Latent Autoimmune Diabetes in the Adults (LADA): A Unique Heterogeneous Clinical Entity or Just an Enigma?

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Abstract

Autoimmune diabetes in adults reflects a broad clinical phenotype ranging from keto acidosis to mild non insulin requiring diabetes with preserved beta cell function. The former is typical of type 1 diabetes mellitus while the latter usually takes an insidious course mimicking type 2 diabetes mellitus. However, younger age at onset and the presence of circulating antibodies, albeit to a lesser extent than type 1 diabetes, distinguishes it from type 2 diabetes. Thus it needed to be labelled as a separate entity and researchers termed it as Latent Autoimmune Diabetes in the Adults (LADA). Its definition, pathogenesis and nomenclature has been questioned repeatedly rendering it a very controversial topic in diabetes. Prospective studies have established that beta cell failure can be there as early as within 5 years in cases of high antibody titre. Moreover, there is marked diminution of beta cell response to intravenous glucagon and glucose in patients of LADA. Consequently, LADA is not always a latent disease. This review is to summarize the discrepancies concerning this topic and the scope of a better justifiable terminology as ‘Autoimmune Diabetes in adults with slowly progressive beta cell failure’ in place of LADA. It also focuses on revision of the existing diagnostic criteria to capture the pathogenesis and thereby set therapeutic targets.

Diabetes mellitus (DM) being a complex disease with variations in its pathogenesis and clinical manifestations encouraged researchers to look beyond the traditional type 1 and type 2 classification. Accordingly with the enthusiasm of researchers there came the term Latent Autoimmune diabetes in adults (LADA). It is a slowly progressive form of diabetes mellitus with autoimmunity mediated destruction of beta cells of pancreas with insulin independence usually for the initial six months after diagnosis and resistance to development of ketoacidosis. Ever since its inception it has been an intriguing entity with the most accepted diagnostic criteria being proposed by Immunology of Diabetes Society (IDS) as: (1) presence of circulating auto antibodies like islet cell autoantibody (ICA), glutamic acid decarboxylase autoantibody (GADAbs), protein tyrosine phosphatase autoantibody (IA-2A); (2) age at onset > 35 years; (3) insulin independence for at least 6 months after diagnosis.¹ The prevalence of LADA varies between 10 to 20% in different populations, the sensitivity being increased by screening for GADAbs in newly diagnosed patients with type 2 DM.²

Diagnostic hallmark of LADA is the seropositivity of autoantibodies, viz, ICA, GADAbs, IA-2A with GADAbs being the most sensitive parameter to discriminate autoimmune mediated LADA from phenotypic type 2 diabetes mellitus. Also the level of its titre decides the treatment modality with high titre LADA or LADA 1 benefiting from early insulin supplementation and low titre LADA or LADA type 2 manageable with oral hypoglycaemics.³

As far as the genetic studies of LADA are concerned the expression of HLA-DQB1*0201/*0302 has been much less observed in LADA in comparison to type
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1DM whereas the frequency of protective HLA-DQB*0602 has been much more in LADA than type 1 DM patients. On the other hand, recent studies illustrated the contribution of several genetic loci of type 1 DM in development of LADA including the MHC region as well as at PTPN22, SH2B3 and INS. The type 2 DM risk allele at TCF7L2 have a significantly lower frequency in LADA patients. Thus LADA is genetically closer to type 1 DM as compared to type 2.

Clinical spectrum of patients with LADA show considerable overlap with that of type 1 DM and type 2DM on the basis of their antibody titre. In contrast to type 2 diabetes mellitus these patients even when insulin non requiring have a lower age at diabetes onset, lower body mass index (BMI) and waist-hip ratio (WHR), but a more pronounced loss of C-peptide and an increased likelihood of insulin treatment. As compared to type 1 DM, these patients have a more gradual decline in beta cell function, less liable to ketoacidosis and a higher C-peptide level with a later age of onset. However, with high titre GADAb LADA patients exhibit an earlier propensity to insulin requirement. Thus clinical profile of LADA patients seems an admixture of those of type 1 and type 2 DM patients. This prompted researchers to coin a new term type 1.5 DM as an eponym for LADA. Some experts have even named it as ‘Double Diabetes’. The prevalence of microvascular complications are similar in LADA and type 2 DM with a lower likelihood of nephropathy as reported in some studies. LADA generally exhibits a more favourable cardiovascular risk profile than type 2 DM patients but sufficient evidences are lacking to support a less aggressive protocol for cardiovascular risk factors in patients with LADA.

