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TOPIC HIGHLIGHT

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Latent autoimmune diabetes in adults: A distinct but heterogeneous clinical entity

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Abstract

Latent autoimmune diabetes in adults (LADA) accounts for 2%-12% of all cases of diabetes. Patients are typically diagnosed after 35 years of age and are often misdiagnosed as type Ⅱ Diabetes Mellitus (DM). Glycemic control is initially achieved with sulfonylureas but patients eventually become insulin dependent more rapidly than with type Ⅱ DM patients. Although they have a type Ⅱ DM phenotype, patients have circulating beta (β) cell autoantibodies, a hallmark of type Ⅰ DM. Alternative terms that have been used to describe this condition include type 1.5 diabetes, latent type Ⅰ diabetes, slowly progressive Insulin Dependent Diabetes Mellitus, or youth onset diabetes of maturity. With regards to its autoimmune basis and rapid requirement for insulin, it has been suggested that LADA is a slowly progressive form of type Ⅰ DM. However, recent work has revealed genetic and immunological differences between LADA and type Ⅰ DM. The heterogeneity of LADA has also led to the proposal of criteria for its diagnosis by the Immunology of Diabetes Society. Although many workers have advocated a clinically oriented approach for screening of LADA, there are no universally accepted criteria for autoantibody testing in adult onset diabetes. Following recent advances in immunomodulatory therapies in type Ⅰ DM, the same strategy is being explored in LADA. This review deals with the contribution of the genetic, immunological and metabolic components involved in the pathophysiology of LADA and recent approaches in screening of this distinct but heterogeneous clinical entity.

Key words: Latent autoimmune diabetes in adults; Glutamic acid decarboxylase autoantibodies; Type 1 diabetes; Type 2 diabetes

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INTRODUCTION

The global prevalence of diabetes mellitus (DM) was estimated to be 2.8% in the year 2000 and is expected to rise to 4.4% in 2030[1]. The morbidity and mortality associated with this disease places a huge burden on the health sector. Many preventive and interventional policies have been formulated which mainly focus on a timely and effective treatment. Therapy differs between type Ⅰ and

type Ⅱ DM as the underlying pathophysiology of the disease process in the two is different. An autoimmune destruction of β-pancreatic cells characterizes type Ⅰ DM with presence of T cell reactivity to islet antigens and circulating autoantibodies to glutamic acid decarboxylase 65 (GADA 65)/islet cell cytoplasm (ICA)/tyrosine phosphatase like protein (IA-2A)/insulin (IAA). With type Ⅱ DM, genetic and environmental factors play a major causative role. Phenotypic variations between the two types are also seen with type Ⅰ DM having a younger age of onset, increased frequency of ketosis, association with other auto immune diseases and requirement for insulin from the start while type Ⅱ DM is mainly seen in the older age group who are often obese and is treated with diet and/or oral hypoglycaemic drugs. These form the basis for a clinical diagnosis and treatment.

Often, the absence of phenotypic features of type Ⅰ DM is taken as an indication of type Ⅱ DM. However, there is another subset of adult patients who were initially categorised as type Ⅱ DM phenotype but were positive for autoantibodies, a hallmark of β cell destruction[2,3]. These patients account for 2%-12% of all cases of diabetes[4] and the term 'Latent autoimmune diabetes of adults' (LADA) was given by Zimmet *et al* to describe them[3,5]. They typically are diagnosed after 35 years of age and have initial good glycemic control with sulfonylureas but eventually become insulin dependent more rapidly than type Ⅱ DM patients. Alternative terms that have been used to describe this condition include type 1.5 diabetes, latent type Ⅰ diabetes, slowly progressive Insulin Dependent Diabetes Mellitus (IDDM), youth onset diabetes of maturity[6,7]. Due to the latent nature of the disease and its is not easily discernible signs and symptoms, LADA patients are often misdiagnosed as type Ⅱ DM and started on oral hypoglycemics. However, glycemic control deteriorates after a few months/years of therapy and by the time insulin therapy is started, the disease often progresses to the morbid stage which could have been delayed with timely initation of insulin therapy. With the recognition of a LADA subset of patients, numerous works have been documented with respect to its pathophysiology and genetics, diagnostic criteria, classification, therapy. However, due to heterogeneity in its immunological, genetic and metabolic features, LADA still remains a diagnostic challenge.

