When to suspect 'funny' diabetes

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Diabetes comes in many shapes and forms. It is important for the general physician to recognise when clinical characteristics, response to treatment and associated features suggest an alternative variety of diabetes, over and above the traditional type 1 and type 2 forms which are far more common. Key to these suspicions are taking a clear history of the development of the diabetes and being aware of the family history.

Introduction

The diagnostic criteria, classification and behaviour of diabetes mellitus is a source of extensive intellectual challenge among diabetologists.[1] A recent Royal College of General Practitioner's report suggested problems with regard to the coding of this condition, with up to 15% of patients misdiagnosed or categorised as having the wrong disease type (see www.clininf.eu/cod/).[2,3] For a long time, we have been aware of the multiple aetiologies of diabetes from pancreatic damage, to steroid effects, immune malfunction, obesity, endocrine perturbations and mitochondrial disease, but now we can add a plethora of different genetic causes of diabetes to the mix. This can add to the confusion of specialists and non-specialists alike.

Type 2 diabetes, by far the most common subtype, is itself a heterogeneous disorder. Large-scale genetic studies have shown that there are over 60 genetic variations that contribute to the risk of developing type 2 diabetes, though the biggest risks are still environmental.[4] There has also been a wealth of research into monogenic forms of diabetes, which can often evade detection in clinical practice.[5] For the doctor on the ward and in the outpatient department, the key is knowing when to have the suspicion that you may be dealing with something other than type 1 or type 2 diabetes. A correct diagnosis can lead to the correct treatment, appropriate education, family screening and the best use of resources. We present four clinical scenarios to highlight the many flavours of diabetes and why these variations are important.

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Case scenario 1

A 24-year-old man with diabetes diagnosed at the age of 14 was found to have glycosuria during a routine check up. He was treated as having type 1 diabetes with basal-bolus insulin therapy. He attended his hospital annual review, where his treatment and diagnosis were reviewed. He had a sub-optimal glycated haemoglobin (HbA1c) of 68 mmol/mol (8.4%). There was a strong family history of the disease in that his father, grandmother and great grandfather all had diabetes diagnosed at a young age. He admitted to missing his insulin occasionally but had never developed ketoacidosis.

Despite attendance on a dose adjustment for normal eating (DAFNE) structured education course and intensification of his insulin treatment, the patient's overall glycaemic control did not improve and he was noted to have heavy glycosuria despite capillary blood glucose values within the target range.

Given the family history, the glycosuria and the failure to achieve good glycaemic control on insulin therapy, consideration was given to the possibility of an alternative diabetes-type diagnosis. The patient's pancreatic auto-antibodies were negative; his urine C-peptide test was positive, showing that he was still producing endogenous insulin. Subsequent genetic testing revealed a mutation that had caused his diabetes in the hepatocyte nuclear factor 1 homeobox A (*HNF1A*) gene (classified as HNF1A-maturity onset of the young (MODY)). This was important as it revealed that the patient's current insulin treatment regime was not best suited to his condition.

The decision was made to switch the patient onto a sulphonylurea and wean down the insulin. This initially caused some problematic hypoglycaemia and the insulin was subsequently stopped altogether. He felt much better and had more stable blood glucose values. Three months later, his HbA1c had significantly improved to 55 mol/mol (7.2%). After 10 years on insulin, the patient was able to manage with just gliclazide 20 mg bd.

Familial monogenic diabetes (historically known as maturity onset diabetes of youth) is a group of autosomal dominant disorders, which typically develop from adolescence. Glycosuria often precedes the diagnosis. The commonest forms result from inactivating mutations of transcription factors (hepatocyte nuclear factors), which lead to abnormal glucose and insulin metabolism. There is a reduction in the amount of insulin secretion in response to glucose, which deteriorates with age.[6]

Patients with mutations in *HNF1A* have a low renal threshold for glucose and are also more susceptible to developing early

microvascular complications, such as nephropathy and retinopathy, as well as cardiovascular disease. Hence early recognition of this condition and appropriate intervention are very important.[7]

Maturity onset diabetes patients are extremely sensitive to sulphonylureas, and these are the mainstay of treatment during the initial stages. Monogenic diabetes patients with mutations in HNF1A and HNF4A transcription factors can be extremely sensitive to sulphonylureas and these are the mainstay of treatment during the initial stages. Dipeptidyl peptidase-4 (DPP-IV) inhibitors could be useful in addition. Also, physical exercise is beneficial for improving glycaemic control. Insulin might, however, become necessary in the later stages.[8]

Case scenario 2

A 35-year-old Afro-Caribbean man with type 1 diabetes attended his primary care doctor with symptoms of recurrent hypoglycaemia. He had been diagnosed 2 years previously following a hospital admission with diabetic ketoacidosis (DKA) and was subsequently treated with a basal bolus insulin regime. He had been following his DAFNE principles and had very good glycaemic control with an HbA1c of 6.6% (49 mmol/mol) but his capillary blood glucose monitoring demonstrated frequent hypoglycaemia despite relatively small doses of insulin.

