**Natural history and immunopathogenesis of type 1 diabetes**

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**INTRODUCTION**

Type 1 diabetes (T1D) develops in the majority of cases as result of chronic progressive β-cell destruction. This inflammatory damage depends on a selective loss of immune tolerance, that leads to an extensive infiltration of both helper and cytotoxic T-lymphocytes in the pancreatic islets. The autoimmune mechanism is proven by the presence of a pool of autoantibodies (Abs) against structural and secretory β-cell proteins even before the disease onset (anti-glutamic acid decarboxylase [GAD], anti-tyrosine phosphatase [IA 2], anti-insulin). This process, once started, and in presence of 2 or more Abs, leads to the disease in almost every subject. Different pathogenic components participate in the development of T1D, considered, therefore, a typical multifactorial autoimmune disease. Genetic features, immunological aspects and environmental factors have a different weight in determining the onset of type 1 diabetes depending on the age at the diagnosis. The genetic susceptibility extends from a marked effect in childhood-onset T1D to the relatively limited effect detected in LADA (Latent Autoimmune Diabetes of the Adult), as shown, for example, by the age-dependent diminishing twin concordance. It is clear, therefore, that there is a continuum in the pathological factors that lead to an age-related increased influence of immunological and environmental components despite the reduction in genetics weight. It is interesting to note that new elements are emerging in the natural history and immunopathogenesis of T1D including epidemiology, genetics, immunology and the effect of environment on clinical presentation.

**EPIDEMIOLOGY**

During past years, an increase in incidence and earlier age of onset of T1D have been observed worldwide. In a 10-years (1996-2005) prospective study of T1D incidence among Moscow young population (age: 0-14 yrs) a significantly higher incidence of T1D than 1970s and 1980s has been shown (average incidence: 12.9 per 100,000 vs 5 and 9 per 100,000 during the previous decades, respectively). This was the first study to report on validated incidence
data for T1D in Russia and also show that incidence of T1D in Moscow is comparable to that of those European countries having an intermediate incidence rates. It should also be noted that the average incidence rate increased during the years, reaching a peak in 2005; it could be justified by the arising diffusion of environmental risk factors even in Eastern Europe population.\(^4\)

**GENETICS**

The greatest susceptibility to T1D is determined by genes involved in immune response. In particular, the HLA complex gene region (short arm of chromosome 6) determines about 40% of the familiar clustering of the disease. HLA molecules play a major role in controlling immune responses by binding antigenic peptides of foreign and endogenous origin and presenting them to T-lymphocytes. Other genes (INS, PTPN22, CTLA4, etc.) are involved in the determination of genetic susceptibility but they play a minor role.\(^5\) The HLA complex locus is the most polymorphic gene region. The HLA-encoded risk of diabetes is determined by the HLA genotype (HLA haplotypes of both chromosomes) and there is a spectrum of risk: the highest risk is associated with heterozygous DR3/4 genotype, which is found in over one third of patients, but only in 2-3% of healthy individuals. Other genotypes are classified as moderate and low risk HLA haplotypes. Recent studies demonstrate that the genetic contribution in individuals diagnosed with T1D has changed over the last five decades. The incidence of childhood-onset of T1D has been increasing progressively over the last half century and it is accounted for by individuals with lower-risk HLA genotype who, in the past, would not have developed diabetes in childhood.\(^6\) As demonstration of the major role of HLA genotype in disease development, recent studies identify a relationship between the HLA-encoded risk and titers of beta cell autoantibodies.

