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Review

Autoimmunity in latent autoimmune diabetes in adults

Alessandro P. Delitala*

U.O.C di Medicina Generale 2, Azienda Ospedaliero-Universitaria di Sassari, Sassari, Italy

* **Correspondence**: Email: aledelitala@tiscali.it; Tel: +39079228240; Fax: +3907928207.

Abstract: Latent autoimmune diabetes in adults (LADA) is clinically characterized by onset after age 30, absence of ketoacidosis, insulin independence for at least 6 months after diagnosis, and presence of circulating islet-cell antibodies. These include glutamic acid decarboxylase (GADA) autoantibodies, tyrosine phosphatase-2 autoantibodies, or zinc-transporter 8 autoantibodies. In particular, GADA are the most frequent autoantibody in LADA and can be detected in serum for many years post diagnosis. High concentrations of GADA have been considered as a marker of faster islet-cell exhaustion in these patients. Moreover, LADA patients have other circulating non islet antibodies, such as antibodies against thyroperoxidase and antibodies against gastric parietal cells, that reflect the presence of a high intensity of immune processes. Although the presence of each antibody taken individually shows scarce predictive value for the progression of the disease, their simultaneous presence might predict the insulin dependence in this LADA subgroup. The occurrence of islet autoantibodies in these patients might identify specific phenotypes of LADA with more homogeneous characteristics that are prone to faster exhaustion of β cell function. The high prevalence of these autoantibodies is clinically relevant and their measurement should be introduced as screening in clinical practice in order to identify the clinical presence of other organ specific autoimmune diseases.

Keywords: LADA; autoimmunity; organ specific autoimmunity; antibody against thyroperoxidase; antibody against gastric parietal cells; GADA; β cell function

1. Autoimmunity in LADA

Immune mediated diabetes is characterized by the presence of circulating specific antibodies against pancreatic islets such as glutamic acid decarboxylase autoantibodies (GADA), tyrosine phosphatase-2 autoantibodies (IA-2A), or zinc-transporter 8 autoantibodies (ZnT8A). These autoantibodies are present in type 1 diabetes (T1D) in which insulin deficiency is caused by immune-mediated destruction of insulin-secreting islet cells [1]. This type of diabetes is the most prevalent form of diabetes in children, but also occurs in adult population. Type 1 diabetes is frequently associated with other organ specific autoimmune diseases, including autoimmune thyroid disorders, Addison disease, hypoparathyroidism, or celiac disease [2]. Latent autoimmune diabetes in adult (LADA) is another form of immune-mediated diabetes of adults which phenotypically resembles type 2 diabetes (T2D), is usually diagnosed after age 30 (or 35 accordingly to other authors) and is identified by the presence of circulating autoantibodies against pancreatic β cells [3]. About 5–10% of all patients diagnosed with T2D have markers of β cells autoimmunity although the real prevalence of this form of diabetes is still unclear, but it is suggested that this clinical entity may represent together with T1D a broad clinical spectrum that represent autoimmune diabetes [4]. By analogy with T1D, LADA may be associated with other immune mediated clinical conditions that should be evaluated to prevent morbidity related to unrecognized diseases. Moreover, the existence of non-islet organ specific antibodies, might predict the insulin dependence in these patients [5]. Based on these findings, the aim of this review was to assess the prevalence and the role of organ specific autoantibodies in LADA.

2. LADA

About 5–10% of all patients diagnosed with T2D have autoantibodies against pancreatic β cells in their peripheral blood, such GADA and IA-2A [6–8]. This form of autoimmune diabetes was defined by Zimmet as LADA [9]. The clinical features of this type of diabetes include the absence of ketoacidosis and insulin dependence for variable periods of time, thus showing clinical aspects intermediate between T1D and T2D. The proportion of LADA patients among patients diagnosed with T2D varies probably due to selection biases in reported clinical series [4], including patient age at diagnosis, selection criteria, autoantibodies assays or disease duration at study entry. However, most of these studies have clearly established the existence of a clinical phenotype distinct from GADA negative patients that are classified as T2D. LADA might represent a part of clinical spectrum encompassing all forms of autoimmune diabetes. A number of genes likely playing a role in T1D have been associated with LADA such as those located in the Human Leukocyte Antigens (HLA) class II locus, the gene encoding insulin, as well as genes encoding cytotoxic T-lymphocitic associated protein 4 (CTLA-4) [10,11]. In addition, while C1858T single-nucleotide polymorphism in the PTPN22 gene has been associated with increased susceptibility to T1D, its frequency was found lower in LADA patients. Previous reports also suggested that LADA shares the same genetic features of T2D. For example, Grant et al. found a strong genetic linkage with T2D within the transcription factor 7-like 2 (TCF7L2) gene which has been found to be a susceptibility locus for LADA in Europeans [12,13]. These data suggest that this form of diabetes might represent a genetic

