# LADA: Fact or fairy tale?

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Over the years, people who have worked in and around diabetes will be familiar with changes in terminology with regards to the types of diabetes. Examples include juvenile diabetes, mature-onset diabetes, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus and so on. In recent years, however, it seems we have become quite content with the terms "type 1 diabetes", "type 2 diabetes", "secondary diabetes" and "monogenetic diabetes".

What concerns me is that we are now exposed to additional types of diabetes, which are based on little hard evidence and more based on opinion and theory. The one that stands out for me is LADA (latent autoimmune diabetes of adults). LADA is also known as type 1½ or slow-onset type 1 diabetes. My question is whether there is really any difference between type 1 diabetes in adults and slow-onset type 1 diabetes in adults (or LADA)? And does it really matter?

In some medical press, the term LADA and late-onset type 1 diabetes are used synonymously. However, some specialists want us to believe that LADA is not type 1 diabetes but another autoimmune type of diabetes altogether.

The onset of type 1 diabetes in adults is extremely variable. Some will present acutely as in childhood type 1 diabetes, with extreme osmotic symptoms, weight loss and ketosis, while some will be found either incidentally or early on in their disease progression with few symptoms, no weight loss or ketones, and will often not require insulin therapy at diagnosis even though they are antibody positive.

To discriminate LADA from type 1 and/or type 2 diabetes, diagnosis of LADA is supposed to be based on three criteria as given by The Immunology of Diabetes Society (Sanjeevi et al, 2003):

- Adult age of onset (>30 years of age).
- Presence of at least one circulating auto-antibody.
- Initial insulin independence (for the first six months).

## Is there any evidence to support "LADA" based on auto-antibodies?

In 2003, Hosszufalusi et al looked at people with adult-onset type 1 diabetes and those classified as having LADA. The study found no difference in the predisposing human leukocyte antigen genotypes between the two groups. The only difference they could find was that the LADA group were more likely to be positive for only one auto-antibody, compared to the adult-onset type 1 group, who were more likely to have multiple auto-antibodies; however, single antibodies and multiple antibodies were found in both groups. The titres of islet-cell antibodies, insulinoma antigen-2 antibodies and glutamic acid decarboxylase antibodies did not differ between LADA and adult-onset type 1 diabetes (Hosszufalusi et al, 2003.)

The LADA and adult type 1 diabetes individuals studied in this research had similar phenotypes and similar c-peptide levels at diagnosis, but those with LADA showed a slower decline in insulin production than the adult-onset type 1 diabetes.

## What about time to insulin dependence?

Although it is possible that there are differences in the degree of immune regulation or antigenic differences in people who develop type 1 diabetes in adulthood, surely this does not mean it is a different type of diabetes altogether? The main discriminating factor

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in the medical press appears to be the onset of insulin dependence post-diagnosis of autoimmune diabetes in adults, and as mentioned earlier, this is one of the determining features of LADA set down by The Immunology of Diabetes Society. It is more likely that many of the observed differences in people diagnosed with LADA are due to age-related effects on the immune system or because, in those diagnosed with LADA, diabetes occurs earlier in the beta-cell-destructive process due to the greater insulin resistance.

## LADA: Is it real or is it just fantasy?

How many people have we seen with type 1 diabetes diagnosed in childhood or early adulthood that are now in their 40s and are overweight and yet have seen an improvement in their control with the addition of metformin. If this person was to develop type 1 diabetes in their 40s, their onset would possibly be slower due to their insulin resistance, not because they have a different type of diabetes.

In the future, as immunomodulatory therapies that could slow or stop the type 1 diabetes disease process become available, testing these therapies in people with differing auto-antibodies on diagnosis of their type 1 diabetes will be necessary. If the efficacy of such treatment varies depending on the auto-antibodies present at diagnosis, identification of auto-antibodies at diagnosis would become clinically important, but even then, does this mean the type of diabetes is different or does it mean that the immune response is different in different people?

If you would be interested in contributing to this debate, please email jdn@sbcommunicationsgroup.com. ■

Hosszufalusi N, Vatay A, Rajczy K et al (2003) Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult onset type I diabetes with rapid progression. *Diabetes Care* **26**: 452–7

Sanjeevi CB, Balaji M, Balai V, Seshiah V (2003) Autoantibodies to GAD65 and IA-2A antibodies are increased but not tissue transglutaminase (TTG-Ab) in type 2 diabetes mellitus (T2DM) patients from South India. *Ann N Y Acad Sci* **1005**: 387–9