Monogenic diabetes and the role of the diabetes nurse

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Summary

Diabetes specialist nurses are ideally placed to identify patients with monogenic diabetes but may lack knowledge of the key features and fail to recognise potential cases. Once the diagnosis of diabetes has been made this may not be revisited and may be assumed to be correct. However, increasing knowledge and awareness of monogenic diabetes will allow health care professionals to question the diagnosis of their patients where appropriate and lead to greater recognition and correct treatment of monogenic diabetes.

Maturity onset diabetes of the young (MODY) is typically detected in individuals diagnosed with diabetes before the age of 25 years who also have a parent with diabetes. They are non-insulin dependent but are often mistaken to have type 1 diabetes and are insulin treated. Patients meeting these criteria should be considered for further investigation to ensure their diagnosis is correct. Neonatal diabetes can also be caused by a single genetic change, and patients diagnosed with diabetes within the first six months of life should be referred for genetic testing whatever their current age.

This paper highlights three useful means of aiding differential diagnosis: urinary C-peptide creatinine ratio (UCPCR), pancreatic autoantibodies, and use of the online MODY probability calculator. Case studies are used to illustrate the key diagnostic features of MODY and indicate how awareness of family history and other features raised suspicion of an alternative cause of diabetes in these families. Treatment change following a positive molecular genetic diagnosis is also described.

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Key words

diabetes specialist nurse; monogenic diabetes; maturity onset diabetes of the young (MODY); neonatal diabetes; genetic testing

Introduction

Diabetes specialist nurses (DSNs) have a key role to play in both the diagnosis and management of people with diabetes. Although type 1 and type 2 diabetes predominate, there are other causes of diabetes that need to be recognised as they require different treatment and family follow up. DSNs are ideally placed to ensure their patients receive the correct diagnosis and treatment.

Monogenic diabetes is caused by a single genetic change and accounts for 2% of all diabetes.[1,2] It is important that it is recognised as many patients with monogenic diabetes can be successfully managed on sulphonylurea tablets as opposed to insulin injections,[3–7] and some require no treatment.[8,9] Despite increasing awareness of monogenic diabetes, the majority of patients are initially misdiagnosed and referrals for genetic testing are sporadic.[10] Following a positive molecular genetic test result, DSNs can assist with treatment change and follow up of other family members.

Increased knowledge of the key characteristics of monogenic diabetes among DSNs and other diabetes health care professionals is required to ensure these patients are recognised and offered genetic testing. Non-genetic tests can aid differential diagnosis in patients where there is suspicion of monogenic diabetes, and the different genes causing MODY display distinct features which can be identified by those with knowledge of the condition. This article, through the use of case studies, will enable the reader to recognise the key characteristics of monogenic diabetes and become familiar with the most appropriate treatment in each case.

Characteristics of monogenic diabetes

Maturity onset diabetes of the young

There are three key diagnostic criteria for maturity onset diabetes of the young (MODY): (1) early onset diabetes (diagnosis of diabetes less than 25 years of age in at least one and, ideally, two family members); (2) off insulin treatment or measurable C-peptide at least three years (ideally, five years) after diagnosis; and (3) autosomal dominant inheritance (diabetes is present in a parent [two generations] and, ideally, a grandparent or child [three generations]).[11] (See Table 1.) These patients continue to produce endogenous insulin, but this may not have been tested and many are initially assumed to have type 1 diabetes due to their age at presentation and are insulin treated from diagnosis.

Neonatal diabetes

Diabetes diagnosed at less than six months of age is likely to have a monogenic cause[12–14] and patients should be referred for genetic testing irrespective of their current age.

Aids to differential diagnosis

Urinary C-peptide creatinine ratio (UCPCR) is a measure of endogenous insulin and can be useful to identify patients, previously considered to have type 1 diabetes, who are still producing insulin of their own many years after diagnosis.[15,16] This test is most useful more than five years post diagnosis as insulin production is common during the honeymoon period.

