Recognising the diversity of autoimmune diabetes in adults

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Type 1 or autoimmune diabetes can occur at any age and may present as rapidly or slowly progressive disease. The availability of robust islet autoantibody assays has enabled detection of different forms of autoimmune diabetes and given clinicians a greater appreciation for its varied presentations, including classic juvenile-onset type 1 diabetes, adult-onset type 1 diabetes and the more slowly progressive latent autoimmune diabetes in adults (LADA).

Key points

- **Type 1 diabetes can occur at any age.**
- **Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of type 1 diabetes and is present in up to one in 10 adults with presumed type 2 diabetes.**
- **Significant overlap exists between LADA and other types of diabetes.**
- **There are immunoassays for specific islet antigens that enable recognition of autoimmune diabetes across different age groups and presentations of diabetes.**

ENDOCRINOLOGY TODAY 2014; 3(1): 39-41

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I recall an 80-year-old woman who presented one busy evening while I was working as a medical registrar. The patient was unwell with diabetic ketoacidosis, in the context of 'type 2 diabetes' documented in previous hospital admissions. Based on teaching from my undergraduate lectures that insulin-dependent diabetes (type 1 diabetes) usually occurs in children and rarely in adults, I thought, 'she can't possibly have developed type 1 diabetes as an elderly person'. After grappling with the concept for a few moments, I documented her metabolic status and handed the patient over to the night registrar as a 'patient with unstable type 2 diabetes'. To this day, I do not know precisely what form of diabetes this elderly woman had, but reflecting on this clinical scenario (with the benefit of hindsight and a few grey hairs), I would not be surprised if she indeed had developed type 1 diabetes late in life. Clinical medicine and research have taught me that it is harder to unlearn the incorrect old than to learn the correct afresh.

The many forms of autoimmune diabetes

Type 1 diabetes is an organ-specific autoimmune disease, often associated with HLA DR3 and/or DR4 phenotypes along with circulating islet autoantibodies, characterised by progressive beta-cell dysfunction and destruction due to lymphocytic infiltration of the islets. Over 40 years ago, the pathogenesis of 'insulin-dependent diabetes' was believed to be rapid, but much research has shown that its pathogenesis is typically slow. Natural history studies of type 1 diabetes have demonstrated circulating islet autoantibodies are present for many years before the development of diabetes with studies of monozygotic twins demonstrating development of diabetes in a twin

Clinical screening tool for autoimmune diabetes in adults[2]

There are five clinical hallmarks that raise the suspicion of autoimmune diabetes or LADA in patients presenting with presumed type 2 diabetes. The positive predictive value for LADA is approximately 20% (i.e. one in five such patients will have LADA) when at least two of the following characteristics are present:

- age <50 years
- symptomatic diabetes presentation (polydipsia, polyuria or unintentional weight loss)
- BMI <25 kg/m^2
- personal history of an organ-specific autoimmune disorder (autoimmune thyroid disease, coeliac disease, autoimmune gastritis or pernicious anaemia, Addison's disease, vitiligo)
- family history of an organ-specific autoimmune disorder.

Given the higher risk for LADA, an adult with presumed type 2 diabetes presenting with at least two out of these five clinical characteristics may merit islet autoantibody screening.

up to 20 years after diabetes in the index twin case. Type 1 diabetes does classically occur in children or young adults; however, its occurrence later in adulthood is well described and there is some suggestion that its incidence has a bimodal profile with peaks in the teenage years and then in mid-adulthood.

Latent autoimmune diabetes in adults (LADA) is being recognised more frequently. This is a slowly progressive form of type 1 diabetes characterised by positivity for circulating islet autoantibodies and an initial period of insulin independence (for at least six months following diagnosis) that is often followed by eventual need for insulin therapy due to progressive insulin deficiency. Management of LADA is different to that of adult-onset type 1 diabetes (in the latter, patients commence insulin therapy immediately after diagnosis). LADA is present in up to one in 10 adults with presumed type 2 diabetes, where its clinical significance is a higher risk of progressing to insulin therapy within six years of diagnosis because patients are often primarily insulin deficient and may be at risk for diabetic ketoacidosis and having other organ-specific autoimmune diseases.[1]

Recognising autoimmune diabetes

There are several scenarios in which the possibility of autoimmune diabetes needs to be considered in adults. A simple clinical assessment tool that can be used to identify patients with presumed type 2 diabetes who are at higher risk for LADA is described in the Box.[2] It is important to appreciate that significant overlap exists between LADA and other types of diabetes (Table).

Scenario 1: initial diabetes diagnosis

Whenever diabetes is diagnosed in an adult, consideration should be given to the alternative forms of the disease. These include autoimmune diabetes, monogenic diabetes or secondary diabetes (e.g. due to pancreatic pathology or an endocrinopathy such as Cushing's syndrome, acromegaly or thyrotoxicosis).

