Uncommon forms of diabetes

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ABSTRACT

Diabetes mellitus is a common condition which all clinicians will encounter in their clinical practice. The most common form is type 2 diabetes followed by type 1 diabetes. However, there are many other atypical forms of diabetes which are important for a clinician to consider as it can impact on the diagnosis and their management.

This article focuses on maturity onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), ketosis-prone diabetes and other secondary forms of diabetes such as pancreatic cancer and haemochromatosis. We briefly describe the key clinical features of these forms of diabetes and their investigations and treatment.

Introduction

In the UK, around 90% of people with diabetes have type 2 diabetes (T2D), around 8% have type 1 diabetes (T1D) and around 2% have other forms of diabetes.[1]

Typically, we see T1D present in a young, lean patient with marked symptoms of polyuria, polydipsia, weight loss and diabetic ketoacidosis (DKA). In T2D, they are usually older, overweight and they are usually managed with oral medications initially. We should consider other forms of diabetes if the presentation is not typical; for example, we should consider maturity onset diabetes of the young (MODY) in a young, lean person with mild hyperglycaemia and a strong family history of diabetes diagnosed at a young age. We should think about latent autoimmune diabetes in adults (LADA) in a middle aged, lean patient with hyperglycaemia. We should consider ketosis-prone diabetes in a an overweight, non-White patient with DKA.

Here, we will focus on MODY, LADA, ketosis-prone diabetes and some secondary causes of diabetes. Other forms of diabetes are listed in Table 1.[2]

Maturity onset diabetes of the young

MODY is a group of monogenic beta-cell disorders, also known as monogenic diabetes. They are characterised by young age of onset (usually <25 years), autosomal dominant transmission, absence of autoimmune markers, absence of insulin resistance and insulin independence. It is estimated to account for 1%–2% of patients diagnosed with diabetes and, in the UK, the prevalence of MODY is estimated to be at 108 cases per million.[3] However, it may be a significant underestimate and these figures are not accurate until large population screening studies are performed. The most common mutations are hepatocyte nuclear factor-1-alpha (*HNF1*α; 52%), glucokinase (*GCK*; 32%) and *HNF4*α (10%), see Table 2.[3]

Hepatocyte nuclear factor-1-alpha gene

Formerly called MODY3, mutations on the *HNF1*α gene on chromosome 3 are associated with a progressive defect of insulin secretion.[4] Mutations here also result in low renal threshold for glucose and thus mutation carriers have detectable glycosuria.[5]

Key points

- Suspect other uncommon forms of diabetes if the clinical picture does not fit type 1 or type 2 diabetes. History, family history and phenotype of patient is useful. Screen for pancreatic cancer if there is new onset type 2 diabetes in older people with dramatic weight loss and features of exocrine insufficiency.
- If a patient presents with or develops diabetic ketoacidosis (DKA), they should be discharged on insulin; this includes ketosis-prone diabetes (in this case, their insulin requirement can be re-evaluated in an outpatient setting after the acute episode).
- Useful investigations to diagnose different forms of diabetes are glucose paired with C-peptide and diabetes autoantibodies.
- People with uncommon forms of diabetes can develop microvascular and macrovascular complications of diabetes and regular screening of complications should still be carried out.
- Contact the local diabetes team at an early stage for any unusual presentation of diabetes.

KEYWORDS: uncommon, atypical, diabetes, LADA, MODY

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Table 1. Aetiological classification of diabetes mellitus[2]

Gestational diabetes	
Genetic defects of beta-cell function	Transient neonatal diabetes Permanent neonatal diabetes Mitochondrial DNA mutations
Genetic defects in insulin action	Type A insulin resistance Leprechaunism Rabson–Mendenhall syndrome Lipoatrophic diabetes
Disease of the exocrine pancreas	Pancreatitis Trauma/pancreatectomy Neoplasia Cystic fibrosis Haemochromatosis Fibrocalculous pancreatopathy
Endocrinopathies	Acromegaly Cushing's syndrome Glucagonoma Phaeochromocytoma Hyperthyroidism Somatostatinoma
Drug induced	Pentamidine Nicotinic acid Glucocorticoids Thyroid hormone Diazoxide Beta-adrenergic agonists Thiazides Gamma-interferon Immunotherapy etc
Infections	Congenital rubella Cytomegalovirus
Uncommon forms of immune-mediated diabetes	Stiff-man syndrome Anti-insulin receptor antibodies
Other genetic syndromes associated with diabetes	Down syndrome Klinefelter syndrome Turner syndrome Wolfram syndrome Friedreich ataxia Huntington chorea Laurence–Moon–Biedl syndrome Myotonic dystrophy Porphyria Prader–Willi syndrome

People with *HNF-1* MODY can develop microvascular and macrovascular complications seen in T1D and T2D and, in addition, have an increased risk of cardiovascular mortality.[6]

They are exquisitely sensitive to sulphonylureas and often maintain excellent glycaemic control for years on these medications, with some patients eventually requiring insulin therapy.

