Diagnosing monogenic diabetes in clinical practice

Does your patient have monogenic diabetes or some other form of diabetes? In clinical practice, this may not be immediately apparent – and some cases can present a diagnostic dilemma for the diabetes multidisciplinary team.

Here, using case examples provided by contributors to this question and examples derived from Oxford, Professor Katharine Owen explores the best ways in which to approach such dilemmas.

Key considerations are highlighted, and practical advice is given in relation to diagnostic parameters.

**Introduction**

The following cases illustrate some common scenarios that may arise in paediatric or adult clinics. Here is some advice from 10 years experience running a monogenic diabetes clinic:

- Aim to get the aetiology right from diagnosis of diabetes. While we all feel great after taking a patient with maturity-onset diabetes of the young (MODY) off insulin, mostly those individuals would have preferred not to have taken it in the first place (see the patient’s perspective in a previous article¹).

Work with local GPs to ensure that young patients are systematically reviewed at diagnosis and use tools such as antibodies to identify those who do not fit neatly in the diagnostic boxes. See Figure 1 for a suggested diagnostic protocol.

- Genetic testing to confirm clinical suspicion is best practice and where available should be offered to patients and families. Making important treatment decisions such as withdrawing insulin is much more straightforward with a firm diagnostic test result. If you are not sure, then refer to the nearest monogenic diabetes clinic or involve a genetic diabetes nurse (www.diabetesgenes.org/content/genetic-diabetes-nurses-locations-map).

**Figure 1. Investigation of new diabetes diagnosed before 30 years of age. (NB: for those presenting acutely treat as per usual practice with insulin. Check aetiology later)**

BMI = body mass index; BP = blood pressure; BW = birthweight; CRP = C-reactive protein; DKA = diabetic ketoacidosis; FBG = fasting blood glucose; FH = family history; GAD = glutamate decarboxylase; GCK = glucokinase; GDM = gestational diabetes; GU = genito-urinary; HNF = hepatocyte nuclear factor; IA-2 = islet-antigen-2; IGT = impaired glucose tolerance; MODY = maturity-onset diabetes of the young; NAFLD = non-alcoholic fatty liver disease; PCOS = polycystic ovarian syndrome; TG = triglycerides.

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MODY Diagnostic app can help identify those at high risk based on clinical features.
- Diabetes diagnosed in the first year of life should be investigated for genetic causes, even if the person involved is now an adult.

**Case 1. A teenager with subacute presentation of diabetes**

See Case vignette no. 1 (provided by Dr Kausik Banerjee).

**Learning points**

Subacute presentation of diabetes and negative-cell antibodies should raise clinical suspicion that this is not type 1 diabetes. Requesting genetic testing close to diagnosis may avoid insulin use in well, non-ketotic individuals.

**Comment**

This vignette demonstrates a fairly classic presentation of HNF1A-MODY, which might be picked up incidentally but commonly causes mild to moderate osmotic symptoms as hyperglycaemia progresses. HNF4A-MODY presents and can be managed in an identical way. The usual differential diagnosis in those under 20 is from type 1 diabetes.

Negative antibodies and a stable metabolic presentation would suggest either monogenic diabetes or young-onset type 2, and the clinical features should give a clue to the most likely cause.

An important question is whether insulin needs to be started in those who are metabolically well with blood glucose <15mmol/L. If the patient agrees to perform regular glucose and ketone monitoring and keep in contact with the team, then it seems reasonable to observe, make any obvious dietary modifications, and reconsider commencing treatment once antibodies are back and a few days of monitoring have been reviewed.

If well otherwise with no ketones, but with some blood glucose readings >10mmol/L, an HbA1c >8% (64mmol/mol) and a strong clinical suspicion of MODY, low-dose sulphonylurea (SU) therapy could be started while genetic testing is requested. If the clinical features are more suggestive of young-onset type 2, metformin would be appropriate. If blood glucose are <10mmol/L with no symptoms, then Glucokinase gene sequencing should be requested. In practice, it can be difficult to differentiate early HNF1A- or HNF4A-MODY from Glucokinase-MODY so all three genes may need to be sequenced.

If there are any uncertainties at all, then insulin should be started for safety. If an HNF1A or HNF4A mutation is confirmed, then insulin can be stopped using the protocol on the Diabetes Genes website (www.diabetesgenes.org/content/guidance-transferring-hnf1a-or-hnf4a-patients-insulin-sulphonylureas).