Scenario 2: rapidly progressing diabetes

Autoimmune diabetes in adults needs to be considered in a patient who is experiencing more rapidly progressive diabetes consisting of suboptimal glycaemic control despite escalation of oral hypoglycaemic therapy and adequate lifestyle measures. In this scenario, the clinician should have an increased level of suspicion that the lack of glycaemic control may be due to insulin deficiency secondary to autoimmune beta-cell pathological changes. In this situation, it would be reasonable to perform islet antibody testing to exclude

Table. Different types of diabetes: clinical features at presentation

Clinical feature	LADA	Adult-onset type 1 diabetes	Juvenile-onset type 1 diabetes	Type 2 diabetes
Age of onset	Adult	Adult	Age <18 years	Usually adult
Symptomatic presentation	Often present	Yes	Yes	Often not present
Overweight or obesity	Majority, but normal BMI can be a specific marker for autoimmune diabetes	May be present but not typical	May be present but not typical	Majority
Personal or family history of autoimmunity	Often present	Often present	Often present	Usually not present

Abbreviations: LADA = latent autoimmune diabetes in adults; BMI = body mass index.

autoimmune diabetes. In my experience, suboptimal glycaemia in such patients can be prolonged because it is not attributed to autoimmune diabetes and insulin deficiency. Multiple variables are considered in the decision to progress from oral therapies to insulin in diabetes patients, including glycaemic control, adiposity and patient preference and suitability. If a clinician is confronted by a diabetes patient with rapidly evolving hyperglycaemia that is not responding to lifestyle changes on maximal oral hypoglycaemic therapies, along with islet autoimmunity (and insulin deficiency) then insulin therapy should be instituted.

Scenario 3: 'brittle diabetes'

Autoimmune diabetes may need to be considered in a patient who has already progressed to subcutaneous insulin therapy yet exhibits highly labile and unpredictable blood glucose levels ('brittle diabetes'), especially if the clinical hallmarks of LADA were present at diagnosis. Consideration of LADA is especially important in patients using basal or premixed insulin alone because recognition of autoimmune diabetes may encourage more rapid intensification of the insulin regimen.

Islet autoantibody and C-peptide tests

The development of robust immunoassays for specific islet antigens has paved the way for recognition of autoimmune diabetes across different age groups and presentations of diabetes. Autoantibodies to glutamic acid decarboxylase (GAD), tyrosine phosphatase-like insulinoma antigen 2 (IA-2), insulin and zinc transporter 8 (ZnT8) may be present in autoimmune diabetes. GAD, IA-2 and insulin autoantibodies can be detected by commercial ELISA assays, whereas commercials assays for ZnT8 antibodies are not in widespread use in Australia currently. In classic adult-onset type 1 diabetes, approximately 90% of patients are positive for at least one autoantibody. LADA is defined as being positive for an islet autoantibody, with most patients being positive for GAD antibody alone. Patients with LADA typically present with more preserved beta-cell function than those with classic type 1 diabetes but can experience marked loss of beta-cell function within six years of diagnosis, eventually resulting in insulin dependence. If islet autoantibody positivity is present in adult-onset diabetes, implying autoimmune diabetes, a fasting C-peptide test in combination with fasting plasma glucose can provide a guide regarding the degree of insulin deficiency. Ultimately, glycaemic measures such as glycosylated haemoglobin will be the major determinant for escalating diabetes therapies and progressing to subcutaneous insulin.

Treatment

For patients with adult-onset type 1 diabetes or LADA, referral to an endocrinologist is recommended because the behaviour of these forms of diabetes is distinct from type 2 diabetes with greater fluctuations in blood glucose levels and risk of diabetic ketoacidosis (hyperglycaemia in conjunction with ketonaeamia or ketonuria and acidosis). In patients with classic adult-onset type 1 diabetes or LADA who are not responding to oral hypoglycaemic therapy, insulin is required, preferably a basal–bolus insulin regimen. In patients who have progressed to insulin therapy, consideration should be given to formal education in carbohydrate counting to determine the prandial insulin dose, such as the Dose Adjustment For Needs Education (DAFNE) courses; the use of an insulin pump (continuous subcutaneous insulin infusion [CSII]) is an option. Management of these patients includes the routine aspects required for all patients with diabetes, including annual screening for diabetes-related complications and lifestyle education in relation to diet and exercise.

Care of these patients should be shared between the primary care health team (including a GP and practice nurse), an endocrinologist and diabetes multidisciplinary team, which may include a diabetes nurse educator, dietitian, podiatrist and exercise physiologist. Other medical specialists are often involved in the care of these patients for significant diabetes-related complications. Screening for other organ-specific autoimmunity in LADA is performed by many clinicians, given the strong genetic association and hence relatively higher frequency of other autoimmune conditions, such as autoimmune thyroiditis, autoimmune gastritis and coeliac disease. An organ-specific autoimmune screen may consist of testing for thyroid function and serology for thyroid peroxidase, parietal cell, intrinsic factor and transglutaminase antibodies. The recognition of LADA can be associated with the subsequent detection of other occult autoimmune diseases and may be a benefit of recognising autoimmune diabetes initially.

Conclusion

In adult-onset diabetes it is important to consider the possibility of autoimmune diabetes if a patient presents with suggestive clinical features or if the course of their diabetes is more rapidly progressive than usually seen. Clinical features at presentation of diabetes associated with a greater likelihood of autoimmune diabetes include: age less than 50 years, symptomatic presentation with polydipsia, polyuria or unintentional weight loss, BMI less than 25 kg/m^2, and a personal history and family history of an organ-specific autoimmune disorder. A diagnosis of autoimmune diabetes can be made by testing for GAD, IA-2 and insulin autoantibodies. **ET**

References

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COMPETING INTERESTS: None.