

Detecting monogenic diabetes in the paediatric clinic: Three case studies highlighting diagnosis

Maggie Shepherd, Julie Cropper

Although type 1 diabetes accounts for most cases of diabetes presenting in childhood, skills and knowledge enabling paediatric teams to confidently identify other forms of diabetes are clearly required. Ensuring correct diagnosis by recognising cases of “non-type 1” diabetes in children and young people is crucial as it has implications for treatment and follow up. This article highlights three cases of diabetes presenting in children with features suggesting potential monogenic causes of diabetes. The cases include hepatocyte nuclear factor 1-alpha maturity onset diabetes of the young (MODY), glucokinase MODY and KCNJ11 neonatal diabetes. The implications of the correct diagnosis are also discussed.

Although the vast majority of children and young people with diabetes in the UK have type 1 diabetes, an increasing number are diagnosed with type 2 diabetes, recently reported at around 2% (Diabetes UK, 2012). Other causes of childhood diabetes include neonatal diabetes, maturity-onset diabetes of the young (MODY), secondary diabetes and syndromic diabetes (Royal College of Paediatrics and Child Health, 2009). In Caucasian children in the UK the prevalence of MODY and type 2 diabetes are similar (Ehtisham et al, 2004). However, the correct classification of paediatric diabetes can be challenging; there may be confusion between the presenting features of different types of diabetes, which can lead to erroneous diagnosis (Ehtisham et al, 2004).

Monogenic diabetes results from mutations in single genes that regulate beta-cell function, but is commonly misdiagnosed as type 1 or type 2 diabetes (Lambert et al, 2003; Shepherd, 2008), and only a minority of estimated cases have been confirmed by genetic testing in the UK (Shields et al, 2010). Individuals with

monogenic diabetes do not need to be insulin resistant or obese to develop diabetes (Ehtisham et al, 2004).

Guidelines have been developed to highlight when a diagnosis of monogenic diabetes should be considered in children (*Box 1*) and when to suspect that a diagnosis of type 1 or type 2 diabetes is not correct (Hattersley et al, 2006). The approaches are separated into:

- Those diagnosed less than 6 months of age (indicating neonatal diabetes).

Box 1. When to consider monogenic diabetes in children.

- Diabetes diagnosed below the age of 6 months (neonatal diabetes)
- Family history of diabetes with an affected parent
- Mild fasting hyperglycaemia (5.2–8 mmol/L), especially if young or familial
- Diabetes associated with extra-pancreatic features

From Hattersley et al (2006).

Citation: Shepherd M, Cropper J (2013) Detecting monogenic diabetes in the paediatric clinic: Three case studies highlighting diagnosis. *Diabetes Care for Children & Young People* 2: 19–23

Article points

1. Most children and young people presenting with diabetes have type 1 diabetes; however, it is important to consider other forms of diabetes, such as monogenic diabetes.
2. Monogenic diabetes results from mutations in single genes that regulate beta-cell function, and includes hepatocyte nuclear factor 1-alpha maturity-onset diabetes of the young (MODY), glucokinase MODY and KCNJ11 neonatal diabetes.
3. Urinary C-peptide creatinine ratio, pancreatic antibody testing and use of the MODY probability calculator can be used to detect individuals requiring genetic testing.

Key words

- Maturity-onset diabetes of the young
- Monogenic diabetes

Authors

Maggie Shepherd, Honorary Reader, University of Exeter Medical School, and Senior Research Fellow, NIHR Exeter Clinical Research Facility, Royal Devon and Exeter NHS Foundation Trust; Julie Cropper, Children's Diabetes Nurse Specialist and Genetic Diabetes Nurse, Leeds Teaching Hospitals NHS Trust.

“MODY is typically characterised by diabetes being passed down from an affected parent from one generation to the next, with diagnosis aged <25 years in at least one family member and non-insulin-dependent diabetes.”

- Those who may otherwise have been labelled as having type 1 diabetes (where a child with diabetes has an affected parent and evidence of endogenous insulin production outside the honeymoon period).
- Those who may otherwise have been labelled as having type 2 diabetes who are not markedly obese, do not have acanthosis nigricans or other evidence of insulin resistance and are from a low-prevalence ethnic group (Hattersley et al, 2006).

These guidelines should be used in the clinical setting to identify cases of atypical type 1 diabetes or type 2 diabetes, which warrant further investigation.

This article discusses three cases of paediatric diabetes and illustrates why monogenic diabetes was suspected and the impact the correct diagnosis had on individual management and family follow up.