Once a mutation has been confirmed, follow up of family members is mandatory – starting with the parents/children of the proband and close relatives who have diabetes. For paediatric teams, the local adult diabetes team can help with diabetic family members and the GP for apparently unaffected relatives. If there is a local genetic diabetes nurse, then they can help facilitate this process and link to teams in other parts of the country.

In this case, where no family history is reported then both parents should have a diabetes test. If normal then a discussion regarding a predictive genetic test (i.e. a genetic test in an unaffected person) is reasonable and can be organised with the local clinical genetics team. If this is not desired then the parents should be counselled that they are at risk of carrying the faulty copy of HNF1A and an annual diabetes test is suggested. Most people with HNF1A or HNF4A mutations develop diabetes by age 45. Spontaneous mutations can occur, so that sometimes there is genuinely no family history of diabetes. In other cases, the age of diagnosis can vary widely within families, so that individuals aged 45–55 have not yet developed diabetes (particularly if they are lean or fit).
Case vignette no. 2: A young child with incidental diabetes

An 18-month-old girl was incidentally found to be hyperglycaemic (blood glucose 10mmol/L) during an acute admission. She was admitted with a lower respiratory tract infection, secondary to infection with multiple viruses (confirmed isolates), for which she was receiving regular β2-agonist therapy, antibiotics and systemic corticosteroids.

She is the third of four children to British (maternal) and Eastern European (paternal) parents.

Hyperglycaemia was persistently demonstrated through the acute illness and was associated with minimal ketonuria but no acidaemia at any stage. Glucose was elevated up to 16mmol/L. The local paediatric team initially felt that her hyperglycaemia was attributable to the specific therapies that she was receiving, which are sometimes seen to cause transient hyperglycaemia in children. The child was discharged following resolution of the acute episode and her hyperglycaemia appeared to settle towards the end of the admission. An outpatient plan was made to perform a sweat chloride test (in the context of recurrent severe acute lower respiratory tract infection episodes) and an oral glucose tolerance test (OGTT), with review under a general paediatrician in clinic. She was initiated on a low-dose inhaled corticosteroid and oral interleukin-1 antagonist in the intervening period.

The sweat test was performed and was normal. Her OGTT, however, showed impaired glucose tolerance (t1h = 5.7mmol/L, t2h = 8.0mmol/L). On review, a significant family history was revealed. Firstly, the child’s mother had experienced gestational diabetes (resolved post-natally) while pregnant with her. Interestingly, there was a history of established MODY , albeit in more distant relatives living abroad, in the child’s maternal great-uncle and subsequently in two further generations (see Figure 2, Family pedigree).

Genetic testing revealed a glucokinase mutation. The family were counselled that this type of diabetes is unlikely to cause any long-term vascular complications and does not typically require any therapy with either insulin or oral hypoglycaemic agents. The family were also counselled regarding screening of both the girl’s mother and grandfather, who are also likely mutation carriers.

At age 3.5 years, this girl remains well. She is being followed up on an annual basis by the paediatric diabetes team and is on no regular medications.

Case 2: A young child with incidental diabetes

See Case vignette no. 2 (provided by Dr Kausik Banerjee).

Learning points

About half of cases of incidental findings of diabetes in the first or second decade of life is due to glucokinase mutations. This is associated with normal vascular outcomes and does not require treatment.

Comment

A finding of incidental hyperglycaemia in a child is due to a glucokinase mutation (GCK-MODY) in about 50% of cases.3 GCK-MODY leads to a resetting of the glucose threshold for insulin secretion so that those affected have fasting hyperglycaemia. Higher blood glucose levels can be observed during intercurrent illness.

GCK-MODY is unique among causes of hyperglycaemia because glucose metabolism remains regulated, albeit with glucose levels shifted 2–3mmol/L higher. This ability of the β-cell to continue to respond to rising glucose explains the limited peak in glucose after a carbohydrate challenge and this is in turn responsible for the good vascular outcomes seen. Glucose-lowering treatments have little impact on HbA1c, which remains just above the normal range.4

Family members with diabetes should be screened as they should be able to stop treatment if their hyperglycaemia is due to GCK-MODY. Treatment decisions should be made on the basis of genetic testing, as mixed forms of diabetes in families are often seen.5

The pedigree in Figure 2 is typical for GCK-MODY, showing apparent ‘gaps’ in inheritance of diabetes because the hyperglycaemia is usually asymptomatic.

Women often present in pregnancy and may find it hard to meet treatment targets. If the baby has not inherited the mutation, then the mother’s mild hyperglycaemia can lead to macrosomia. However, where both mother and baby have the mutation, fetal insulin production and birthweight are normal.6 Therefore in women known to have GCK-MODY, monitoring of fetal size is recommended and treatment (usually with insulin) should only...