IMMUNOLOGY

Antigen spreading, a common feature of autoimmune diseases is seen in type Ⅰ DM, where tolerance to more and more islet antigens is lost with the result that multiple auto antibodies are found in circulation. These antibodies are also seen in the LADA subset of patients where single antibody positivity for GAD is more prevalent and IAA and IA-2A are less often reported[2,3]. Although the presence of any one of these autoantibodies in LADA predicts inevitable β cell failure, multiple autoantibodies in circulation or a high titre correlate with rapid β cell destruction. On the other hand, patients with a single antibody, mainly GADA, which is the commonest in LADA, or a low titre, have a much slower development of β cell failure[8,9]. It also has been observed that first-degree relatives of patients with multiple autoantibodies have a higher risk of developing type Ⅰ DM[10]. The presence of circulating autoantibodies as well as the early requirement of insulin has led to workers suggesting that LADA is a spectrum of type Ⅰ DM with a much slower progression[6]. The slower progression has been attributed to a more restricted antigen spreading in LADA than in type Ⅰ DM leading to a more aggressive disease in the latter. Works on epitope specificity of GADA in type Ⅰ DM and LADA have also revealed that the autoantibodies in both diseases are mainly directed towards the C-terminal and middle epitopes[11,12].

However, other observations provide evidence of immunological differences between the two conditions. Seissler *et al* found that ICA staining could be blocked upon the addition of GADA and IA-2 from sera of type Ⅰ DM but not from LADA patients. They explained this observation with the hypothesis of a higher prevalence of other unidentified autoantibodies[13]. A Japanese study on slowly progressive IDDM (recognised as a Japanese equivalent of LADA), demonstrated the presence of a unique epitope at the N-terminal of GAD 65[14]. This finding, contradictory to previous works on the Caucasian population, has been explained by the association of different HLA genes with LADA in Japanese population. Studies on T-cell response to islet proteins in both classical type Ⅰ and autoantibody positive diabetes in adults have also shown significant antigenic differences in the proteins recognised by the T cells in the two diseases[15]. It was also observed in LADA patients that, irrespective of autoantibody status, T-cell reactive patients had a significantly lower glucagon stimulated C-peptide than patients with no T cell reactivity to islet proteins and thus T cell reactivity in LADA correlated with a more severe β cell lesion[16].

GENETIC SUSCEPTIBILITY

Many studies have reported an association of type Ⅰ DM with high risk genes, HLA-DR3, -DR4 and their alleles DQB1*0302 and DQB1*0201 HLA[17-20]. The prevalence of these genes has been linked with age of onset of dia betes. These genes have also been implicated in the sus ceptibility to LADA. It has been observed that there is a decreased presence of these alleles in adult patients diag nosed with type Ⅰ DM as compared to younger onset type Ⅰ DM[19,20]. However, another study reported the presence of DQB1*0302 (34%) and DQB1*0201/DQB1*0302 (8%) in LADA patients with similar preva lence in type Ⅰ DM patients[21]. This equal prevalence in both diseases has been explained by an earlier age of diagnosis of type Ⅰ DM (> 20 years) while the type Ⅰ DM patients included in the former two studies were dia gnosed at > 25 years of age. The United Kingdom Pro

spective Diabetes Study (UKPDS) also showed a similar decreased prevalence of DR3/DR4-DQB1*0302 with onset at > 45 years[4]. Thus, their presence reflects the future development of autoimmune diabetes and also influences the age of onset, with a higher prevalence seen in younger age onset type Ⅰ DM. Other HLA alleles that are relatively more common in LADA patients are DR2 and DQB1*0602. These alleles are strongly protective against childhood type Ⅰ DM and hence are rarely seen in type Ⅰ DM cases. It also has been suggested that the protective mechanism of DR2DQB1*0602 in adult autoimmune diabetes (LADA) is less effective[22]. Thus, type Ⅰ DM with more susceptible genes and absence of protective genes, presents with a more aggressive, younger onset disease.

