DIAGNOSTIC TESTS

Non-type 1, non-type 2 diabetes: what's in a name?

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SUMMARY

Most patients who develop diabetes are classified as having either type 1 or type 2 diabetes. However, a small proportion of patients do not fit these classifications and are said to have non-type 1, non-type 2 diabetes.

Type 1 diabetes usually presents in childhood and adolescence, but if pancreatic function fails slowly it may present in later life. This has been called latent autoimmune diabetes in adults.

Type 2 diabetes usually presents in later life, but a few people develop its features at an early age. They may have maturity-onset diabetes of the young, which is now known to be caused by specific genetic defects.

The genetic defects of maturity-onset diabetes of the young are autosomal dominant, so there is a strong family history. Knowing which gene is affected is important as this may influence treatment.

Introduction

Diabetes mellitus is most often a result of the combination of insulin resistance and insulin deficiency. Hyperglycaemia occurs because there is an inadequate concentration of insulin (insulin deficiency) to overcome the degree of insulin resistance present.

In type 1 diabetes there is autoimmune destruction of pancreatic beta cells. The rate of this destruction varies, being more rapid in children and adolescents and slower in adults. This explains why it classically presents before the age of 30 years and patients quickly become insulin dependent. The slower onset type 1 diabetes in adults is sometimes referred to as latent autoimmune diabetes.

In type 2 diabetes the patient secretes insulin, but there is a decrease in insulin sensitivity which is usually called insulin resistance. Ageing, obesity and physical inactivity are commonly associated with insulin resistance. The natural history of type 2 diabetes is that insulin secretion falls with duration of the disease and can result in absolute insulin deficiency.

The biochemical mechanisms underlying insulin resistance or a poor insulin secretory response by the beta cells of the pancreas are not fully understood. There is evidence for a genetic contribution to both.[1] In the past, patients with insulin deficiency were considered to have type 1 diabetes while those with insulin resistance had type 2 diabetes. However, not all patients present with classical phenotype. There are young people who have features of type 2 diabetes and there are older people with slowly progressing insulin-dependent diabetes. The classification of diabetes has therefore been revised (see Box).

Box **Types and causes of diabetes**

Type 1 – insulin deficiency predominantly due to autoimmunity (includes latent autoimmune diabetes in adults)

Type 2 – predominantly insulin resistance with relative insulin deficiency

Genetic defects (includes maturity-onset diabetes of the young (MODY) and mitochondrial diabetes)

Pancreatic diseases e.g. pancreatitis

Endocrinopathies e.g. Cushing's disease

Gestational diabetes

Drugs e.g. corticosteroids, olanzapine

Clinical classification

Diabetes can be diagnosed by a high concentration of glucose or glycated haemoglobin (HbA1c) in the blood. Every time you see a patient with newly diagnosed diabetes, you should ask yourself the question 'What is the underlying cause of this diabetes?' Sometimes the answer is obvious, but often it is unclear.

Type 1 diabetes accounts for 5–10% of cases. There is usually no family history of diabetes. Type 1 diabetes presents classically with weight loss, polyuria, polydipsia and ketosis in a younger patient, however it can be detected at any stage in its evolution. The presence of a variety of autoantibodies confirms the diagnosis of type 1 diabetes. These include autoantibodies to islet cells, insulin and glutamic acid decarboxylase, but their absence does not exclude the diagnosis.

Type 2 diabetes accounts for 90–95% of cases. It can be considered as a disease for which the cause has not yet been identified. There is often a family history of diabetes. The patients are usually over 30 years old with a high body mass index. If not obese, they have central obesity. This is more common in Asian patients.

Within the classical type 2 group of older, overweight, non-ketotic patients, about 5% have evidence of beta cell autoimmunity.[2] This means that they have type 1 diabetes, but with a much slower onset than the classical presentation. This has been called latent autoimmune diabetes in adults. These patients will require insulin earlier than patients without autoantibodies, however, many practitioners are slow to start insulin in patients who have not been diagnosed as having type 1 diabetes, even when treatment for type 2 diabetes does not achieve a target concentration of HbA1c.

Treatment should be guided by the clinical picture predominantly and not the diagnosis. Clinical features include the degree of hyperglycaemia, the presence or absence of ketosis, symptoms and the patient's body mass index and physical activity.

Finding the cause of hyperglycaemia

Clinical questions are 'Does this person have a significant, identifiable contributor to the diabetes in addition to age, physical inactivity and obesity?' and 'How will this alter my management?' To answer these questions requires clinical skill and judgement. Doing every possible test in every patient would be inappropriate.

During the history and physical examination, consider if the patient is on any drugs such as olanzapine which could contribute to hyperglycaemia, or has a disease which is associated with diabetes.[3,4] Endocrinopathies such as acromegaly, Cushing's syndrome or hyperthyroidism and conditions such as pancreatic cancer and haemochromatosis can cause hyperglycaemia.