admixture of the two types of diabetes [14]. Clinical and immunological heterogeneity likely exist in LADA patients, and many studies have been directed toward identification of different phenotypes with more homogeneous immunological characteristics [15,16]. At diagnosis, LADA patients are, by definition, not insulin-dependent and tend to be younger and leaner than patients with T2D, and are more numerous than adult-onset autoimmune T1D [4]. Similarities with T2D were reported also for anthropometric and metabolic data, showing a lower frequency of metabolic syndrome in LADA than in T2D patients [17]. A body composition evaluated in LADA patients by using Dual energy X-rays Absorptiometry also demonstrated a body composition different from that of T2D the former being much closer to adult-onset T1D [18]. The progressive destruction of β cells, although slower than in T2D, has been suggested to be faster in the presence of high GADA titers [19,20]. An inverse relation between GADA titres and C-peptide has also been reported in LADA patients with rapid progression to insulin therapy [21]. This observation might explain the higher incidence of insulin dependence in patients with higher GADA titres, whereas patients with low GADA titres are less insulin dependent and have a better glycemic control. The data suggest the existence of a clear bimodal distribution of GADA titers as well as the association of higher titers with a clinical phenotype more similar to T1D [4,20,22]. Although the possible influence of GADA titers on progression toward insulin dependence is not universally accepted [23], the biochemical data, taken together, suggest the existence of an intrinsic phenotypic heterogeneity of LADA.

3. Immunological features

Serum islet autoimmunity is present in majority of patients with autoimmune diabetes. These islet autoantibodies include ICAs (islet cell autoantibodies), IAAs (against native insulin), GADA, IA-2A, or ZnT8A. Several studies have compared autoantibody frequency in T1D and LADA patients. In general, ICA, IAA, IA-2 and ZnT8A are more frequent in T1D, whereas GADA were equally common [24–27]. In particular, GADA are the most frequent autoantibody in LADA and can be detected in serum for many years post diagnosis, whereas the other autoantibodies against islet tend to disappear.

Patients with autoimmune diabetes mellitus can suffer from other autoimmune clinical conditions. Serum thyroid autoantibodies have been often found in T1D with a frequency which is significantly higher than that observed among non-diabetic subjects [28,29]. Moreover, patients with T1D and thyroid autoantibodies positivity often develop clinically overt thyroid disease within a few years. Furthermore, these patients are prone to develop clinically other organ-specific autoimmune diseases such as Addison's disease or celiac disease [30].

The prevalence of extra pancreatic organ-specific autoantibodies has been studied also in LADA patients [2], although with different results, particularly as far as positivity for thyroid antibodies concerns [20,31,32]. However, the prevalence of antibodies against thyroperoxidase (TPOA) has been found to be higher in T2D patients with GADA positive than in GADA negative T2D patients [20,33]. The mechanisms of this clinical association have been variously suggested, although without univocal conclusions. A recent study performed in LADA patients has suggested that the presence of most virulent Helicobacter Pylori might be a risk factor for the presence of thyroid autoimmunity in these patients as well as a possible trigger for immune mechanisms involved in the pathogenesis of

