Latent autoimmune diabetes in adults (LADA) is dead: long live autoimmune diabetes!

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Abbreviation

LADA Latent autoimmune diabetes in adults

Latent autoimmune diabetes in adults (LADA) prevails as a name in diabetes research although it was ranked as the second silliest name some years ago [1]. LADA describes a subgroup of patients who develop phenotypic type 2 diabetes but with markers of autoimmunity [2, 3]. In 2005, we tried to describe the background to LADA and establish a definition based on adult age at onset, presence of autoantibodies and lack of requirement for insulin at least 6 months after diagnosis [4]. Both the age and the insulin criteria were soon questioned [1, 5], but they also gained some support [6]. The question of how to define LADA has resulted in numerous articles and debates discussing whether LADA is a disease on its own or just a variant of type 1 diabetes [7–9]. Thus, it could be questioned whether the introduction of the term LADA has been an asset or an obstacle to our understanding of diabetes.

The first question we should ask is: what good has the concept of LADA done for science and patients? In defence of LADA we may note that the categorisation has put the existence of autoimmune diabetes in adults on the scientific map. We know that by including LADA in type 1 diabetes, as recommended by the WHO [10], more adults than children are affected by autoimmune diabetes [11]. We know more about cellular and humoral responses [12–15], metabolic traits [16, 17] and genetic background [18] in adult patients with autoimmune diabetes. Thus, the LADA concept has been an efficient tool for studying and communicating different pathophysiological aspects of autoimmune diabetes in adults. Another reason for classifying diabetes is to facilitate studies on treatment and prevention where strict inclusion criteria are needed. It was concluded in a recent Cochrane Review [19] that there were few randomised controlled trials of good quality available to evaluate which treatment is optimal for LADA patients, but using sulfonylurea seemed unfavourable for beta cell function. The review also noted that the definition of LADA was imprecise, which hampered comparison between the studies. Taken together, the scientific use of LADA has up to now been better and more productive than its clinical use.

So, what is the problem with the concept of LADA? The main problem is how to define LADA. This leads to futile discussion that does not take our understanding of autoimmune diabetes any further; it might even be an obstacle to our way of thinking. This could be exemplified by studies trying to subgroup LADA, which already is a subgroup. There are manuscripts proposing different kinds of LADA based on the antibody titre, with low-titre and high-titre LADA [20, 21]. We even will have patients who fulfil the age and treatment criteria with T cell reactivity to

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islet antigens but no autoantibodies. Will that lead to new sub-sub-categorisations, e.g. T cell LADA (T-LADA) as opposed to the antibody-positive subjects named B cell LADA (B-LADA)? If we add categorisations based on degree of obesity, residual beta cell function (C-peptide), genetics (type 1 diabetes genes, type 2 diabetes genes or a mix), antibody titre (low or high), epitope specificity (C-terminal, middle or N-terminal), what antigen the T cell assay is positive for (GAD65, insulin or others), to our present categorisation based on age, treatment and autoantibody positivity, the confusion will be complete.

Let us scrutinise the different criteria of LADA. The first is adult age, often defined as >35 years [3]. As pointed out by others [1, 5] this is a very arbitrary limit. What is the significant difference in the autoimmune disease perspective between a 34-year-old and a 36-year-old, with phenotypic type 2 diabetes and GAD65 antibodies but not initially insulin-dependent? The high percentage of autoantibodies in youths diagnosed with type 2 diabetes illustrate that classification criteria are equally problematic in all the various intermediate forms of diabetes described in children and young people [22, 23]. Moreover, why could not an adolescent or young adult (<35 years of age) with a type 2 diabetes phenotype, who initially responds well to metformin but has autoantibodies, be a LADA patient? Hence, we would argue that having no age limit would help us to understand the underlying pathophysiology of the disease, which should be our main scientific focus.

The second problematic criterion is the treatment requirement: no exogenous insulin at onset with the arbitrary time limit of 6 months. In our previous article [4], insulin treatment was not strictly defined. For example, does it include night-time insulin which is efficacious [24] and is recommended in many countries as an adjunct to metformin early in type 2 diabetes; or does it specifically include diabetes treatment with only insulin? And how do we categorise adult patients with autoantibodies who receive an initial single treatment with insulin for a short time (weeks to a few months) and then are subsequently treated with oral hypoglycaemic agents for many years? These and many other possible insulin-treatment regimens illustrate the elusiveness of the treatment criterion. And, adding further difficulty, the criterion is too dependent on the subjective judgement of the treating physician and the prevailing treatment paradigm in the physician's site of practise.