Genetics

More recently, the search for an explanation of the patient's hyperglycaemia has been expanded to include the question 'Does this patient have a genetic contributor to the diabetes which can be identified and which would alter management?'.

Genetic mutations have been found in young people who present with features of type 2 diabetes. These conditions are collectively known as maturity-onset diabetes of the young (MODY). They are different from the type 2 diabetes which is now occurring in obese young people. The mutations cause dysfunction of pancreatic beta cells, but autoantibodies are usually absent.

MODY accounts for 1–2% of cases of diabetes. It is usually diagnosed before the age of 25 years. As there is autosomal dominant inheritance, there is a strong family history of diabetes present in every generation. The six genes listed in the Table account for most cases of MODY. The most common conditions are MODY 2 and 3. Identifying the mutation may significantly alter treatment.

MODY 1 and 3

Mutations in the hepatic nuclear factor genes result in MODY 1 and 3. These mutations are associated with hyperglycaemia that leads to microvascular complications so these patients require treatment. They may have been born large, and experienced postnatal hypoglycaemia, and they have glycosuria. The mutations produce an insulin deficiency picture which is likely to be mistaken for type 1 diabetes, but the patients do not become totally insulin deficient with time.

The patients may be particularly sensitive to therapy with sulfonylureas. Early in the disease, glycaemic control may be better with a sulfonylurea than with insulin.

MODY 2

In MODY 2 a mutation causes a defect in glucokinase – a glycolytic enzyme. This results in fasting hyperglycaemia, but little postprandial hyperglycaemia. During a glucose tolerance test, despite the fasting hyperglycaemia, the rise in blood glucose after a glucose load is less than 3 mmol/L.

Recognising MODY 2 is important as it is not associated with microvascular complications and so it does not require any treatment to control blood glucose. However, there are two major caveats.

Table **The genetics of maturity-onset diabetes of the young (MODY)**

Condition	Gene affected	Chromosome affected
MODY 1	HNF-4 alpha	Chromosome 20
MODY 2*	glucokinase	Chromosome 7
MODY 3†	HNF-1 alpha	Chromosome 12
MODY 4	IPF-1	Chromosome 13
MODY 5	HNF-1	Chromosome 17
MODY 6	NeuroD1	Chromosome 2

* 13% of MODY cases
† 70% of MODY cases
HNF hepatocyte nuclear factor
IPF insulin promoter factor

The hyperglycaemia is often first detected during pregnancy and may require treatment. The risk to the fetus depends on whether the fetus also has the mutation or not. Unaffected fetuses are at risk of being oversized, while affected fetuses may be undersized if the mother's hyperglycaemia is treated.[‡] The other caveat is that a glucokinase mutation does not protect against developing type 2 diabetes. The risk is thought to be the same as in the general population. People with MODY 2 should be monitored (using HbA1c) to detect worsening hyperglycaemia.

Mitochondrial diabetes

In mitochondrial diabetes a mutation is inherited from the mother. It is usually associated with hearing impairment. The mutation in mitochondrial DNA results in a gradual functional decline in the pancreatic beta cells.

A practical approach

A stepwise approach to a patient with newly diagnosed diabetes, or a patient with diabetes who you are seeing for the first time, might be:

- does the person have type 1 diabetes? (younger, thinner, acute onset hyperglycaemia)
  - if uncertain, consider measuring autoantibodies to confirm the diagnosis
- if not type 1 diabetes
  - is this simply type 2 diabetes or is there another obvious contributing factor such as a disease or drugs either known or not yet recognised?
  - consider other aetiologies including MODY (identify them as antibody negative for further possible investigation as more information on aetiology appears in the future)
- if MODY is suspected use the diabetesgenes.org website calculator[§] and refer to a specialist.

Future developments

It is not cost-effective to do genetic testing on everyone with diabetes. Research is looking for markers which may suggest MODY. One example is high-sensitivity C-reactive protein. Its concentration may be lower in patients with HNF-1 alpha mutations.

The general use of the term MODY is likely to decline with increased understanding of the underlying genetic disorders.

Conclusion

The diagnosis of diabetes can usually be made by using the information obtained from history and physical examination. A few patients who were previously thought to have type 1 or type 2 diabetes have been found to have a genetic disorder. These patients have by definition non-type 1, non-type 2 diabetes.

Patients with MODY have a strong family history of diabetes, but no autoantibodies or features of insulin resistance. These patients are often misdiagnosed – identifying the mutation may change the way they are managed. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Diabetes due to a glucokinase mutation needs to be treated with insulin.

6. Type 1 diabetes can be excluded if the patient has no autoantibodies.

Answers on page 219

[‡] www.diabetesgenes.org/content/glucokinase

[§] see www.diabetesgenes.org/content/mody-probability-calculator for the prototype MODY Probability Calculator

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