Till date there has been no definitive guideline for treatment of LADA. In the initial stages of insulin dependence treatment should be done with insulin sensitisers like thiazolidinediones and dipeptidyl peptidase 4 inhibitors i.e. gliptins. As per studies sulfonylureas worsen metabolic profile by depleting the beta cells. There has been much argument about the role of early insulin therapy but corroborative evidences are lacking. Ongoing trials for novel therapies like peptide DIAPEP 277 cross reactive with the original hsp 60 epitope for diabeticogenic T cells and Vaccination with GAD(DIAMYD) are yet to produce any prospective outcome. Immunomodulators like cyclosporine (inhibitor of T cell activation), Abetacept (CTLA-4 inhibitor) and Rituximab (anti CD20 Ab) have beneficial roles but the subsequent side effects seen in their trials are discouraging. There are still controversies in defining and understanding the pathogenesis of LADA. For instance the age criterion in definition of LADA is questionable as it is only an arbitrary limit. There cannot be any reason to exclude a young adult of <35 years age with a phenotypic type 2 DM responding initially well to metformin but having high titre of autoantibodies. Broadening the age group will enable to screen more patients and correctly diagnose them as LADA. Secondly the treatment criterion concerning insulin dependence also depends upon the physicians discretion and the paradigm of treatment prevalent in his area of practice. Furthermore, precipitating factors like infection leading to diabetic ketoacidosis warrant early use of insulin. The last criterion of auto antibody positivity regarded as the most valid amongst all even has certain pitfalls. These are due to falsepositives, i.e, individuals without LADA but having auto antibodies, and the lack of concordances between different modes of assay in adolescents and adults due to differences in epitope and and antibody levels, influencing the performance of the assays. The existing criteria of LADA fails to delineate the pathogenesis that necessitates specific preventive and therapeutic approaches. It implies slowly progressive decline in beta cell function for the etiopathogenesis of LADA. However, Zhou Z and Wu H in their multicentric study proposed insulin resistance as the key mediator of slow onset autoimmune diabetes. LADA is indeed a manifestation of dwindled insulin secretion rendered insufficient by insulin resistance. Thus, incorporation of insulin resistance in the criteria would have made it a therapeutic target to deal with underlying metabolic and cardiovascular complications in LADA. In a cohort study conducted by Mishra R et al. the allelic heterogeneity of LADA was established with relative contribution of both type 1 and type 2 diabetes loci. To summarise, LADA although considered a unique and heterogeneous clinical entity, there has been ongoing arguments and discussions regarding its validity. Immunologically it is barely distinguishable from type 1 DM although the latter has a greater load of auto antibodies with lower c-peptide levels and more rapid c-peptide loss. Phenotypically, LADA bears close resemblance to type 2 DM except for greater...
propensity to insulin requirement. Genetically there is relative contribution of both T1DM and T2DM genetic loci. There have been numerous studies questioning and reformulating the definition of LADA but all these have ended in futile discussions with no definitive contribution to a sound treatment protocol. It has been stressed that the term LADA be replaced by autoimmune diabetes so that the process of autoimmunity can be focused upon to improve the lifestyle and curb the complications of these patients. It must be accepted that autoimmunity being the culprit may come in different shapes i.e. in all ages, in all populations, different genotypes and can be contributed by B and T cells both, thereby absence of autoantibodies do not negate any underlying autoimmune process. Furthermore, patients of LADA at diagnosis have partially compromised beta cell function signifying that LADA is not a latent disease and autoimmune diabetes in adults with slowly progressive beta cell failure (ADASP) may be a better nomenclature.

To conclude LADA thus stands as a questionable entity in the literature and awaits a better terminology for its nomenclature.

REFERENCES


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