UCPCR is a cheap, easy and reliable measure of endogenous insulin,[15,17] but serum C-peptide can also be used.[18] If post meal UCPCR is >0.2nmol/mmol, this indicates continued insulin production and can support the possibility of MODY or a 'non type 1' diagnosis.[16]

Pancreatic antibodies are also useful in distinguishing between type 1 diabetes and MODY.[19] In Exeter, GAD and IA2 can be measured and are useful in those previously considered to have type 1 diabetes.[19] Although most useful close to diagnosis, they can remain 'positive' for many years. Approximately 70% of adults and 94% of children will be positive to one or more pancreatic antibodies at diagnosis.[20] If patients are negative to both GAD and IA2 antibodies this can support the possibility of MODY or 'non type 1'.

The MODY online probability calculator[21] is another tool that is accessible to all (via www.diabetesgenes.org) and can give a probability of an individual having MODY.

This simply requires inputting of eight pieces of data – current age, age at diagnosis, current and previous treatment, BMI, sex, HbA_{1c}, and parental family history of diabetes – and then the probability of MODY is calculated; this can aid identification of those patients most appropriate to refer on for genetic testing.

Early onset diabetes	Diagnosis of diabetes below 25 years of age in at least 1 and, ideally, 2 family members
Non-insulin dependent diabetes	Off insulin treatment or measurable C-peptide at least 3 (ideally 5) years post diagnosis
Autosomal dominant inheritance	Diabetes in a parent (2 generations) and ideally in a grandparent or child (3 generations)

Table 1. Three key diagnostic criteria for maturity onset diabetes of the young (MODY)

What's the diagnosis?

The following case studies illustrate the key features of the different causes of monogenic diabetes. (Pseudonyms have been used in the case studies to ensure anonymity.) In each case there are aspects which can be identified as 'atypical' and awareness of these features raised questions about the original diagnosis.

Case 1

John was diagnosed with diabetes at the age of 19 years with blood glucose of 19mmol/L.[22] He was slim, BMI 22, had polydipsia and lethargy and 2+ ketones in his urine. He was presumed to have 'type 1' diabetes and commenced on Novorapid 4 units pre meals, Levemir 8 units before bed. On these details alone, John could well be considered to have type 1 diabetes; however, looking at the family history provides additional useful information. His mother had been diagnosed with diabetes in pregnancy at the age of 24 years and post pregnancy was treated with low-dose sulphonylureas, gliclazide 40mg once daily. She was slim: BMI 21.

It is the mother's details that raised suspicion of an alternative diagnosis. She was unusually slim to have gestational diabetes and clearly did not have type 1 as she did not require insulin post pregnancy; a diagnosis of 'type 2' diabetes was also unlikely as she was young, slim and Caucasian. She was also sensitive to low-dose sulphonlyureas, a characteristic of the most common cause of MODY.

The local DSN (who had received specialist training in monogenic diabetes) referred John for additional tests to clarify whether genetic testing was appropriate. UCPCR of 1.14nmol/mmol indicated continued endogenous insulin production 3.5 years post diagnosis. Both GAD and IA2 pancreatic antibodies were negative supporting a non-autoimmune cause. The MODY probability calculator score indicated a 1 in 15 chance of him having a monogenic cause of his diabetes.

John was referred for genetic testing and HNF1A MODY confirmed. As a consequence, John was able to stop insulin and is now well controlled on gliclazide 20mg once daily. His glycaemic control has improved and his home blood glucose levels are 4–8mmol/L. He has no hypoglycaemia and quality of life has improved: *'It's fantastic not to have to inject and the worry of hypos has gone.'* John's sisters were offered pre-symptomatic genetic tests and HbA_{1c} following genetic counselling. John is aware his son is at a 50% risk of having inherited the affected *HNF1A* gene but has decided against genetic testing at this point as his son is very young.