The patient's GP arranged for him to have his anti-glutamic acid decarboxylase (GAD) and IA-2 antibodies checked, both were negative. His urinary C-peptide was raised, however, demonstrating that again there was persistent endogenous insulin production. There is a recognised sub-set of patients with DKA who subsequently do not require long-term insulin therapy. Several may have a condition that resembles type 2 diabetes, in that they have an obese phenotype and a strong family history of diabetes.

The possibility of ketosis-prone type 2 diabetes was raised given the patient's ethnic background and the patient was commenced on metformin and weaned off the insulin completely, with no deterioration in his HbA1c levels.

Ketosis-prone type 2 diabetes (sometimes known as J-type, Flatbush or type 1.5 diabetes) is a recognised variant of type 2 diabetes in which the patient's treatment requirements may change over time depending on their underlying levels of metabolic stress.[9] This means that they may intermittently be at risk of ketoacidosis and require insulin therapy, whereas at other times they are able to manage their diabetes with just oral hypoglycaemic agents or even diet alone. Ketosis-prone type 2 diabetes is more common in patients from an Afro-Caribbean ethnic background.

Traditionally, confirmation of this diagnosis was based on glucagon-stimulated C-peptide measurement, but both the clinical phenotype and the increased availability of urinary C-peptide measurement have made the diagnosis easier.[10]

Recognition of clinical patterns such as those seen in this patient has led to the development of a new system of classification of diabetes, known as the Aβ system, which is based on the presence of auto-antibodies and whether there is persistent pancreatic beta cell function (see Table 1).[11] Ketosis-prone diabetes equates to an A– / β+ phenotype.

Key points

> Slim rather than overweight or obese phenotypes should raise suspicion of something different to Type 2 diabetes

> Fasting hyperglycaemia both inside and outside of pregnancy may indicate monogenic diabetes

> Glycosuria in the presence of normoglycaemia may indicate non-standard diabetes

> A strong family history of diabetes (two or more first degree relatives), as well as of other conditions, is an important indicator of non-standard diabetes, especially if the patient is diagnosed under the age of 35 years

> Very young age of onset diabetes presenting under the age of six months (neonatal diabetes) requires genetic investigation

> Not all adolescent diabetes is type 1, especially if the child is overweight

> Residual endogenous insulin secretion for at least 5 years after diagnosis in those labelled clinically as having type 1 diabetes should be investigated further

> Young age of onset and absence of the features of the metabolic syndrome, or absence of insulin resistance in patients labelled as having type 2 diabetes, should be investigated further

KEYWORDS: Maturity onset of the young, monogenic diabetes, ketosis prone type 2 diabetes, latent autoimmune diabetes of adult onset, molecular genetics ■

Case scenario 3

A 26-year-old woman was referred to the antenatal diabetes clinic as she was 16 weeks pregnant (her second pregnancy) and had undergone testing for diabetes with an oral glucose tolerance test (OGTT). During her first pregnancy, she had been diagnosed with gestational diabetes and required insulin treatment. Post-partum the diabetes had resolved, but she was informed that she had 'impaired fasting glucose' and was known to have several close relatives with diabetes.

The OGTT demonstrated a fasting plasma glucose level of 6.2 mmol/l and a 120 minutes value of 7.9 mmol/l. Her pre-pregnancy body mass index (BMI) was 22. The decision

Table 1. The Aβ system for classifying diabetes.

	β-cell function present	β-cell function absent
Presence of auto-antibodies	A+/β+	A+/β–
Absence of auto-antibodies	A–/β+	A–/β–

was taken to monitor the patient's capillary blood glucose values and fetal growth. From 26 weeks, her glucose values started to rise above the target range (<5.0 mmol/l pre-meal and <7.0 mmol/l at 1 hour post meal). The growth trajectory of the baby's abdominal circumference accelerated and the abdominal circumference measurements were disproportionately above the 75th centile. Insulin treatment was started and the patient required large doses to get good metabolic control (>1 unit of insulin per kg per day). The baby was delivered at 38 weeks and weighed in at 4.1 kg. Following delivery, the patient's follow-up OGTT showed a persistently raised fasting blood glucose value of 6.1 mmol/l; she was asymptomatic and given diet and lifestyle advice. The pattern of a slim woman being diagnosed with gestational diabetes, the persistently elevated fasting blood glucose with a small increment on the OGTT, plus the family history of diabetes raised the possibility of a mutation in the glucokinase (GCK) gene. Subsequent GCK genetic testing proved positive for the mother and negative for the child. GCK is an enzyme within the pancreatic beta cell which is important for homeostatic regulation of plasma glucose levels.

