What is type 1 diabetes?

SL Thrower

PJ Bingley

Abstract

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by hyperglycaemia secondary to inadequate production of insulin by the pancreas. This is the result of T cell-mediated autoimmune destruction of the insulin-producing β cells in the islets of Langerhans, and is associated with circulating autoantibodies to β-cell antigens. The classic clinical presentation of T1DM is an acute onset of symptoms caused by β-cell failure. The typical symptom triad is weight loss, polyuria and polydipsia. These are metabolic consequences of insulin deficiency, which also leads to risk of ketoacidosis. T1DM is a complex disease resulting from multiple genetic and environmental aetiological factors. The incidence of childhood T1DM is currently increasing worldwide. The disease has a long preclinical prodrome before frank failure of β-cell function. The autoimmune process generally starts in infancy, but the rate of autoimmune β-cell destruction varies widely between individuals. While T1DM presents most commonly in children and young adults, it can present at any age. The clinical presentation in adults is often less acute. More than 50% of cases present after age 20 years. The long preclinical prodrome raises the possibility of intervention to delay or prevent clinical onset of disease.

Keywords Aetiology; autoantibody; autoimmunity; classification; diagnosis; epidemiology; immunology; type 1 diabetes

What's new?

- Recognition that peak incidence of autoantibody positivity occurs before the age of 2 years in genetically susceptible individuals and that the presence of multiple autoantibodies equate to certain T1DM
- Although vitamin D is important in immune system functioning, and case-control studies have shown that the incidence of T1DM is lower in individuals taking vitamin D supplementation, randomized controlled trials of vitamin D supplementation as a means of primary disease prevention have shown mixed results, whereas the results of pilot studies modifying the intake of cows' milk protein in infants' diets have been promising
- The first phase II clinical trials of various immunomodulatory agents such as monoclonal antibodies against CD3 and CD20 have reported their results. None has shown convincing evidence of long-term clinical efficacy to date. Many trials in this field are ongoing

Introduction

Type 1 diabetes mellitus (T1DM), formerly known as insulin-dependent diabetes, is a chronic disease characterized by hyperglycaemia secondary to inadequate production of insulin by the pancreas. This occurs as a result of autoimmune destruction of the insulin-producing β cells in the islets of Langerhans. The typical triad of symptoms at presentation — weight loss, polyuria and polydipsia — occurs as a metabolic consequence of inadequate insulin production, which itself leads to a risk of ketoacidosis. It is now recognized that the rate at which this autoimmune β-cell destruction occurs can vary widely between individuals. Although presentation is most common in childhood and early adulthood, T1DM can present at any age and at least 50% of cases occur after age 20 years.

Classification of T1DM

T1DM accounts for 5–10% of the total number of cases of diabetes mellitus worldwide. The WHO classification of diabetes defines T1DM as being primarily due to β-cell destruction, usually leading to absolute insulin deficiency. In most cases there is evidence of an autoimmune pathogenesis — autoantibodies to β-cell antigens in the serum and markers of human leucocyte antigen (HLA) genetic susceptibility — at the time of diagnosis.

In practical terms, patients with T1DM are prone to develop ketoacidosis and require treatment with exogenous insulin. However, one should bear in mind that type 2 diabetes (T2DM) can present with an episode of ketoacidosis, and slow-onset T1DM may initially have been effectively treated with oral hypoglycaemic agents. These less characteristic scenarios can result in potential diagnostic confusion, particularly as increasing rates of obesity (both in childhood and adulthood) at presentation of diabetes can further complicate interpretation of the clinical picture and can lead occasionally to inappropriate decisions about long-term treatment.

Immunology of T1DM

T1DM is an organ-specific autoimmune disease in which self-reactive T lymphocytes, activated by autoantigen, destroy the pancreatic insulin-producing β islet cells in the islets of Langerhans.

Cellular autoimmunity

It is generally accepted that the destruction of β islet cells is mediated by cellular immune responses.[1] The evidence for this is as follows:

- T cells (predominantly CD4+ and CD8+) infiltrate the islets in a process known as 'insulitis' (Figure 1).
- Disease progression can be delayed by immunosuppressive drugs that inhibit effector T cell function.
- Circulating autoreactive T cells can be detected in individuals presenting with newly diagnosed disease.

In a normally functioning immune system, self-reactive T lymphocytes would be eliminated, or their activity controlled, by

S L Thrower *MD MRCP is a Specialist Registrar in Diabetes and Endocrinology in the Severn Deanery, UK. Competing interests: none declared.*

P J Bingley *MD FRCP is a Professor of Diabetes at the University of Bristol, UK. Competing interests: none declared.*

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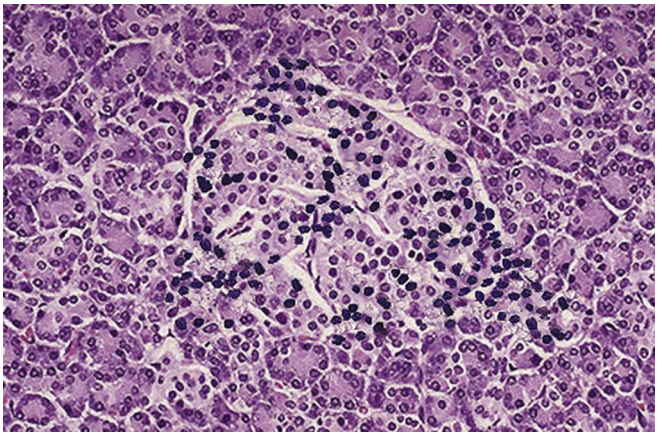