Glucokinase gene

Formerly called MODY2, the *GCK* gene is found on chromosome 7. This mutation results in a higher threshold for glucose stimulated insulin secretion. Insulin secretion remains regulated and thus hyperglycaemia is often mild and stable. Patients are asymptomatic and hyperglycaemia is often found incidentally or during pregnancy.[4]

Diabetes-related microvascular complications are not observed.[7] There are no large studies assessing long term macrovascular outcomes, but *GCK* mutation carriers appear to have normal cardiovascular risk profiles.[8]

Treatment is not needed outside of pregnancy. During pregnancy, women are monitored closely, and occasionally insulin therapy is used, but if the fetus is macrosomic, the mainstay of treatment is early delivery.

Hepatocyte nuclear factor-4-alpha gene

Formerly known as MODY1, the *HNF4α* gene is found on chromosome 20 and is expressed both in the liver and in pancreatic beta cells. It functions to regulate positively the activity of *HNF1α* and is therefore similarly associated with an abnormal insulin secretory response to glucose.[9] Unlike *HNF1α*, mutation carriers of *HNF4α* have normal renal glucose threshold.

Similar to *HNF1α*, patients can develop microvascular and macrovascular complications and are also extremely sensitive to sulphonylureas.

Investigations

Clinicians should suspect MODY if patients are young, have a strong family history of diabetes diagnosed at a young age (<30 years old), have no features suggestive of insulin resistance and are not insulin-dependent. These investigations are helpful to aid clinical suspicion: negative autoantibody profile (islet cell cytoplasmic autoantibodies (ICA), glutamic acid decarboxylase autoantibodies (GAD65), insulinoma-associated-2 autoantibodies (IA2), zinc transporter-8 autoantibodies (ZnT8)) and sufficient C-peptide levels in comparison with paired serum glucose levels.

High sensitivity C reactive protein, which is under transcriptional control by *HNF1α*, has been seen to be lower in patients with *HNF1α* mutations. Given its modest cost and availability, they could be used as a biomarker to identify those with *HNF1α* MODY.[4] There is also a role for urinary C-peptide creatinine ratio as a practical outpatient tool in discriminating between *HNF1α*/*HNF4α* MODY (>0.2 nmol/mmol) and T1D of more than 5 years duration.[10] There is an online MODY probability calculator which can aid to quantify our clinical suspicion of MODY, and it can be found on: www.diabetesgenes.org.

Ultimately, diagnosis is via MODY genetic testing and recently this has been easier to access in the UK. Physicians should refer to their local diabetes or clinical genetics team to discuss this. A MODY genetic testing form can also be found on the given website.

Latent autoimmune diabetes in adults

LADA is a heterogeneous condition which shares characteristics of both T1D and T2D. Typically, LADA presents like T2D but is associated with progression to early insulin therapy. It is debated whether LADA is a distinct entity, or simply part of the spectrum of T1D. Studies suggest that LADA accounts for 2%–12% of adult-onset diabetes.[11]

Compared with T2D, people with LADA tend to be younger, leaner and have a personal or family history of autoimmune

Table 2. Comparison of maturity onset diabetes of the young subtypes

MODY mutation	*HNF1*α (previously MODY3)	*GCK* (previously MODY2)	*HNF4*α (previously MODY1)
Estimated frequency	52%	32%	10%
Chromosome affected	3	7	20
Defect	Progressive reduced insulin secretory response to glucose	Higher threshold for glucose stimulated insulin	Regulates activity of *HNF1*α therefore also show abnormal insulin secretory response to glucose
Clinical features	Low renal threshold for glucose (glycosuria)	Mild, stable and asymptomatic; hyperglycaemia often found incidentally	Normal renal threshold for glucose
Risk of microvascular/ macrovascular disease	Yes	Not observed	Yes
Optimal treatment	Sulphonylureas, but may progress to insulin	Not required; will need close monitoring during pregnancy	Sulphonylureas, but may progress to insulin

*HNF1*α = hepatocyte nuclear factor-1-alpha; *GCK* = glucokinase; *HNF4*α = hepatocyte nuclear factor-4-alpha.

disease. Features of the metabolic syndrome tend to be present in a similar or higher frequency in LADA compared with T1D. There is considerable heterogeneity and is sometimes phenotypically and characteristically indistinguishable from T1D or T2D.[12] It is thought that LADA is a more insidious presentation of T1D but, unlike typical T1D, does not present acutely with DKA or an insulin-requiring diabetes emergency. Typically, they present >30 years of age, are independent of insulin at diagnosis for more than 6 months and have positive diabetes autoantibodies.

From an analysis of patients enrolled in the UKPDS trial, there was no significant difference in cardiovascular outcomes compared with patients with T2D, after adjustment for confounders.[13] Patients with LADA were also seen to have a higher risk of microvascular complications compared with T2D, secondary to worse glycaemic control. Therefore, optimisation of glycaemic control and secondary prevention of diabetic complications should be an important aspect in the management of LADA.[14]

Investigations

As mentioned, positivity for diabetes autoantibodies is a feature of LADA, out of which, GAD65 antibody is the most sensitive with up to 90% of LADA patients positive.[15] Therefore, GAD65 antibody is a good screening antibody, and if there is still a strong suspicion of LADA in a GAD65 antibody negative patient, other diabetes autoantibodies should be assayed.