HNF1A MODY

HNF1A MODY (Table 2) is characterised by sensitivity to low-dose sulphonylureas[4,7] and a low renal threshold for glucose[23] as well as the three key diagnostic criteria of a young age of diagnosis, affected parent and continued insulin

Gene involved	HNF1A	HNF4A	GCK	HNF1B	KCNJ11 / ABCC8
Age diabetes diagnosed	Typically <25 years	Typically <25 years	Raised blood glucose present from birth (but often first detected during routine screening)	Most have early onset diabetes (but diabetes can present at any age)	Neonatal diabetes diagnosed within first 6 months of life
Parent affected	Yes	Yes	One parent expected to have raised blood glucose but may not have been tested/ detected	50% of cases do not have a parent affected	Vast majority of cases caused by 'de novo' mutations so do not have an affected parent
Other key features	Sensitivity to sulphonylureas Low renal threshold for glucose	Sensitivity to sulphonylureas Macrosomia and neonatal hypoglycaemia may be present	Mild, stable hyperglycaemia, fasting glucose 5.5–8mmol/L, mean HbA_{1c} 50mmol/mol (6.7%) Minimal risk of complications	Renal cysts or other renal developmental abnormality, e.g. single or horseshoe kidney Diabetes may present later than renal abnormality	20% have neurological features including developmental delay and muscle weakness Diabetes may be transient or permanent
Optimal treatment	Low-dose sulphonylurea (gliclazide)	Low-dose sulphonylurea (gliclazide)	No treatment required	Insulin	High-dose sulphonylurea (glibenclamide)

Table 2. Additional key features of the specific genes causing monogenic diabetes

production. Myocardial infarction in HNF1A families has been described[24] and optimal glycaemic control is important to reduce the risk of diabetes complications.

Case 2

David was diagnosed with diabetes at the age of 39 years, assumed to have 'type 2' diabetes and treated with sulphonylureas.[22] His BMI was 30. The diagnosis of 'type 2' diabetes could be appropriate although it may be argued that his age at diagnosis was not typical of type 2 diabetes in a Caucasian. However, once again it was the family history that raised suspicion of an alternative diagnosis. David's sister was diagnosed at 17 years with 'type 1' diabetes but this was detected on routine screening, not typical of the presentation in type 1. David's youngest daughter, Rose, was born macrosomic at 38 weeks' gestation, with a birth weight of 4.2kg. She had neonatal hypoglycaemia, blood glucose 0.4mmol/L at birth requiring treatment with diazoxide and chlorthiazide for six months.[22]

David's UCPCR was 1.6nmol/mmol and both GAD and IA2 were negative. He was referred for genetic testing and HNF4A MODY confirmed. Following this result, his sister had a UCPCR measured indicating she has continued endogenous insulin production (UCPCR 0.8nmmol/mmol) more than 10 years post diagnosis. She was also confirmed to have the same genetic change in *HNF4A*; however, she felt confident on her insulin and decided against trialling sulphonylurea treatment.

David was concerned about his other children, particularly his son who had also been born macrosomic. His son was found to have inherited the same mutation in *HNF4A* and developed diabetes at 15 years of age and is currently treated with low-dose gliclazide. Rose currently has normal glucose tolerance but is expected to develop diabetes in the future as a result of also inheriting the affected *HNF4A* gene. David's eldest daughter did not inherit the affected gene and so is not at increased risk of developing diabetes. David's mother was also found to have the affected *HNF4A* gene.

HNF4A MODY

HNF4A MODY (Table 2), along with the three key diagnostic criteria of MODY, may present with macrosomia due to an over-secretion of insulin in utero and neonatal hypoglycaemia which can

require prolonged treatment.[25] Those with HNF4A mutations typically progress to β-cell failure and diabetes in early adulthood.[25] Patients with HNF4A MODY are sensitive to low-dose sulphonylureas which are the treatment of choice.[26]

Case 3

Brenda was identified with fasting blood glucose of 6.2mmol/L in her third pregnancy at the age of 34 years and was treated with insulin. Post pregnancy she had an oral glucose tolerance test which indicated a fasting glucose of 6.2mmol/L and a 2-hour value of 7.9mmol/L; BMI was 29. HbA_{1c} was 45mmol/mol (6.3%) on no treatment. Her father had been diagnosed with 'type 2' diabetes aged 44 years during a routine medical and was treated with sulphonylurea tablets. In this case, the presentation of 'diabetes' during routine screening in both individuals, in combination with Brenda's oral glucose tolerance test and HbA_{1c} result, raised suspicion of a monogenic cause of her raised blood glucose.