Case 1

Clare presented at the age of 12 years with polyuria, polydipsia and a blood glucose of 15 mmol/L. She was presumed to have type 1 diabetes and was started on insulin. Three years later she was on a basal–bolus insulin regimen of 0.4 units/kg/day; her HbA_{1c} was 7.1% (54 mmol/mol), her height 1.65 m and weight 53 kg. Monogenic diabetes was not considered initially, but was later suspected because of her family history of diabetes, which spanned four generations (*Figure 1*). Clare’s mother, Gloria, was diagnosed with type 1 diabetes at the age of 16 years, and had also been treated with insulin from diagnosis. Gloria was 35, had a BMI of 25 kg/m² and was on a basal–bolus insulin regimen of 1 unit/kg/day; she had poor control, with an HbA_{1c} of 10.9% (96 mmol/mol). Gloria’s father, paternal grandmother and two siblings also had diabetes. Gloria’s younger sister was labelled as having type 2 diabetes, while her other family members were considered as having type 1 diabetes; her father died from a myocardial infarction aged 42.

Three years after her diagnosis of type 1 diabetes, Clare’s postprandial urinary C-peptide creatinine ratio (UCPCR) was 3.6 nmol/mmol, indicating significant endogenous insulin production; she was found negative for glutamic acid decarboxylase (GAD) and insulinoma antigen-2 (IA2) antibodies. These results, along with the four-generation family history of diabetes, supported a likely monogenic cause; the online MODY probability calculator (www.diabetesgenes.org; Shields et al, 2012) predicted a one in two chance of Clare having MODY. Genetic testing for hepatocyte nuclear factor 1-alpha (HNF1A) was recommended, as this is the commonest cause of UK MODY, and this confirmed an HNF1A mutation in both Clare and Gloria. As a consequence, Clare stopped insulin and was transferred to gliclazide 20 mg once-daily; her home blood glucose monitoring is now between 4–7 mmol/L and her most recent HbA_{1c} was 6.5% (48 mmol/mol).

Twenty years after Gloria’s diagnosis of type 1 diabetes, her UCPCR was 1.7 nmol/mmol, again indicating continued insulin production. Gloria was also able to stop insulin and was transferred

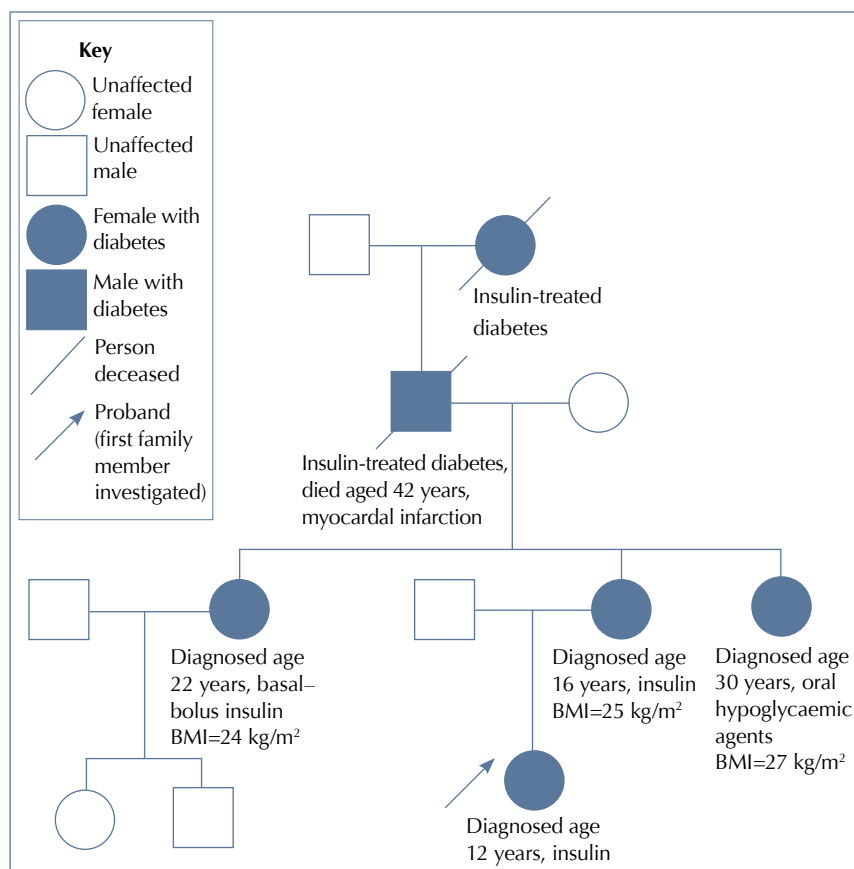


Figure 1. Clare’s family tree spanning four generations illustrating the family members affected by diabetes.

