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Current aspects on the clinical immunology and genetics of autoimmune diabetes in Japan

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Abstract

Japan is one of the countries with lowest incidence rate of childhood type 1 diabetes in the world, averaging 2.4 cases/100,000/year. However, it appears that the prevalence of type 1 diabetes in adulthood is more than twice compared to childhood patients. There are at least three clinical subtypes of type 1 diabetes in Japan, i.e. acute-onset, slow-onset, and fulminant type 1 diabetes. Fulminant type 1 diabetes is a unique subtype of type 1 diabetes that accounts for about 20% of acute-onset type 1 diabetes, and is rare in childhood in Japan. Furthermore, the slow-onset form of type 1 diabetes might be a major subtype of disease in adulthood. In patients with acute-onset type 1 diabetes, about 90% of patients express at least one of GADAbs, IAA, and IA-2Abs at disease onset. Slow-onset form of type 1 diabetes is diagnosed as having type 2 diabetes at disease onset, which is referred as ''latent autoimmune diabetes in adults (LADA)'', ''GADAb$^+$ type 2 diabetes'', or ''slowly progressive type 1 diabetes''. The prevalence of GADAbs in adulthood patients with type 2 diabetes without insulin therapy is 3–4%, and is higher in the patients with shorter duration of diabetes. Although high levels of GADAbs are one of the predictive markers for future insulin requirement, there are a certain number of patients with high titer of GADAbs who do not progress to insulin dependency for many years, and the predictive value of GADAbs positivity for future insulin requirement is estimated about 67% by Baye's theory. Thus, accurate predictive strategies of future insulin deficiency in LADA patients using autoantibody epitope analysis, genetic determination, or T cell assay are needed for the effective immune intervention.
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Keywords: Type 1 diabetes; Autoantibody; GAD; HLA; Incidence

1. Introduction

Type 1 diabetes is characterised by the destruction of insulin-producing pancreatic beta cells by cytotoxic T-cells, resulting in absolute dependence on insulin for survival and maintenance of health [1]. It is well known that Japan is one of the countries with lowest incidence rate of type 1 diabetes in the world. However, the reason why the incidence rate of type 1 diabetes is so low in Japan is largely unknown. Type 1 diabetes has traditionally been considered a disease of childhood, but more recent epidemiological studies have indicated that the incidence is comparable in adults [2]. It has been reported that the incidence of type 1 diabetes in the Japanese population peaks twice: once around the age of 4 (the first peak) and again at puberty (the second peak) [3]. With recent development of a high throughput radioimmunoassay to detect autoantibodies against various islet autoantigens, one can easily find

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autoimmune diabetes in patients diagnosed as having type 2 diabetes. Therefore, there may be more patients with type 1 diabetes in adulthood than previously considered. In this paper, we review current aspects on the clinical immunology of autoimmune diabetes in Japan.

2. Epidemiology and genetics

It has been reported that the highest incidence of type 1 diabetes in the world is in Finland with a rate in excess of 40 cases/year/100,000 individuals [4]. Furthermore, a rapid increase in the incidence of childhood type 1 diabetes with a rapid rate of increase in children <5 years of age has been reported worldwide [4,5]. Several European countries such as the U.K. and Finland have experienced more than a doubling in incidence of type 1 diabetes over the past three decades [6,7]. It was reported that monozygotic twins and first-degree relatives of patients with type 1 diabetes in Japan had a similar risk of disease onset as in the U.S. [8]. These evidences suggest that most of the between-country variation in diabetes risk might relate to genetic differences rather than environmental factors. Fig. 1 shows the trends in incidence of childhood type 1 diabetes in Japan. It has been reported that the incidence rates of type 1 diabetes under 15 years ranged from 0.98 to 2.53 cases/year/100,000 children, and that the annual trend obviously increased over the 20-year period between 1973 and 1992 [5] with a rapid increase among children of 10–14 years of age at onset, in contrast to countries with Caucasoid populations. However, the incidence rate of type 1 diabetes in patients aged 0–14 years appears to have remained constant over the past decade, averaging 2.37 cases/year/100,000 individuals [9,10] (Fig. 1). A significant sex difference (female preponderance; F/M =1.4–1.5) and lack of geographical variation is also noted in Japan [11,12].

