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COMMENTARY

Latent autoimmune diabetes in adults (LADA)—more than a name

L. Groop · T. Tuomi · M. Rowley · P. Zimmet · I. R. Mackay

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In a recent editorial [1], Edwin Gale questioned the rationale for the designation of latent autoimmune diabetes in adults (LADA) [2] as a distinct aetiological entity. The reasons given for this were that measurements of antibodies to GAD are imprecise and cut-off levels are arbitrary, and that the clinical value of a diagnosis of LADA has not been demonstrated. We, however, think that there are persuasive reasons for retention of LADA as a subgroup of diabetes.

The classification of diabetes into two main groups, type 1 and type 2, has led to the belief that all patients can be allocated to one or other of these two categories. However, when we apply distinct criteria for classification, it becomes clear that many patients do not fit readily into either group, and that there is a significant grey area between the two, as evident in epidemiological studies. LADA has provided a much better understanding of this grey area and has shown that there are patients with features of both types of diabetes. At this time, only genetically defined forms of MODY can be considered as aetiologically distinct entities; all other forms of diabetes are 'self-imposed' categories (including type 1 and type 2) based upon arbitrary cut-off levels for various indices. We can indeed consider diabetes as a continuum ranging from autoimmune inflammatory-mediated beta cell attrition at one pole to metabolic beta cell damage at the other, with LADA somewhere in between.

It is often questioned why we do not simply refer to type 1 diabetes in adults, and whether we really need a 'silly name' such as LADA to designate a particular group of patients with autoimmune diabetes. We, however, see good clinical reason for this. It has never been a problem to distinguish these patients from type 1 diabetes, but rather from type 2 diabetes, since, prior to the more widespread use of GAD antibody measurements, these patients were generally misclassified as having type 2 diabetes. In our original report [3] we called this condition latent type 1 diabetes in patients over 35 years, and, later, autoimmune diabetes in adults [4]. On the other hand, we still recognise adult patients with an onset of rapidly progressing autoimmune diabetes who share all the clinical and metabolic features of classical type 1 diabetes in younger patients. This was the rationale for reinstating the word 'latent' to distinguish the slow-onset cases from classical adult type 1 diabetes [2].

We agree with Gale and the authors of an accompanying review [5] that the specifications for the diagnosis of LADA are currently imprecise, i.e. the presence of GAD antibodies in a patient with age at onset of diabetes of >30 years (or 35 years, as we previously proposed), and insulin independence for at least 6 months after diagnosis. Clearly, each of these cut-off values is arbitrary, and the definition of GAD antibody positivity will influence not only the prevalence but also the phenotype of LADA [6]. As Gale points out, GAD antibodies are continuously distributed throughout the population, but this applies to

L. Groop (✉)
Department of Clinical Sciences, Diabetes and Endocrinology,
Lund University, University Hospital Malmo,
20502 Malmo, Sweden
e-mail: Leif.Groop@med.lu.se

L. Groop · T. Tuomi
Department of Medicine, Helsinki University Central Hospital,
Helsinki, Finland

M. Rowley · I. R. Mackay
Department of Biochemistry and Molecular Biology,
Monash University,
Clayton, VIC, Australia

P. Zimmet
International Diabetes Institute,
Melbourne, VIC, Australia

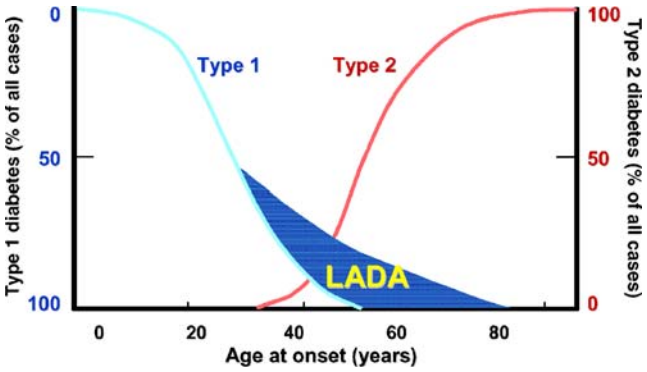

Fig. 1 Contribution of type 1 and type 2 diabetes to all cases of diabetes. At about 35 years of age the incidence of type 2 diabetes increases sharply. Most cases with LADA are aged >35 years

most autoantibodies [7], as described as early as 1963 [8]. However, this has not precluded cut-off values being designated for other autoantibodies or diagnostic analytes in serum to distinguish between health and disease. Also, when GAD antibodies in serum were plotted for 98 healthy subjects, these were normally distributed (R. Spark and I. R. Mackay, unpublished observations), indicating a bimodal distribution for normal individuals and patients with type 1 diabetes. In addition, sera of patients with LADA seem to recognise GAD65 epitopes that are different from those recognised by patients with typical type 1 diabetes [9]. The same concerns apply to age at onset and insulin independence. If the aim is to distinguish LADA from type 2 diabetes, a cut-off age at onset of 35 years is reasonable (Fig. 1). The issue of insulin independence is more problematic and can be resolved only by a large prospective study with predefined criteria for starting insulin therapy and following beta cell function. Although this has been addressed in a substudy of the UKPDS [10], this study was not really designed to answer this question.

We think that LADA is needed as an entity to foster research on these topics and provide more precise answers to the questions raised [1, 2]. Defining a multifactorial disease is a notoriously difficult [11], but in contrast to Gale, we do think that it will become possible to define LADA in a clinically meaningful way that should also provide aetiological information. Among the key issues will be the demonstration that LADA has genetic features in common with both type 1 and type 2 diabetes; this information is now partially available. Patients with LADA have more type 1 high-risk *HLA-DQ* genotypes than patients with type 2 diabetes, but fewer than those with type 1 diabetes [6, 12] and, notably, more protective HLA genotypes than patients with type 1 diabetes [6]. However, still lacking is knowledge on whether patients with LADA have the same frequency of the few type 2 diabetes susceptibility genes that have reproducibly been associated with type 2 diabetes, e.g. the Pro12Ala single-nucleotide polymorphism in *PPARG*, the E23K SNP in *KCNJ11*, or the recently described polymorphisms in *TCF7L2* [13–15].

There is abundant clinical and metabolic information on LADA. Beta cell function deteriorates faster than in type 2 diabetes but slower than in type 1 diabetes [1, 5, 13, 16], and there is no difference in hepatic or peripheral insulin sensitivity between type 1, type 2 and LADA, whether in the diabetic [3] or the prediabetic [17] state. Nevertheless, patients with LADA have fewer features of the metabolic syndrome than patients with type 2 diabetes [6, 18], and have fewer macrovascular complications [18]. Unfortunately, as regards LADA as an entity, we do not yet know the treatment of choice. Most studies thus far have been underpowered, with conclusions that test the limits of the data. This is clearly worthy of an international multicentre effort to compare early insulin therapy with conventional oral treatment strategies on their relative beta cell sparing effects and long-term outcome of the disease. Moreover, LADA is considered our best prospect for assessment of tolerogenic immunotherapy [19].

In conclusion, one of the big challenges facing clinical science is the precise categorisation of subtypes within disease entities so that these can eventually be matched to particular genetic and environmental exposures. This should be possible for LADA within the next few years, provided that diabetologists elect to retain this appellation.

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