Some non-HLA genes have also been linked to LADA. One such is the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene that encodes a co-stimulatory molecule that is involved in the repression of T cell activation[23]. Another associated gene is the MHC class Ⅰ chain related A (MICA) gene, which encodes stress inducible surface proteins recognised by a subset of γδ T cells found in intestinal epithelium. Sequence analysis of MICA gene has revealed, a trinucleotide repeat (GCT) microsatellite polymorphism. An allele of this gene, MICA 5.1 consisting of five repetitions of GCT with an additional nucleotide insertion (GGCT), is significantly increased in LADA, antibody positive NIDDM and adult onset type Ⅰ DM (onset > 25 years) while increased frequency of MICA-5 (having five repeats of GCT) is seen in type Ⅰ DM with onset under the age of 25 years[24,25]. An allelic polymorphism within the promoter region of TNF-α gene (G-A substitution at position 308), associated with higher amounts of TNF-α production, has also been linked with LADA; this allele was found to be significantly lower in LADA as compared to type Ⅰ DM[26].

CLINICAL AND METABOLIC FEATURES OF LADA PATIENTS

To discriminates LADA from type Ⅰ and/or type Ⅱ DM, diagnosis of LADA has been based on three criteria as given by The Immunology of Diabetes Society: (1) Adult age of onset (> 30 years of age); (2) Presence of at least one circulating autoantibodies (GADA/ICA/IAA/IA-2); and (3) Initial insulin independence (for the first six months)[27]. In a retrospective study by Fourlanos *et al*, five clinical parameters were found to be more frequent in LADA than in type Ⅱ DM: (1) Age of onset < 50 years; (2) Acute symptoms (polyuria/polydypsia/weight loss); (3) BMI < 25 kg/m^2; (4) Personal history of other autoimmune diseases; and (5) Family history of autoimmune disease[28]. Other workers have also reported a lower BMI, waist/hip ratio, total CH and TG levels and higher HDL-CH in LADA than in patients with type Ⅱ DM. The prevalence of hypertension was also lower in LADA patients[4,20,21,29]. There was no significant difference between LADA and adult onset type Ⅰ DM with respect to these parameters. Also, the UK PDS findings showed a decreased fasting C-peptide level in LADA and adult onset type Ⅰ diabetes at the onset of diagnosis. However, the C-peptide levels were significantly lower in longer disease duration type Ⅰ DM as compared to LADA, reflecting the more intensive β cell destruction in type Ⅰ DM. Many workers have also investigated the role of insulin resistance as well as its degree in LADA. Using HOMA (homeostasis model assessment) to calculate insulin resistance in LADA, type Ⅰ and Ⅱ DM, Behme *et al* found that insulin resistance was similar in LADA and type Ⅰ DM of longer duration but greater than in recent onset type Ⅰ DM. It was also much lower in LADA as compared to type Ⅱ DM[30]. In another study, insulin resistance in LADA did not differ from that in antibody negative type Ⅱ DM when corrected for BMI but was significantly higher than in normal controls[27]. The authors also suggested a role for obesity in insulin resistance of LADA and, as there are obese LADA patients, clinical outcome in LADA patients is determined by the interaction between insulin resistance and autoimmune β cell destruction.

Based on the titre of GADA, LADA has also been sub-classified as type Ⅰ and type Ⅱ. Patients with higher GADA levels were typed as LADA 1 and had phenotypic similarities with type Ⅰ DM (lower C-peptide levels, lower BMI, more ketosis) while patients with lower levels, sub-classified as LADA 2, identified with type Ⅱ DM although there was more ketosis and less dyslipidemia in LADA as compared to the latter. The frequency of obesity, hypertension, dyslipidemia and CHD was lower in LADA type Ⅰ than in LADA 2. It has also been reported that GADA positive, LADA patients who were treated with insulin mainly had autoantibodies directed towards the COOH terminal (GADA-C) while GADA-M (autoantibodies towards the middle epitope) was more frequent in LADA patients on hypoglycaemic drugs and/or diet.