Figure 2. Pedigree for Case vignette no. 2

GDM = gestational diabetes in the mother. MODY = maturity-onset diabetes of the young.

Female: positive MODY. Genetics confirmed
Male: positive MODY. Genetics confirmed
Female, GDM, not sequenced

Genotype unknown
be started if fetal abdominal circumference is elevated.

**Case 3: A lean adult with type 2 diabetes**

*See Case vignette no. 3 (Oxford case).*

**Learning point**

Monogenic diabetes should be considered in young lean adults presenting with diabetes. A lower HbA1c can be achieved on SU than on metformin.

**Comment**

Despite being young and lean, this patient was assumed to have type 2 diabetes and was not referred to secondary care for investigation or management. Individuals with HNF1A-MODY tend to be non-obese without features of insulin resistance and this should raise the suspicion of monogenic diabetes in young adults under the age of 45 years. A differential diagnosis is with slowly progressive autoimmune diabetes, so antibody testing helps distinguish from this. Low C-reactive protein is a characteristic of those with HNF1A-MODY and can be helpful in differentiating from young-onset type 2 diabetes.

Although individuals with HNF1A-MODY can be treated successfully with metformin, they have a four times greater glucose fall with low-dose SU and in our experience frequently achieve a close to normal HbA1c without significant hypoglycaemia. If started on standard doses of SUs, they usually get hypoglycaemia. However, as SUs are now much less commonly used as first- or second-line treatments, this ‘clue’ to HNF1A-MODY is not often picked up. When hypoglycaemia occurs in HNF1A-MODY, the correct approach is to reduce the dose (even down to 10mg gliclazide) or to use a prandial insulin secretagogue, for example nateglinide, with larger meals rather than stopping treatment.

Women with HNF1A-MODY may present in pregnancy and are managed with standard blood glucose targets. Most will require insulin as pregnancy progresses, but glibenclamide is an option initially for those well controlled on SU agents prior to conceiving – they should be advised to convert to glibenclamide before becoming pregnant.

**Case vignette no. 3: A lean adult with type 2 diabetes**

*(Oxford case)*

A 30-year-old man was recruited to a research study looking into the causes of diabetes. He had been diagnosed with type 2 diabetes a year or so before, when he presented with mild thirst and weight loss. He was medically well with no ketonaemia. At diagnosis his BMI was 22kg/m² and he had negative GAD antibodies. C-reactive protein was very low at <0.03g/L. He was started on metformin 500mg bd and a recent HbA1c was 56mmol/mol.

He had a strong family history of type 2 diabetes. His brother was diagnosed at age 37 after a myocardial infarction and was also managed on metformin. His father was diagnosed in his 40s and had developed significant vascular complications (ischaemic heart disease and diabetic nephropathy leading to a renal transplant). His paternal grandmother had also had diabetes in later life.

MODY testing was arranged as part of the research study and an HNF1A mutation was identified. The same mutation was confirmed in his brother and father. During the investigations his sister became pregnant and was found to have gestational diabetes in the first trimester. She was also confirmed as having the same HNF1A mutation.

The patient changed from metformin to 40mg gliclazide which resulted in a lower HbA1c of 39mmol/mol without hypoglycaemia. His brother remained well controlled on a combination of gliclazide and metformin, while his father had progressed through oral agents to insulin treatment and so sulphonylurea agents were not reintroduced. His sister was treated with insulin during pregnancy, and also changed to low-dose gliclazide after finishing breast feeding.

**Case vignette no. 4: A history of neonatal diabetes is always relevant**

*(Oxford case)*

A 40-year-old man presented with a short history of thirst, significant weight loss and a blood glucose of 13.3mmol/L without ketonaemia. He also had symptoms of peripheral neuropathy. He had a BMI of 20kg/m² and HbA1c of 78mmol/mol. There was no past medical history of note. Given the fairly acute presentation he was commenced on basal bolus insulin from diagnosis.

During an early review, he revealed that his half-brother, now living in Canada, had been diagnosed with diabetes in neonatal life and had been treated with insulin for two years. After this, the diabetes resolved and his brother was now 33 years old and did not have diabetes currently. Their mother had type 2 diabetes diagnosed in her 50s; she was slim and treated with oral agents.