That leaves us with the third criterion, signs or markers of autoimmunity, which today often means GAD65 antibody positivity [25, 26]. In the near future, with improvements of T cell assays, it will probably also include T cell assay positivity [27, 28]. This is the most important criterion, since it indicates a common pathogenic entity, i.e.

autoimmunity. It is this pathway that we may target in preventive trials or modify by our treatment, and to which our scientific efforts should be directed.

As pointed out by Gale [1], there are pitfalls in defining autoimmunity. The main obstacle in antibody assays is defining antibody positivity; it might depend on the assay or even on the age group in which the assays are used. In the latest antibody assay workshops organised by the Immunology of Diabetes Society, the different RIAs and some of the new ELISA kits showed good concordance, high specificity and good sensitivity [29]. However, when comparisons are made in adults [30] the concordance between assays might not be as strong as in children and adolescents [29], indicating that differences in epitope specificity or antibody levels resulting from differences in affinity and/or capacity might influence the performance of the assays. Despite weaknesses in the assays, the presence of autoantibodies probably signifies an autoimmune process. This could be exemplified by the results from UK Prospective Diabetes Study (UKPDS), which showed that among type 2 diabetes patients >55 years of age, 34% of those with GAD65 antibody and 5% antibody-negative required insulin therapy by 6 years [31].

A second problem in defining a cut-off is the distribution of autoantibodies. It is commonly assumed that autoantibodies are continuously distributed [1]. Our present antibody assays are based on measurement of radioactivity in RIAs or fluorescence in ELISAs, which is translated into units, and these units are continuously distributed. We do not know the cause or causes of low assay signals of radioactivity or fluorescence. It could result from background 'noise', different reagents in the assays, non-specific binding or, hopefully, from low levels of the targeted antibodies.

A third problem is the 'false positives', i.e. individuals without diabetes who are autoantibody positive, with a prevalence that is estimated at 1–4% [25, 32, 33]. The question is whether this autoantibody positivity is a sign of an autoimmune process or if this positivity only reflects the weakness of the assay. Some studies suggest a significant autoimmune process in these individuals. For example, in genetically predisposed individuals, e.g. first-degree relatives of type 1 diabetes patients, autoantibody positivity, especially for more than one autoantibody, confers a markedly increased risk of developing type 1 diabetes [34]. The risk of having autoantibodies in the general adult population has not been studied extensively to date, but we have recently shown that autoantibody-positive non-diabetic adult individuals have an increased risk of developing diabetes later in life [35]. However, this observation was made in a relatively small population. Taken together, these findings indicate that there could be an autoimmune process even in the non-diabetic popula-

tion, irrespective of age, which needs to be explored further.

A fourth complicating aspect is that autoimmune markers may change over time, i.e. patients may become antibody- or T cell-negative after having been positive, or vice versa. The disappearance of autoantibodies after the onset of the disease seems to be more common in children [36] than in adults [15, 35] and to be more common for some autoantibodies (ICA) than for others, such as GAD65 antibodies. The problem is how to interpret the disappearance; is the autoimmune process in remission, or is the marker just no longer positive, or both in different patients and/or at different times? This may result in a misleading classification, at least in some individuals, according to the latest WHO classification where two classes of type 1 diabetes were created—autoimmune and idiopathic type 1 diabetes.

To summarise, there are still obstacles to overcome in defining and understanding autoimmunity. However, for the time being we have to rely on and refine our present technologies in measuring autoimmunity.

We think that the categorisation of a disease should be a help for the scientist. The goals of research into the pathophysiology of diabetes are first to improve the management of diabetes but eventually also to cure and prevent the disease. If we think that the autoimmune process is the culprit, our scientific efforts should be focused on understanding the aetiology of the process, how it is regulated and the mechanism behind its effect on the target organ, in order to more effectively treat, prevent or cure autoimmune diabetes. We should accept that the autoimmune process comes in different shapes: in all ages [31, 37, 38], populations [39–42], phenotypes [31], with different genetic backgrounds [18], in healthy individuals [35], and measured by T cell or B cell activity [9], and can even co-exist with other disease processes, e.g. insulin resistance, leading to what we think is type 2 diabetes [17].

Therefore, we propose that the name LADA could be retired; it has helped us in the past but might be an obstacle in the future and it could be replaced by autoimmune diabetes. We hope that by focusing on the autoimmune process we will avoid a situation as in the famous tale of the blind men trying to answer the question: what sort of thing is an elephant? In the Buddhist version of the tale, Buddha rendered this meaning as a conclusion after having heard their divergent descriptions:

*O how they cling and wrangle, some who claim
For preacher and monk the honoured name!
For, quarrelling, each to his view they cling.
Such folk see only one side of a thing.*

Udana 68–69: Parable of the Blind Men and the Elephant

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