Brenda's UCPCR was 2.1nmol/mmol; GAD and IA2 negative, and MODY probability score was a 1 in 2 chance of testing positive for MODY. She was referred for genetic testing and glucokinase MODY confirmed. This reassured Brenda that she needed no treatment for her raised blood glucose and her father was also able to stop his oral hypoglycaemic agents with no deterioration in blood glucose control. Brenda was reassured that even if her children had inherited the affected glucokinase gene they would not require treatment and the risk of diabetes complications was minimal.[27]

GCK MODY

Glucokinase MODY (Table 2) is characterised by mild, stable hyperglycaemia with fasting glucose values typically between 5.5–8mmol/L and mean HbA_{1c} 50mmol/mol (6.7%), range 38–60mmol/mol (5.6–7.6%).[28] Glucokinase patients have high fasting and only a small increase in post-prandial plasma glucose; treatment is not required.[8] It is frequently detected during routine screening – for example, in pregnancy.[29]

Case 4

Monica was diagnosed with diabetes at the age of 21 years when she was 36 weeks' pregnant; her HbA_{1c} was 66mmol/mol (8.2%) and she was started on insulin immediately.[30] During this pregnancy, the fetus was found to have renal cysts and an enlarged kidney incompatible with life and a medical termination was performed. Monica remained on insulin post pregnancy; BMI 21. During her second pregnancy, her fetus was again found to have renal cysts but these were small and not considered life threatening. Monica had a renal ultrasound herself and two small renal cysts were identified; UCPCR was 1.6nmol/mmol, pancreatic antibodies were negative and MODY probability score was a 1 in 25 chance of testing positive for MODY. The combination of diabetes and renal cysts is a recognised feature of HNF1B MODY, also known as RCAD (renal cysts and diabetes), and she was referred for genetic testing. This confirmed an affected *HNF1B* gene caused Monica's diabetes and renal cysts.

Monica struggles with her diabetes with HbA_{1c} up to 184mmol/mol (19.0%) and admits to omitting her insulin on occasions but is prescribed Lantus 30 units twice daily. Her kidney function is regularly monitored and eGFR is 37. Her son (now 16 years) has just developed diabetes, HbA_{1c} 53mmol/mol (7.0%) and is also under the renal team; he has chronic kidney disease stage 3.

HNF1B MODY (renal cysts and diabetes)

See Table 2. HNF1B is typically characterised by renal cysts and diabetes, although the renal histology is variable and single or horseshoe kidneys may be seen.[31] Renal function ranges from normal to dialysis, with some patients requiring renal transplants.[32] Fifty percent of HNF1B mutations are 'de novo' so there may not be an affected parent.[33] The diabetes typically develops after the renal disease, and age at diagnosis is variable but patients usually require insulin.[9]

Case 5

Joe was diagnosed with diabetes at three weeks of age; he presented in diabetic ketoacidosis with a blood glucose of 58mmol/L.[34] He started insulin immediately. There was no family history of diabetes and, although he was pancreatic antibody negative, he had no detectable C-peptide indicating he was not making insulin of his own. He was later noticed to have learning difficulties and muscle weakness.