By this point the β-cell antibody results had returned as negative and the patient was requiring a low insulin dose of 0.3u/kg with a C-peptide of 220pmol/L. This raised the question of monogenic diabetes. The proband was found to have a mutation in the ABCC8 gene. He was then able to stop insulin and convert to gliclazide 40mg daily, achieving an on-target HbA1c of 51mmol/mol.

**Case 4: A history of neonatal diabetes is always relevant**

*See Case vignette no. 4 (Oxford case).*

**Comment**

The crucial clue here is the history of neonatal diabetes in the patient’s half-brother. This would guide first-line genetic testing to causes of neonatal diabetes. Diabetes diagnosed in the first six months of life is very rarely autoimmune, and since 2004 a large number of monogenic causes have been identified. Diabetes which presents in the neonatal period and then resolves is referred to as transient neonatal diabetes. This may relapse in later life.

**ABCC8** is the gene coding for part of the β-cell potassium ATP channel which harbours the SU receptor, a crucial part of the insulin secretion mechanism in the β-cell. Mutations in **ABCC8** disrupt this mechanism, but when SUs bind to the receptor insulin secretion is restored. Mutations in **ABCC8** can cause both permanent and transient neonatal diabetes as well as a later onset MODY-like picture. Diabetes arising in adulthood seems to be sensitive to low-dose SU treatment, while neonatal diabetes requires high doses. It remains a rare
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Case vignette no. 5: What about when a cause is not found?

Case submitted by Dr Paul Grant and Josie Wilson, Diabetes Care For You, Brighton General Hospital, Brighton UK

A 25-year-old man had been diagnosed with presumed type 1 diabetes five years previously.

On review, he was taking Levaquin 10 units od and no mealtime insulin (insulin dose 0.13u/kg). Glycaemic control had been on target with a stable Hba1c in the range of 50–53mmol/mol over several years. There was no family history of diabetes or other significant conditions. His urinary C-peptide levels showed that endogenous insulin secretion had been well preserved over several years. Three autoantibodies were found to be negative. He was of normal BMI with no other features of metabolic syndrome.

Given the low insulin requirement, residual C-peptide and negative antibodies, the possibility of monogenic diabetes was raised. He subsequently had genetic testing using a Next Generation Sequencing panel of 25 genes,13 which showed that he ‘did not have a genetic change in any of the currently known genes that cause monogenic diabetes’.

condition, with knowledge about the phenotype and treatment response still being accumulated, so take advice from experts for management.

Remember any history of neonatal diabetes is important, even if those involved are now adult.

Case 5: What about when a cause is not found?

See Case vignette no. 5 (provided by Dr Paul Grant and Josie Wilson).

Learning points

Sometimes, despite a phenotype which is suggestive of monogenic diabetes, no causative mutation is found. Management should be pragmatic, with consideration of insulin withdrawal in those with persistent endogenous insulin secretion evidenced by presence of C-peptide.

Comment

In this patient, the differential diagnosis is between a slowly progressive antibody-negative autoimmune diabetes, atypical type 2 diabetes or monogenic diabetes, that has either been missed on testing or is due to a gene not included in the panel. Antibodies are negative, but an assessment of Type 1 genetic risk (HLA) might support an autoimmune aetiology. The Next Generation Sequencing panel covers a wide variety of genes that have been implicated in causing diabetes; however, not all regulatory regions are included so some people with a MODY-like picture may eventually be found to have rare disruption of one of the known genes. Interpreting novel sequence variation, particularly in genes which are only rarely implicated in diabetes, is extremely problematic and it is important not to report uncertain findings as positive. Research is still needed to investigate families with strong monogenic phenotypes, but as diabetes is a common condition and most adults will have multifactorial disease, this remains a considerable challenge. Monogenic diabetes is one of the diseases being studied in the 100 000 genome project where whole genome sequencing is being performed on those with potential monogenic diseases of unknown cause (https://www.genomicsengland.co.uk/the-100000-genomes-project/).

As the patient has positive C-peptide, they may be able to withdraw insulin. In the absence of a specific cause of diabetes being identified, the use of metformin (effective in lean type 2) or glitazide (because four subtypes of monogenic diabetes are sensitive to SU agents) would seem to be pragmatic, plus weight loss if overweight. Any withdrawal of insulin should be done with informed consent making clear that it may not be successful and careful monitoring of blood glucose and ketones should be performed during the transition.

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References


Drug notes

Find out how non-diabetes drugs impact diabetes patients. Visit the Practical Diabetes website and click on drug notes

Bromocriptine | Labetalol | Metoclopramide | Nateglinide | Prasugrel | Quinine sulphate | Ranolazine | Spirinolactone | Testosterone | Torcetrapib

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