C-peptide, as a marker of endogenous insulin production, is useful to aid management (see later). With LADA, patients tend to have a low but still detectable level.

Treatment

Treatment of LADA is aimed at preserving insulin secretion capacity, commencing insulin when appropriate and standard secondary prevention of diabetic complications. Sulphonylureas can accelerate the decline of C-peptide levels and are not recommended for the treatment of LADA.[12]

A recent consensus statement from an international expert panel suggests the use of C-peptide to guide management of LADA. C-peptide levels should be done concurrently with plasma glucose which should be between 4.4 to 10 mmol/L. If C-peptide levels are <300 pmol/L, a multiple insulin regimen is recommended, and the patient should be treated as T1D. If C-peptide levels are between 300 to 700 pmol/L, the patient should be treated like having T2D, avoiding the use of sulphonylureas. C-peptide levels should be repeated every 6 months here. If C-peptide levels are >700 pmol/L, treat like T2D and consider repeating C-peptide when there is a deterioration in glucose control.[12]

Ketosis-prone diabetes

Ketosis-prone diabetes is characterised by the presence of DKA in patients who do not fit the typical characteristics of T1D. After initial treatment with insulin and improvement in glycaemic control, there is frequently a marked improvement in beta cell function allowing discontinuation of insulin therapy within a few months.[16] In these patients, there is an acute reduction in insulin secretion and action due to glucose toxicity on the beta cells. Treatment with insulin can improve hyperglycaemia and beta cell function and therefore, ceasing the need for further insulin treatment within a few months.

This is more commonly seen in people of non-White ethnicity, particularly Black African or African–Caribbean people and shows a strong male predominance, strong family history, higher age and higher body mass index.[17,18] There is also a link between glucose-6-phosphate dehydrogenase deficiency (a condition that is frequent in male West Africans) and ketosis-prone diabetes.[19]

It is important to recognise this clinical entity as continuation of unnecessary insulin could cause further weight gain, hypoglycaemia and impact quality of life. Furthermore, incorrectly diagnosing these patients with T2D could neglect the importance of checking ketones when unwell.

Investigations and management

DKA should be managed as per DKA protocols and all patients should be discharged on insulin. Following discharge, patients should be followed up by the diabetes team to reassess beta cell function with C-peptide measurements and to assess autoimmunity. They must have a negative autoantibody profile.

Table 3. Clinical and biochemical features of T1D, T2D, LADA, MODY, ketosis-prone diabetes

	T1D	T2D	MODY	LADA	Ketosis-prone diabetes
Age of onset	Childhood/ adolescence	Adulthood	<30 years old	30–50 years old	Adulthood
Ethnicity	More common in White people	More common in Asian people	Prevalence not known	More common in White people	More common in Black African/African–Caribbean people
Insulin requirement	At diagnosis	Absent or years after diagnosis	Variable	>6 months after diagnosis	If DKA / low C-peptide levels
BMI	Variable	Increased	Variable	Variable	Increased
Diabetes autoantibodies	High titre	Absent	Absent	High/low titre	Absent
C-peptide levels 5 years post-diagnosis	Usually <300 pmol/L	Normal/increased	Usually >300 pmol/L	Decreased but still detectable	Variable

BMI = body mass index; DKA = diabetic ketoacidosis; LADA = latent autoimmune diabetes in adults; MODY = maturity onset diabetes of the young; T1D = type 1 diabetes; T2D = type 2 diabetes.

Typically, C-peptide levels are low at the time of DKA and increase within a few weeks/months.[18]

In patients with sufficient C-peptide in comparison to their paired glucose level, insulin can be safely discontinued in the majority of patients. They can manage with diet or metformin for some years but can relapse with DKA. Patients with insufficient C-peptide in comparison with their paired glucose level will need to continue insulin therapy.[20]

Secondary causes of diabetes

There are many secondary causes of diabetes as highlighted in Table 1. Although much less common, it is important to recognise them so that the primary disease can be treated promptly. We discuss two important causes of secondary diabetes.

Pancreatic cancer

Pancreatic cancer may rarely present with hyperglycaemia due to pancreatic dysfunction from the cancer. Consider screening with computed tomography (CT) for pancreatic cancer if there is new-onset T2D in older people with marked weight loss, loss of appetite, abdominal pain or features of exocrine insufficiency.

Haemochromatosis

Haemochromatosis can present with hyperglycaemia due to iron deposition in the pancreas. There should be a clinical suspicion if there is skin hyperpigmentation, joint pain, hypogonadism or features of liver disease. Laboratory tests that may be associated with haemochromatosis are unexplained liver function abnormalities, high serum ferritin and high transferrin saturations. Diagnosis will come from *HFE* gene mutation tests. Treatment of diabetes in haemochromatosis is similar to T2D and can sometimes also be improved with phlebotomy.[21]

Conclusion

Diabetes is a common condition and affects a large proportion of people that we see in clinical practice. Although the general physician will be familiar with the presentations of T2D and T1D, it is important to consider other uncommon forms of diabetes and, if the presenting features are atypical, to involve the local diabetes team at an early stage (Table 3). ■

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