodium glucose cotransporter 2 (SGLT2) treatment also induces glycosuria, so screening for glycosuria needs to be performed at least 48 hours after the patient's last medication dose.

Stopping insulin therapy

Interestingly, patients with MODY 3 are usually insulin sensitive and have a marked sensitivity to sulfonylureas. Sulfonylureas can augment the secretion of insulin in response to glucose, returning fasting and postprandial glucose levels to normal. A randomised crossover trial involving patients with T2D and *HNF1A* mutations compared the effects of metformin and gliclazide. Patients with *HNF1A* mutations were found to have a fivefold greater response to gliclazide than to metformin, whereas patients with T2D had no difference in response.[6]

Once the *HNF1A* mutation has been diagnosed, most patients who have been on insulin in the short to medium term can be switched from insulin to sulfonylurea monotherapy. Glycaemic control has been achieved with sulfonylurea monotherapy for as long as three decades in some patients;[7,8] however, most patients will eventually require insulin therapy.

HNF4A mutation (MODY 1)

HNF4A mutation also leads to decreased insulin secretion in response to a glucose load. *HNF4A* positively regulates *HNF1A* action. Unique to this mutation, patients may paradoxically present with neonatal hyperinsulinism. This is associated with macrosomia and neonatal hypoglycaemia.[9] During infancy, insulin levels normalise. Later, patients progress to diabetes, with onset during adolescence being common.

Elevated postprandial or two-hour glucose levels on a GTT are the common early defects. The secretory defect is progressive and patients have increased risk for microvascular and macrovascular complications. As for MODY 3, patients with MODY 1 are often responsive to sulfonylureas; however, insulin is more often needed over time.

HNF1B mutation (MODY 5)

Similarly, diabetes due to *HNF1B* mutations features a secretory defect, leading to postprandial hyperglycaemia with the risk of disease complications. As *HNF1B* also regulates gene expression in the kidney and genitourinary tract, patients may present with renal cysts, renal dysplasia, glomerulocystic disease, epididymal cysts, bicornuate uterus or atresia of the vas deferens. *HNF1B* mutations cause renal cysts and diabetes (RCAD) syndrome. Patients often have hyperuricaemia and may develop early-onset gout. There is increased renal loss of magnesium. The presence of renal cysts or anomalies and diabetes, especially in patients who also have high serum urate or low serum magnesium levels, should prompt consideration of genetic testing.

GCK mutation (MODY 2)

The second most common cause of monogenic diabetes is *GCK* gene mutation (MODY 2). Glucokinase is an enzyme that catalyses glucose phosphorylation and enables β-cells of the pancreas to 'sense' and respond appropriately to the BGL. Mutations (either homozygous or heterozygous) result in a higher glucose threshold for insulin secretion. Once the threshold is achieved, insulin secretion is normal, so the two-hour increments in BGL during an oral GTT are small

Table. Clues to the diagnosis of monogenic diabetes compared with type 1 and type 2 diabetes[1-4]

Type of diabetes	Gene	Frequency	Age of onset	Features of diabetes	Obesity more common?	Islet autoantibodies	Increased complications risk?	Other clinical features
Monogenic diabetes (2 to 5% of all cases of diabetes)	*HNF1A*	52-65% of all cases of MODY	Teenager to young adult	Postprandial hyperglycaemia with progressive disease	No	No	Yes	Increased cardiovascular mortality More common in European populations
	GCK	15-32% of all cases of MODY	Birth (often detected later)	Fasting hyperglycaemia Small increment in blood glucose after oral load	No	No	Lower risk	More common in African Americans and minority ethnic populations but also relatively common in Caucasian groups
	HNF4A	3-10% of all cases of MODY	Teenager to young adult	Postprandial hyperglycaemia with progressive disease	No	No	Yes	
	HNF1B	3% of all cases of MODY	Teenager to young adult	Postprandial hyperglycaemia with progressive disease	No	No	Yes	Renal cysts and diabetes (RCAD) syndrome Renal and genital developmental abnormalities Pancreatic atrophy Liver and biliary dysfunction Hypomagnesaemia
	Other	<1% of all cases of MODY	Newborn to young adult	Severe diabetes	No	No	?	Variable, e.g. exocrine dysfunction
T1D		5-10% of all cases of diabetes	>6 months to any age Common <30 years	Hyperglycaemia with diabetic ketoacidosis risk	No	Yes	N/A	Associated with other autoimmune conditions
T2D		>90% of all cases of diabetes	Any age	Progressive disease	Yes	No	N/A	None

Abbreviations: HNF= hepatocyte nuclear factor; GCK= glucokinase; MODY = maturity onset diabetes of the young; T1D = type 1 diabetes; T2D = type 2 diabetes.

(less than 4.6 mmol/L). As patients have a nonprogressive mild hyperglycaemia, development of microvascular or macrovascular complications is rare. Unless more significant glucose elevation develops (e.g. glucose levels greater than 11 mmol/L postprandially), MODY 2 may be controlled by lifestyle measures alone. Abnormal glucose levels may be present from birth. Diabetes diagnosed at less than 6 months of age is usually a genetic form of diabetes.