Box 2. Key characteristics of HNF1A MODY.

- Diabetes diagnosed <25 years in at least one family member
- A parent also affected with diabetes and often a grandparent (indicating autosomal dominant inheritance)
- Non-insulin dependence or, if insulin treated, presence of C-peptide outside the “honeymoon period”
- Sensitivity to sulphonylureas (likely to have hypoglycaemia on standard doses)
- Low renal threshold for glucose

HNF1A=hepatocyte nuclear factor 1-alpha; MODY=maturity-onset diabetes of the young.

to gliclazide 80 mg twice-daily, which improved her glycaemic control, with an HbA_{1c} of 8.8% (73 mmol/mol). Gloria’s siblings are currently undergoing genetic testing.

HNF1A MODY is typically characterised by diabetes being passed down from an affected parent from one generation to the next, with diagnosis aged <25 years in at least one family member and non-insulin-dependent diabetes, although these individuals may be treated with insulin (Stride and Hattersley, 2002) (Box 2). Glycosuria and sensitivity to sulphonylureas are also key features of HNF1A MODY (Pearson et al, 2003; Stride et al, 2005), and myocardial infarction at a young age has been previously reported (Steele et al, 2010). In Clare’s case, the family history of individuals diagnosed with diabetes aged <25 years spanning four generations prompted consideration of a monogenic cause. This was further supported by evidence of insulin production outside the “honeymoon period”, which is atypical in type 1 diabetes, and a negative result for pancreatic antibodies indicating a non-autoimmune cause.

Case 2

Joe was identified with incidental hyperglycaemia when he was 8 years of age following admission for a tonsillectomy; his blood glucose was 7.4 mmol/L and HbA_{1c} was 6.6% (49 mmol/mol). An oral glucose tolerance test indicated a fasting blood glucose of 6.0 mmol/L and a

2-hour postprandial value of 8.9 mmol/L. Joe’s mother had been diagnosed with gestational diabetes during both her pregnancies, and had been treated with insulin; her father had been found to have raised blood glucose during a routine occupational health screen 20 years previously. Joe’s maternal grandfather was treated with 500 mg metformin twice-daily and always maintained HbA_{1c} levels between 6.3–

Box 3. Key characteristics of GCK MODY.

- Fasting blood glucose typically 5.2–8 mmol/L
- HbA_{1c} typically 5.8–7.6% (40–60 mmol/mol)
- Often detected incidentally, such as during a routine medical or pregnancy screening
- Inherited from an affected parent – on testing, one parent will have mildly raised fasting glucose, which may or may not have been previously identified
- Small increment (<3.5 mmol/L) in oral glucose tolerance test

GCK=mutation in the glucokinase gene; MODY=maturity-onset diabetes of the young.

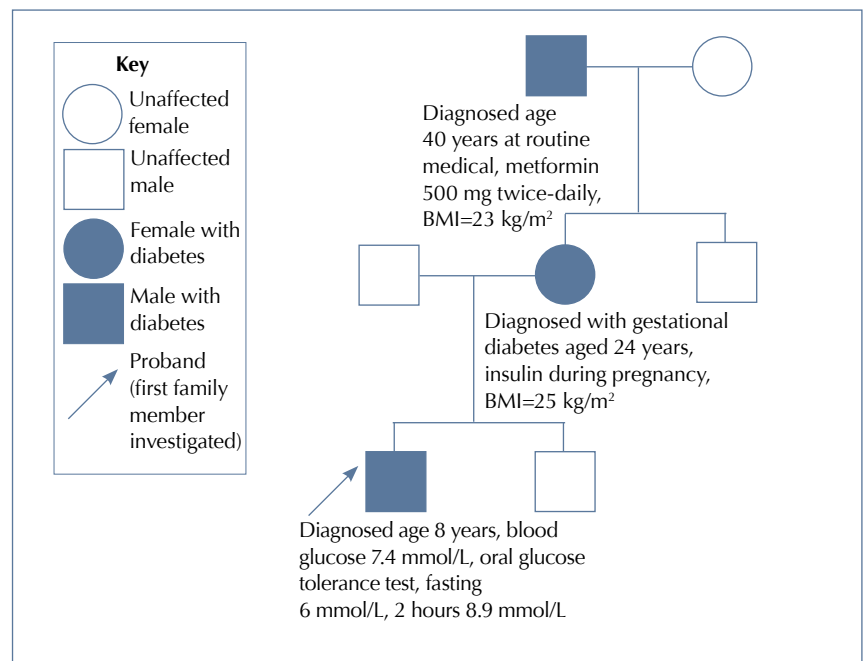


Figure 2. Joe’s family tree indicating incidental findings of mild hyperglycaemia in three generations.