Figure 1 Insulitis. The human islet (centre) is infiltrated with mononuclear cells: macrophages and CD8+ and CD4+ T lymphocytes.

a number of complementary mechanisms, resulting in immune system 'tolerance'.[2] There is increasing evidence to support this immune system regulation as being deficient in T1DM, in particular in the numbers and/or function of a subset of CD4+ T cells central to the maintenance of self tolerance, known as regulatory T cells, or $T_{regs.}$[1,2]

Autoantigen epitopes and epitope spreading

The primary autoantigen in T1DM remains controversial; proinsulin or insulin itself has been suggested. Over time, immunoreactivity spreads to recognize multiple islet cell antigens, a process known as 'epitope spreading'.[3] One proposed mechanism for autoreactivity to these initial epitopes is 'molecular mimicry'. According to this theory the immune system processes and presents a foreign antigen, for example a viral protein, in such a way that it has structural similarities to self-antigen, and cross-reactivity occurs. As autoreactive T cells able to respond to these epitopes become activated, β-cell damage takes place. This damage results in the release of cell debris and further autoantigens. Over time, the repertoire of antigenic epitopes recognized by autoreactive effector T cells grows and the autoimmune response becomes more robust, resulting in further β-cell damage and T1DM.

Autoantibodies

T1DM is heralded by the sequential development of circulating autoantibodies. The role, if any, of these antibodies in the pathogenesis of the disease remains uncertain because they are not directly involved in β islet-cell destruction. However, they can be used to predict T1DM.[4] They generally appear in infancy as early as six months of age, with a peak incidence under two years of age in genetically susceptible individuals,[5] and are detectable many years before the diagnosis of T1DM becomes clinically apparent.[6] The first autoantibodies described were islet cell antibodies (ICA). Antibodies directed against the islet autoantigens — insulin (IAA), glutamate decarboxylase 65 (GADA) and tyrosine phosphatase IA-2 (IA2A) — have since been identified. Most recently, antibodies directed against a further islet autoantigen — the zinc transporter, Slc30A8 (ZnT8) — have been discovered. Combined measurement of IAA, GADA and IA2A can detect autoimmunity in up to 80% of those at risk of developing T1DM or who have newly diagnosed disease. Adding ZnT8A measurement increases the rate of detection of autoimmunity at diagnosis to 98%.[7] The detection of multiple autoantibodies in an individual equates to almost certain future development of T1DM.[8]

Epidemiology of T1DM

T1DM affects approximately 400,000 people in the UK and up to 20 million people globally. The annual incidence of the condition in children under the age of 14 years varies globally, from 0.1/100,000 to 64.2/100,000. Asian countries, such as China, tend to have a low incidence while areas of Europe, such as Finland and Sardinia, report the highest incidence. In the UK, the incidence of childhood T1DM is greater than 20/100,000 per year. In Europe, the incidence has been increasing by approximately 4% per year since 1989.[9] The rise in incidence has been particularly marked in children under the age of 5 years. In the UK, it is predicted that the number of children with T1DM under the age of 15 years will increase from 18,600 in 2005 to 33,300 in 2020. This rapid increase strongly suggests that environmental factors play a role in the aetiology of T1DM.

Aetiology of T1DM

Many genetic and environmental factors have been studied as potential causes of T1DM.

Genetic associations

There is strong clustering of T1DM in some families. The sibling of a child with T1DM has around a 6% lifetime risk of developing the disease and the concordance rate in monozygotic twins is 30—50%.[10] These observations have driven a search for the genetic associations of the condition.

Human leucocyte antigen: genes in the HLA region on chromosome 6p21 are most strongly associated with T1DM, particularly the *HLA-DRB1-DQB1* haplotypes. Two haplotypes, *DRB1*0401-DQB1*0302* and *DRB1*0302-DQB1*0201*, confer susceptibility for T1DM whilst others, such as *DRB1*15-DQB1*06*, are protective.[11] In white populations, which represent the ethnic background of the majority of people with T1DM, 93% of affected individuals carry either an HLA DR3 allele or an HLA DR4 allele, or both. Individuals carrying these two alleles together (i.e. those with the heterozygous genotype *DRB1*0401-DQB1*0302/DRB1*0302-DQB1*0201*) are at highest genetic risk.

Other genetic factors: T1DM is polygenetic and genome-wide association studies confirm that over 40 chromosome regions are involved. However, it is estimated that about 60% of the genetic variability in the condition can be explained on the basis of three T1DM-associated loci combined with chromosome 6p21. These loci are the variable number of tandem repeats near the insulin gene (*INS-VNTR*), the cytotoxic T lymphocyte-associated antigen-4 (*CTLA-4*), and the protein tyrosine phosphatase non-receptor-type 22 (*PTPN22*).[12] These genes all encode for proteins involved in pathways around the key interaction between antigen-presenting cells and T cells. Their mechanism of action is believed to involve their effects on the development and function of autoreactive T cells.

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