SCREENING FOR LADA

The next big question is - Who should be subjected to autoantibody testing? There are still no universally accepted criteria for autoantibody testing in adult onset diabetes. In fact, many clinicians advocate the antibody assay only if there is a suspicion of LADA based on BMI(< 25kg/m^2). Obese, adult onset diabetics are often categorised as type Ⅱ DM and not tested for LADA while adults with normal BMI are potentially suspected for LADA and hence tested[7]. This criterion is not satisfactory as there are studies in which LADA patients had mean BMI in the overweight or obese category[8] and with increasing obesity, it becomes difficult to distinguish LADA from type Ⅱ DM based on BMI. Also with the heterogeneous manifestations of LADA, reliable clinical strategies have to be formulated to identify LADA in adult onset diabetes so that they can be subjected to the antibody assay. The five point LADA clinical risk score, given by Fournalos *et al*

in a prospective study, had a sensitivity and specificity of 90% and 71% respectively, in identifying LADA patients, with the presence of at least two given clinical features. The presence of only 1 feature/none had a negative predictive value of 99%[28]. Monge *et al* also proposed a clinically oriented approach for LADA screening which was based on body weight and/or BMI along with fasting blood glucose and HbA 1c, and gave a prevalence of 31.8%[31]. Some studies have emphasized on potential role of C-peptide in early detection of LADA patients, reserving more expensive antibody testing for high suspect cases. One such study by Aggarwal *et al* showned decreased C-peptide levels in patients suspected of having LADA as compared to classic type Ⅱ diabetics[32].

Given the many studies showing a higher prevalence of GAD autoantibodies in LADA and also the ease with which it can be assayed, measurement of GADA provides a screening procedure for detecting future B cell dysfunction. However with reports of single ICA positivity in LADA patients, it has been suggested that both ICA and GADA testing may be used to screen for LADA[20]. Analysis of UKPDS also showned that the presence of both ICA and GADA was a stronger predictor of insulin requirement than GADA alone in patients > 45 years of age[4]. However, ICA disappears with increasing disease duration, as in type Ⅰ DM, while all patients with GADA positivity at diagnosis remains GADA positive indefinitely. Hence GADA measurements can be carried out years after diagnosis with preserved sensitivity. Testing for other autoantibodies in high risk (LADA clinical risk score > 2) GADA negative patients should also be carried out as some of these patients may be IA-2A and/or IAA positive. This is significant as there are reports of ethnic differences in GADA positivity with higher frequency in Caucasian, late onset, type Ⅰ DM than in Asian late onset type Ⅰ DM subjects. An epitope-specific assay could also increase the diagnostic specificity of GADA for future insulin requirement[6,11]. However, given the contradictory reports by Kobayashi *et al* and Falorni *et al*, more studies on the issue are needed before these epitope-based assays can be implemented for population screening.

In conclusion, it can be concluded that LADA should be approached as a clinical entity different from type Ⅰ and type Ⅱ DM although it showa overlapping features of both types. Also, a standardised nomenclature of LADA should be propagated in view of its heterogeneous manifestation. This is especially important with regards to the subtypes of LADA based on GADA levels[26]. Early instigation of insulin therapy is a must in LADA type Ⅰ (high GADA levels) to delay the rapid islet cell failure. For those individuals with low GADA levels, classified as LADA type 2, the phenotype is very similar to type Ⅱ DM and the treatment strategy appears to be ambiguous. Should insulin be started in combination with oral hypoglycemics to delay the progression of β cell destruction and also tackle the insulin resistance? Also, with the recent developments in immunomodulatory therapies (anti-CD3 monoclonal antibodies) in type Ⅰ DM, the question arises of whether these immunomodulatory interventions would also be effective in LADA as both conditions have similar autoimmune mediated β cell destruction. On the other hand, with potential differences in antigenicity and genetic background in LADA, one cannot simply assume that these therapies would be equally effective in LADA as in type Ⅰ DM. These issues can be addressed only with more prospective, long-term clinical studies.

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