**IMMUNOLOGY**

The titer of autoantibodies against beta cells represent an index of immune system activity and may reflect the degree and speed of beta cell destruction. Recently, Buzzetti et al\(^7\) demonstrated that in adult onset autoimmune diabetes GADA titer follows a bimodal distribution: this type of distribution identifies two groups of patients: a) patients with a high GADA titer in which the autoimmune process is presumably strong, and b) patients with low GADA titer reflecting a less intense autoimmune process. The heterogeneity based on the GADA titer was supported by genetic analysis: DRB1*03 – DQB1*0201 was found with the highest frequency in patients with high GADA titers, with a decreasing trend in patients with low GADA titers. These data confirm that genetics is a major determinant of autoimmunity. However, adult onset autoimmune diabetes is a particular form of diabetes that differs from classical childhood T1D, being often characterized by a slowly progressive autoimmune process with a phenotype indistinguishable from classical type 2 diabetes (T2D). In these patients, GADA titer may be used to stratify the risk of progression to insulin dependence. Subjects with low GADA titer have less prominent characteristics of insulin deficiency. In these subjects factors other than genetic susceptibility may have a major role in disease development. In fact, patients with low GADA titer show intermediate values between patients with high GADA titers and those with T2D. In addition, these subjects present features of a mild insulin resistance phenotype, suggesting that new factors or modified classical factors are needed for the development of diabetes in association with a low-grade autoimmune response. These studies indicate that both autoimmunity and insulin resistance may contribute to the pathogenesis of autoimmune diabetes with a variable degree of synergism. Therefore, other factors can explain the new features of autoimmune diabetes (increase of forms associated with a low/intermediate HLA-risk and increase of slowly progressive forms of autoimmune diabetes).

**CLINICAL PRESENTATION AND THE ENVIRONMENT**

Recently, Hekkala et al\(^8\) observed a decreased frequency of diabetic ketoacidosis among under 15 subjects with T1D, but children younger than 2 years, in association with an increased rate of incidence in Finland and in almost every European State. In addition, an increased prevalence of overweight children has been reported in Europe, especially in the Southern countries. Several “obesogenic” factors have been considered to explain this critical and unhealthy situation: a sedentary life-style, lack of physical activity, even because of the absence of parks and play areas, consumption of energy-dense foods and soft drinks in place of fruit and vegetables. Sandhu et al\(^9\) have demonstrated a higher prevalence of overweight among T1D children than normal subjects. The difference increases in females and during the years, according to previous studies that showed a pubertal but not pre-pubertal-difference in body mass index (BMI) between T1D patients and healthy children. In this unhealthy setting of increased obesity, a new entity of diabetes has been described: double diabetes (DD)\(^10\). DD is the result of the interaction between obese/overweight phenotype and β-cell autoimmunity and could be defined as the presence of obesity or overweight in patients with basal C-peptide levels > 0.3 nmol and GADA positivity. In our pilot study, designed to evaluate the prevalence of DD in a Caucasian population of 5-20 yrs diabetic patients, we found
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a prevalence of 4.96% of subjects with DD. This new expression of diabetes, and its relatively high prevalence among autoimmune diabetic population, may be explained by the “accelerator hypothesis”. Based on this theory, fatty mass may contribute β-cell autoimmunity and apoptosis in the process that leads to the loss of β-cells and, finally, to the development of T1D. The study of Guglielmi et al12 which has evaluated the effects of a dietary restriction vs “ad libitum” diet on the development of diabetes in non-obese diabetic (NOD) mice, showed a significantly reduced onset of diabetes in mice using a low-calories and high protein-content diet.

CONCLUSION

T1D is a multifactorial autoimmune disease resulting of synergistic effects of genetic, environmental and immunological factors. Genetic susceptibility accounts for at least half of the lifetime risk, and the weight of genetic component could predict the early onset of disease. In recent years the incidence of T1D has been increasing progressively, particularly in early age. However, the rising incidence of T1D was accompanied by changes in clinical presentation. Particularly, a new form of diabetes, DD, with childhood onset, signs of autoimmunity (typical of T1D) and characterised by obesity and insulin resistance (typical of T2D) is appearing, suggesting that the weight of environmental component on the genesis of autoimmune diabetes may have a progressively increasing role and may contribute to trigger autoimmunity also in individuals with lower-risk genotype who, in the past, would not have developed diabetes in childhood.

Conflict of interest

The authors declare they have no conflict of interest.

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