autoimmune diabetes. The role of CTLA-4 variant, a protein which has a regulatory role on effector T cells of the immune response [34], was also investigated on the susceptibility of LADA [33]. The results confirmed that the CTLA-4 G6230A variant is associated with T1D, but not with LADA susceptibility. However, this variant can identify a particular subset of LADA patients with a more clinically severe disease thus confirming the existence of intrinsic phenotypic heterogeneity of LADA. Interestingly, an increased risk of thyroid failure was also found in those LADA patients with a G allele-containing genotype, suggesting that the presence of thyroid failure may indicate more active autoimmune processes in LADA patients. The marked heterogeneity in clinical features and immunological markers suggests the existence of multiple mechanisms underlying its pathogenesis. Thus, in GADA positive the occurrence of anti-thyroid antibodies are rather frequent with a higher prevalence in females compared with males [35]. Apart from GADA, the occurrence of both TPOA and IA-2A seems to identify subgroups of LADA patients. In particular the presence of TPOA seems to modulate the effect of IA-2A, since its negativity seems to have a protective effect on disease progression [32]. However, it should be noted that IA-2 immunoreactivity in LADA patients could be underestimate. Indeed Tiberti et al. tested seven IA-2 constructs demonstrating different sensitivity of humoral IA-2 immunoreactivity, with the highest sensitivity for IA-2 (256–760) fragment [25].

Apart from HLA genotype, number of autoantibodies, more than high titers of GADA, seems to predict disease progression in LADA patients [32]. In particular, the potential of several markers to correlate with progression toward insulin dependence have been investigated. These aspects have recently been evaluated in a cohort of LADA patients from ethnically homogeneous population [5]. In particular, a panel of autoantibodies directed against islet- and non-islet-related antigens was studied. The proportion of TPOA and ZnT8A in LADA patients was comparable to that observed in patients with T1D [36]. Moreover, the presence of any of the two TPOA and ZnT8A seems to predict the progression of disease with a sensitivity of 62% in the studied population. A high prevalence of antiparietal gastric cell (APCA) was also reported in this population. Interestingly, together with GADA, and the IA-2A the presence of ZnT8A has been reported to increase the rate of β cells autoimmunity in the clinical presentation of T1D [37]. Thus, these circulating autoantibodies might be together a marker of accelerated progression of the disease [5,38].

Recent studies showed that antibodies specific to oxidative post-translational modification insulin has emerged as a novel biomarker for the prediction of insulin dependent diabetes [39,40]. Despite are present before the clinical onset of clinical onset of type 1 diabetes in children [41], no data on LADA patients has still been reported.

Additional data suggest that the prevalence of ZnT8A is increased in patients with high GADA titer [2]. Several studies aimed at correlating several markers with the progression of β cell failure have been investigated. Beside the presence of specific anti islet specific autoantibodies, whose role as marker of progression of the disease is generally acknowledged, the available data support the hypothesis that the presence of non-islet organ specific autoantibodies might contribute to identify those LADA patients who are at high risk of developing insulin dependence. In particular, the simultaneous presence of these autoantibodies significantly increase the specificity of these autoantibodies in predicting a more rapid progression of the disease [5]. The data also confirm the high intensity of autoimmune processes in this population. However, a recent study speculated a

possible and different pathogenetic mechanism. Indeed, the IA-2 (256–270) antibody in T2D increased with increasing BMI, resembling the classical T2D phenotype (obese, higher BMI, increased waist circumference) and a lower progression to insulin requirement that GADA positive patients, thus suggesting a possible low-grade chronic inflammation process [42].

4. Conclusion

LADA is a rather common form of diabetes accounting for more than 10% of all cases classified T2D. LADA patients have disease onset after age 30 and usually do not require insulin treatment at least in the first 6 months. The hallmark of the disease is the presence of several circulating antibodies against islet-cell antigens, such as GADA, IA-2A and ZnT8A. LADA might be clinically considered a variant of late-onset T1D with a delayed progression. High concentrations of GADA have been considered as a marker of faster islet-cell exhaustion in these patients. However, LADA patients have other circulating non islet antibodies, such as TPOA and APCA, that reflect the presence of a high intensity of immune processes. Although each antibody taken individually shows scarce predictive value for the progression of the disease, their simultaneous presence might predict the insulin dependence in this LADA phenotype, thus identifying specific subgroups of patients with more homogeneous characteristics. Finally, the high prevalence of these autoantibodies is clinically relevant and their measurement should be introduced as screening in clinical practice.

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None

Conflict of interest

The author declares no conflicts of interest in this paper

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