7.6% (45–60 mmol/mol). Joe’s paediatric team recognised this atypical presentation of diabetes with mild hyperglycaemia in three generations (Figure 2). Samples were sent for GAD and IA2 pancreatic antibodies, which were negative. Genetic testing confirmed that Joe had GCK MODY (MODY caused by a mutation in the glucokinase gene), which allayed concerns about the possibility of early-onset type 1 diabetes; Joe was discharged with no treatment. His mother and maternal grandfather were also confirmed with GCK MODY; his grandfather was able to stop his metformin with no deterioration in glycaemic control.

GCK MODY is characterised by a mild, stable hyperglycaemia (Stride and Hattersley, 2002), fasting blood glucose typically between 5.2–8 mmol/L (Froguel et al, 1993; Page et al, 1995; Stride and Hattersley, 2002) and an HbA_{1c} between 5.8–7.6% (40–60 mmol/mol).

Box 4. Key characteristics of KCNJ11 neonatal diabetes.

- Diabetes diagnosed before 6 months of age
- Some mutations in *KCNJ11* are associated with developmental delay and muscle weakness
- Most cases can be successfully treated with glibenclamide
- Most cases are spontaneous, meaning there will be no family history of diabetes

KCNJ11=mutation in the *KCNJ11* gene.

It is often detected on routine screening and requires no treatment outside pregnancy (Stride and Hattersley, 2002; Box 3).

Case 3

Steven was diagnosed with diabetes aged 3 months. He presented with diabetic ketoacidosis (blood glucose 29 mmol/L), and was immediately started on insulin. There was no family history of diabetes (Figure 3), and his HbA_{1c} at diagnosis was 13.0% (119 mmol/mol). He was later transferred to an insulin pump as his glycaemic control was problematic. Aged 9 years he moved areas and his new diabetes team queried his type 1 diagnosis because of his age at presentation. A blood sample was sent for genetic testing for the genes causing neonatal diabetes, and a mutation in *KCNJ11* (the gene that encodes Kir6.2) was identified. This confirmed a diagnosis of KCNJ11 neonatal diabetes. Both of Steven’s parents were tested and neither were found to have a mutation in the *KCNJ11* gene indicating the mutation had arisen *de novo* (or spontaneously) in Steven. Consequently, Steven was able to stop his insulin and transfer to glibenclamide 10 mg twice-daily with improvement in glycaemic control (HbA_{1c} 5.8%; 40 mmol/mol).

KCNJ11 neonatal diabetes is typically diagnosed below 6 months of age (Hattersley and Ashcroft, 2005; Box 4). Isolated diabetes is the most common clinical picture accounting for 80% of cases of KCNJ11, although neurological features are present in around 20% (Hattersley and Ashcroft, 2005). Most cases can be successfully treated with high doses of glibenclamide (Pearson et al, 2006), which can also lead to some improvements in neurological function (Slingerland et al, 2006; 2008). The age of diagnosis alone in this case should have prompted swift referral for genetic testing. There are a number of different genes known to cause neonatal diabetes, and genetic testing is offered free of charge for individuals diagnosed with diabetes aged <9 months.

Discussion

Although type 1 diabetes accounts for most cases of diabetes diagnosed in childhood or adolescence, recognition of monogenic diabetes

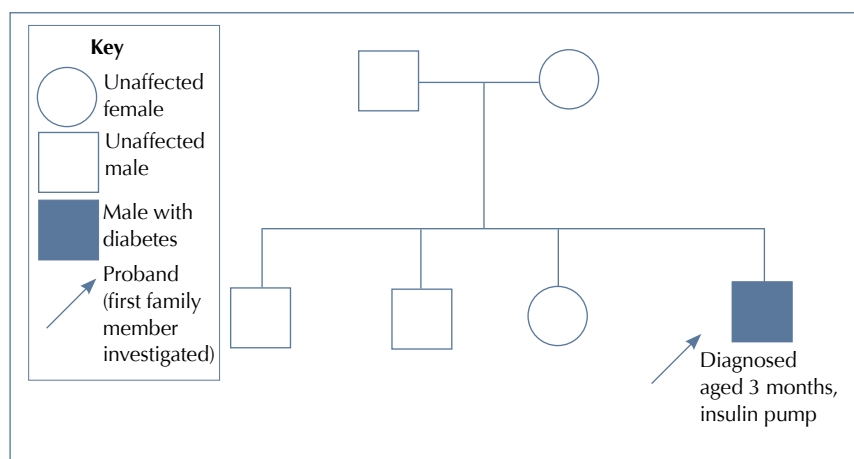


Figure 3. Steven’s family tree indicating no family history of diabetes.