Despite Joe's lack of family history and undetectable C-peptide it was his age of diagnosis that highlighted he was most likely to have a genetic cause of his diabetes. There is no need to use the MODY probability calculator for those diagnosed less than six months of age and they can be referred immediately for genetic testing. Joe was confirmed to have KCNJ11 neonatal diabetes and as a consequence was able to stop his insulin and is now managed on glibenclamide 5mg twice daily. The treatment change led to improvements in quality of life: *'Family life has completely changed; he is more independent, he has not had one hypo, his concentration has improved, our whole world isn't "just diabetes" any more.'*[34]

KCNJ11 neonatal diabetes

See Table 2. Forty percent of cases of permanent neonatal diabetes are

KEY POINTS

- The majority of patients with monogenic diabetes are initially misdiagnosed. It is important that it is recognised as many, following a positive genetic diagnosis, can be successfully managed on sulphonylurea tablets as opposed to insulin injections and some require no treatment
- Any patient diagnosed less than 25 years of age with a parent with diabetes may benefit from investigations into pancreatic antibody status and endogenous insulin production (if not previously conducted) and their details entered into the online MODY calculator (www.diabetesgenes.org) to identify which patients should be referred for genetic testing
- Diabetes diagnosed less than six months of age is likely to have a monogenic cause and patients should be referred for genetic testing irrespective of their current age

caused by KCNJ11 mutations[13,14,35] and mutations in ABCC8 are another common cause.[12,36] Twenty percent of patients have neurological features.[37] Both KCNJ11 and ABCC8 neonatal diabetes can be successfully managed with high-dose sulphonylureas[38,39] which allow closure of the KATP channel enabling patients to produce insulin of their own. Glibenclamide is typically used as it crosses the blood brain barrier and may help neurological features.[40–42] There is often no family history as the majority of mutations are 'de novo'.[43] All patients diagnosed with diabetes below six months of age should be referred for genetic testing whatever their current age.

Summary

Awareness of monogenic diabetes will help ensure the diagnosis and treatment of diabetes are correct. Familiarity with the key characteristics of monogenic diabetes and the features associated with the different genes affected can allow DSNs and other health care professionals to identify patients whose original diagnosis may warrant confirmation.

This paper describes how using strategies, including biochemical tests (pancreatic antibodies, urinary C-peptide creatinine ratio) and the online MODY calculator, can help identify patients who may require genetic testing to clarify their diagnosis. Any patient diagnosed less than 25 years of age who has a parent with diabetes could benefit from investigations into pancreatic antibody status and endogenous insulin production if not previously conducted. If patients are negative to pancreatic antibodies and have measurable C-peptide more than five years post diagnosis, then we would recommend taking a closer look at the family history, clinical presentation and treatment and entering the clinical details on to the online MODY probability calculator to identify whether genetic testing would be appropriate. All patients diagnosed less than six months of age should be referred for genetic testing, whatever their current age. In addition, it can be helpful to be aware of patients whose diabetes seems 'atypical' who may benefit from further investigation into family history and discussion with the Exeter team in the UK.

Details of the samples required for genetic testing and where to send them, along with details of the UCPCR and pancreatic antibody tests, can be found on www.diabetesgenes.org.

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Declaration of interests

There are no conflicts of interest declared.

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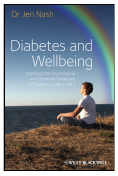
Book review

Diabetes and wellbeing



By Dr Jen Nash
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This book, subtitled 'Managing the psychological and emotional challenges of diabetes types 1 and 2', will be useful to people living with diabetes, as well as those supporting them, and to the health care team.

The psychological and psychosocial aspects of diabetes are addressed throughout the book. Chapters 3, 4 and 5 explore ways to deal with the diagnosis and manage depression and fear associated with diabetes. Chapter 7 addresses the importance of effective communication skills and provides strategies for supporting behaviour change in contacts with others. It also covers intimate relationships and the impact of diabetes on these.

The relationship between food and diabetes can be very challenging throughout living with diabetes. Chapter 6 takes a candid approach to managing food and emotional eating, and presents CBT-based techniques to help the management of emotions around food. Later in the chapter the area of eating disorders and diabetes is discussed, with detailed advice and tools. Chapter 8 explores implementing change with some basic goal setting and positive reinforcement techniques. Chapter 9 looks at managing setbacks and staying solution-focused.

Overall, the book is a useful resource for anyone wanting to know more about the complexities of diabetes and seeking information on how to address some of the key issues.

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