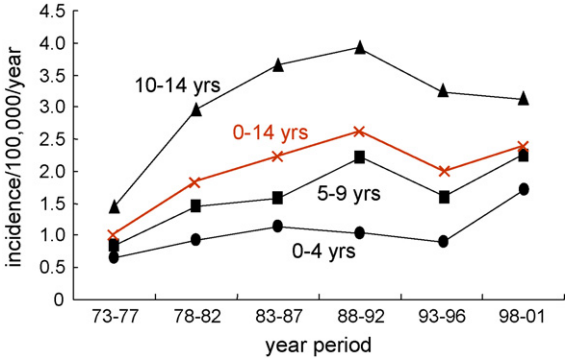

Fig. 1. Trends in incidence of child-onset type 1 diabetes in Japan.

In Japan, there are at least three clinical subtypes of type 1 diabetes, i.e. fulminant, acute-onset, and slow-onset form of type 1 diabetes [13]. Among childhood type 1 diabetes, it is estimated that 90% of patients are classified into acute-onset form, and 10% are classified into slow-onset form, respectively. The fulminant type 1 diabetes is rare in children and the frequency is estimated at <1% (Fig. 2). In contrast, around two-thirds of adulthood type 1 diabetic patients are classified into slow-onset from, 27% into acute-onset from, and 6% into fulminant type 1 diabetes, respectively, based on the nationwide survey of fulminant type 1 diabetes [14] (Fig. 2).

It is well known that the genetic background of Japanese type 1 diabetes differs from that of Caucasians [15]. The two major high-risk class II HLA haplotypes in Caucasoid patients are HLA-*DRB1*0301-DQB1*0201* and *DRB1*0401-DQB1*0302*. In contrast, the major susceptible haplotypes in Japanese type 1 diabetes are *DRB1*0405-DQB1*0401* and *DRB1*0901-DQB1*0303*, and *DRB1*0301-DQB1*0201* is extremely rare in the Japanese general population. However, it has been reported that *DQB1*0402*, which differs by only one amino acid from the *DQB1*0401* molecule and is relatively rare in the general population of Caucasoid populations, is a highly susceptible DQ allele in that ethnic group according to the transmission disequilibrium test [16]. In contrast, HLA-*DRB1*1501-DQB1*0602* and *DRB1*1502-DQB1*0601* are negatively associated with type 1 diabetes in Japanese population. HLA-*DQB1*0602* is also associated with disease protection in patients of Caucasoid and Black origin [17], suggesting that *DQB1*0602* is a primary protective molecule. Among Japanese patients with type 1 diabetes both haplotypes confer susceptibility to childhood-onset type 1 diabetes, whereas *DRB1*0405-DQB1*0401* is the only susceptibility haplotype in adulthood type 1 diabetes [18], suggesting that *DRB1*0901-DQB1*0303* may uniquely predispose to early onset of disease. Furthermore, it has been suggested that the genetic contribution of the *DRB1*0405-*

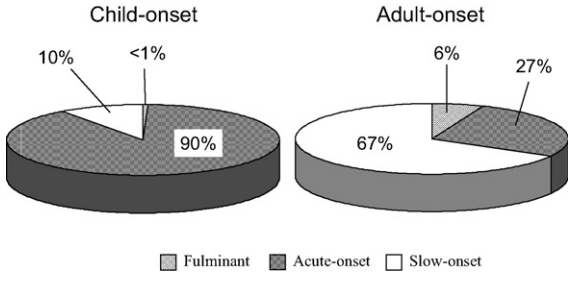

Fig. 2. Proportion of clinical subtypes of type 1 diabetes.

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