Inactivating mutations in the GCK gene lead to altered insulin secretion, causing a higher glucose set point. This generally leads to mild fasting hyperglycaemia (5.5–8.0 mmol/l) and outside the context of pregnancy does not require treatment.[12] When an OGTT is performed, it is characterised by an elevated fasting glucose level which may only show a small relative incremental increase after 2 hours. This may mean that it is missed unless the values measured at both time points are digested correctly.[13]

Insulin treatment should be considered where the fetus has not inherited the GCK mutation because there is an increased risk of macrosomia and hence obstetric problems including shoulder dystocia and obstructed labour. If the fetus does carry the GCK mutation, then the mother does not need insulin treatment and can have a normal pregnancy. A fetal abdominal circumference disproportionately >75th centile is used as a surrogate for the fetus not carrying the GCK mutation (as it is unable to handle the excess glucose) and glucose lowering treatment is more strongly indicated.

Treatment and monitoring is unnecessary outside pregnancy as patients do not get the typical complications of diabetes[14] and glucose-lowering therapies are usually ineffective in terms of lowering HbA1c. The inheritance of such mutations is autosomal dominant so it always useful to inform relatives who may otherwise be treated incorrectly.

Case scenario 4

A 38-year-old man presented to his GP with a six-month history of weight loss and thirst, he had a background history of eczema and hearing impairment, and his mother also had diabetes. He had a BMI of 28 and was diagnosed with type 2 diabetes, which was initially treated with metformin. Unfortunately, the patient became unwell soon afterwards with a metabolic acidosis. He was admitted to hospital whereupon he met the diabetes registrar who thought that he may actually have type 1 diabetes (or latent autoimmune diabetes of adult onset) and switched him over to a basal bolus insulin regime. Auto-antibodies were requested and the patient was sent home with outpatient follow-up. He was put on the waiting list for a DAFNE-structured education course to aid his diabetes self-management.

When the patient returned to the outpatient clinic, it was discovered that his anti-GAD and anti-insulin antibodies were all negative and he was having recurrent hypoglycaemia on minimal amounts of insulin. More detail was then uncovered regarding his family history, which showed a strong clustering of diabetes down the maternal line as well as deafness.

The patient underwent genetic testing, which uncovered a genetic mutation (3242A>G) in the mitochondrial DNA-encoded tRNA (Leu, UUR) gene. This mutation has a well-recognised association with bilateral sensorineural deafness. A decision was made to try a sulphonylurea; the patient responded to this initially but was back on basal-bolus insulin therapy within 2 years.

Mitochondrial diabetes does show a pronounced age-dependent deterioration of pancreatic function, indicating gradual deterioration of beta-cell function.[14] Metformin is contraindicated in these patients because of the (theoretical) risk of lactic acidosis.[15]

Given that the transmission of mitochondrial DNA only occurs through the maternal line, there was no concern that the patient's children would be affected. However, his younger sister became pregnant and was worried that she may have the mutation and pass this on to her offspring.

During the pregnancy, she developed both gestational diabetes (diet controlled) and worsening shortness of breath, which was a consequence of new onset cardiac failure. She gave birth to a baby girl (3.5 kg) at 34 weeks. The diabetes did not resolve post-partum and she continued to be monitored and managed with diet and lifestyle measures. Both mother and daughter tested positive for the same mitochondrial DNA mutation.

Mitochondrially inherited diabetes and deafness (MIDD) is characterised by varying penetrance of diabetes and deafness inherited through the maternal line. The vast majority of cases are caused by the A3243G mitochondrial DNA mutation. Co-morbidities that are strongly associated with mitochondrial diabetes include cardiomyopathy, renal failure and gastrointestinal abnormalities.[16]

Studies of patients with mitochondrial mutations demonstrate the crucial role that the ATP/ADP ratio plays in the process of glucose-induced insulin secretion. The A3243G mutation was originally detected in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS syndrome).[17] Family members with this mutation can vary in the deficit they suffer from diabetes alone, to MIDD to MELAS. This reflects the level of mutated mitochondrial DNA in the target organs (known as heteroplasmy).

Summary

Diabetes mellitus is a heterogeneous collection of diseases characterised by the presence of chronic hyperglycaemia. There are at least 50 different types and variants. The risk of developing diabetes involves a complex interaction between genetic and environmental factors. A huge bulk of work in the past decade has provided us with information on the underlying pathophysiology of the disease process and has consequently made a difference to our approach in clinical practice.

We should arguably be more suspicious that we are dealing with non-standard diabetes when the patient's phenotype, background and clinical history do not correspond with that which we might expect. The best clinical practice guidelines

produced in 2008 advocate testing for genetic forms of diabetes, especially when the onset is under 25 years and there is a family history of diabetes.[18] This is particularly important in the context of monogenic diabetes because there is the potential to spare a patient from the burden of a lifetime of insulin therapy and the ability to use molecular diagnostic techniques to help screen at-risk family members. Currently, there are ongoing studies looking at the use of highly sensitive C-reactive protein as a biomarker for monogenic diabetes[19] and the excellent MODY risk calculator on the University of Exeter website (www.diabetesgenes.org).[20] ∎

Acknowledgements

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