Considerations in pregnancy

Women with any form of MODY are often first diagnosed during pregnancy. In MODY 2 (*GCK* mutation), fasting glucose is greater than 5.1 mmol/L and the increment in glucose during the GTT is usually less than 4.6 mmol/L, and often only 1.5 to 3 mmol/L.

In MODY 2, if both the fetus and mother have *GCK* mutations, the fetus will only secrete insulin at a higher maternal glucose. Thus, if the mother is treated to normal, this decreases the glucose signal to fetal β-cells, reducing fetal insulin secretion and increasing the risk of a growth retarded/small for gestational age baby.[10,11] In an unaffected fetus with a mother with MODY 2, tight maternal glycaemic control is needed to avoid excess fetal insulin secretion and macrosomia.

As mentioned above, offspring with *HNF4A* mutations (MODY 1) may hypersecrete insulin and be macrosomic.

Ultrasound in pregnancy showing fetal genitourinary abnormalities (e.g. single kidney) and maternal diabetes, especially if the mother has renal anomalies, should prompt consideration of *HNF1B* mutation (MODY 5).

In some cases, opportunistic genetic diagnosis during early fetal life (when chorionic villus sampling or amniocentesis is performed for another indication) has resulted in gestational diabetes mellitus treatment being changed.[12] However, as genetic testing may be invasive, costly and limited in availability, referring patients to an experienced endocrinologist and/or genetics team would help them in making informed decisions and providing informed consent.

Other genes with mutations responsible for monogenic diabetes

Other genes that are known to cause MODY are:

- *PDX1* (pancreatic and duodenal homeobox 1, causing MODY 4)
- *TCF2* (hepatic transcription factor 2; MODY 5)
- *NEUROD1* (neuronal differentiation 1; MODY 6)
- *KLF11* (Kruppel-like factor 11; MODY 7)
- *CEL* (carboxyl ester lipase; MODY 8 or diabetes-pancreatic exocrine dysfunction syndrome)
- *PAX4* (MODY 9)
- *INS* (the insulin gene; MODY 10)
- *BLK* (MODY 11)
- *KCNJ11* (inwardly rectifying potassium channel; MODY 13).

There is no MODY 12.

A helpful website with a MODY probability calculator is available on the UK DiabetesGenes website (http://www.diabetesgenes.org).

Summary

Monogenic diabetes is often missed as patients are frequently misdiagnosed as having T1D or T2D. It should be considered especially in patients diagnosed with T2D who are not obese or who have inappropriate glycosuria, and patients diagnosed with T1D with no features of autoimmunity. People with renal or genitourinary anomalies are more likely to have *HNF1B* mutations. Making the correct diagnosis will help inform patients of their likely prognosis and excitingly enable some patients, to their great relief, to stop insulin therapy and switch to sulfonylurea monotherapy.

As genetic testing may be costly and is limited in availability, referral of patients to an experienced clinician would help them in making informed decisions and providing informed consent when undergoing genetic testing. **ET**

References

1. Anik A, Catli G, Abaci A, Bober E. Maturity-onset diabetes of the young (MODY): an update. J Pediatr Endocrinol Metab 2015; 28: 251-263.
2. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). Diabetes Metab Syndr Obes 2012; 5: 101-108.
3. Kavvoura FK, Owen KR. Maturity onset diabetes of the young: clinical characteristics, diagnosis and management. Pediatr Endocrinol Rev 2012; 10: 234-242.
4. Kropff J, Selwood MP, McCarthy MI, Farmer AJ, Owen KR. Prevalence of monogenic diabetes in young adults: a community-based, cross-sectional study in Oxfordshire, UK. Diabetologia 2011; 54: 1261-1263.
5. Rubio-Cabezas O, Hattersley AT, Njolstad PR, et al. ISPAD clinical practice consensus guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2014; 15 Suppl 20: 47-64.
6. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet 2003; 362: 1275-1281.
7. Fajans SS, Brown MB. Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. Diabetes Care 1993; 16: 1254-1261.
8. Bacon S, Kyithar MP, Rizvi SR, et al. Successful maintenance on sulfonylurea therapy and low diabetes complication rates in a HNF1A-MODY cohort. Diabet Med 2015; doi: 10.1111/dme.12992. [Epub ahead of print].
9. Pearson ER, Boj SF, Steele AM, Barrett T, et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. PLoS Med 2007; 4: e118.
10. Spyer G, Hattersley AT, Sykes JE, Sturley RH, MacLeod KM. Influence of maternal and fetal glucokinase mutations in gestational diabetes. Am J Obst Gynecol 2001; 185: 240-241.
11. Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S. Mutations in the glucokinase gene of the fetus result in reduced birth weight. Nat Genet 1998; 19: 268-270.
12. Chakera AJ, Carleton VL, Ellard S, et al. Antenatal diagnosis of fetal genotype determines if maternal hyperglycemia due to a glucokinase mutation requires treatment. Diabetes Care 2012; 35: 1832-1834.

COMPETING INTERESTS. None.