is important because of the lifelong impact on treatment. Correct diagnosis also has implications for the follow up and counselling of family members. The ISPAD Clinical Practice Consensus Guidelines for the diagnosis and management of monogenic diabetes in children and adolescents (Hattersley et al, 2006) can help to identify those with atypical type 1 or type 2 diabetes, who may benefit from additional tests to aid differential diagnosis. There is strong evidence to support the need to ensure aetiological classification of diabetes in all young people irrespective of their presentation by use of antibody and C-peptide measurement (Dabelea et al, 2012).

The need for a systematic series of tests to aid diagnosis should be emphasised, and UCPCR, pancreatic antibody testing and the MODY probability calculator can all be used to further define those most appropriate to progress to genetic testing. Increasing awareness of possible differential diagnosis of diabetes in children and young people is important. There are other forms of monogenic diabetes that are not discussed in this article, which may also present in childhood and adolescence; further information, and details of your local genetic diabetes nurse and regional monogenic diabetes clinic (where available) can be found at www.diabetesgenes.org. ■

Maggie Shepherd is supported by the NIHR Exeter Clinical Research Facility.

Dabelea D, Mayer-Davis EJ, Andrews JS et al (2012) Clinical evolution of beta cell function in youth with diabetes: the SEARCH for Diabetes in Youth study. *Diabetologia* **55**: 3359–68

Diabetes UK (2012) *Diabetes in the UK 2012: Key Statistics on Diabetes*. Available at: <http://bit.ly/Uu13Vz> (accessed 28.1.13)

Ehtisham S, Hattersley AT, Dunger DB et al (2004) First UK survey of paediatric type 2 diabetes and MODY. *Arch Dis Child* **89**: 526–9

Froguel P, Zouali H, Vionnet N et al (1993) Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. *N Engl J Med* **328**: 697–702

Hattersley AT, Ashcroft FM (2005) Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. *Diabetes* **54**: 2503–13

Hattersley A, Bruining J, Shield J et al (2006) ISPAD Clinical Practice Consensus Guidelines 2006-2007. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* **7**: 352–60

Lambert AP, Ellard S, Allen LI et al (2003) Identifying hepatic nuclear factor 1-alpha mutations in children and young adults with a clinical diagnosis of type 1 diabetes. *Diabetes Care* **26**: 333–7

Page RC, Hattersley AT, Levy JC et al (1995) Clinical characteristics of subjects with a missense mutation in glucokinase. *Diabet Med* **12**: 209–17

Pearson ER, Strakey B, Powell RJ et al (2003) Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* **362**: 1275–81

Pearson ER, Flecthner I, Njolstad PR et al (2006) Switching from insulin to sulphonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* **355**: 467–77

Royal College of Paediatrics and Child Health (2009) *Growing up with Diabetes: Children and young people with diabetes in England*. RCPCH, London. Available at: <http://bit.ly/15bAv11> (accessed 13.02.13)

Shepherd M (2008) Impact of misdiagnosis in *HNFI1A*: A case study. *Journal of Diabetes Nursing* **12**: 14–8

Shields BM, Hicks S, Shepherd MH et al (2010) Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* **53**: 2504–8

Shields BM, McDonald TJ, Ellard S et al (2012) The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia* **55**: 1265–72

Slingerland AS, Nuboer R, Hadders-Algra M et al (2006) Improved motor development and good long-term glycaemic control with sulphonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the *KCNJ11* gene. *Diabetologia* **49**: 2559–63

Slingerland AS, Hurks W, Noordam K et al (2008) Sulphonylurea therapy improves cognition in a patient with the V59M *KCNJ11* mutation. *Diabet Med* **25**: 277–81

Steele AM, Shields BM, Shepherd M et al (2010) Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the *HNFI1A* gene. *Diabet Med* **27**: 157–61

Stride A, Hattersley AT (2002) Different genes, different diabetes: Lessons from maturity-onset diabetes of the young. *Ann Med* **34**: 207–16

Stride A, Ellard S, Clark P et al (2005) Beta-cell dysfunction, insulin sensitivity and glycosuria precede diabetes in hepatocyte nuclear factor-1 mutation carriers. *Diabetes Care* **28**: 1751–6

“There is strong evidence to support the need to ensure aetiological classification of diabetes in all young people irrespective of their presentation by use of antibody and c-peptide measurement.”