What's in a Name

Latent autoimmune diabetes of adults, type 1.5, adult-onset, and type 1 diabetes

Shortly after the original description of islet cell antibodies (ICAs) as a marker for childhood type 1 diabetes, it was realized that some adult-onset patients are also ICA positive (1). With the discovery of GAD antibodies as another marker of type 1 diabetes, Paul Zimmet et al. (2) introduced the term "latent autoimmune diabetes of adults" (LADA) to describe an important minority of adult-onset patients with diabetes. Typical patients are positive for GAD antibodies, 35 years of age or older, nonobese, and present without ketoacidosis and weight loss. Although many maintain good glycemic control for several years with sulfonylureas, these patients become "insulin dependent" more rapidly than antibody-negative type 2 diabetic patients (2).

Unfortunately, the phenotype of adult-onset diabetic patients, including their presentation, is extremely variable, resulting in confusion with the nomenclature and classification of these patients. Besides LADA, these patients have been named type 1.5 diabetes, "slowly progressive type 1 diabetes," "latent type 1 diabetes," "youth-onset diabetes of maturity," and even LADA-type 1 and LADA-type 2 (3). How should these patients be classified?

A major question facing the diabetes community is whether all autoantibody-positive diabetes is due to the same pathophysiological disease process. Is autoimmune diabetes in adults due to the same underlying disease process as childhood type 1 diabetes? Or do some patients with autoimmune diabetes in adulthood have a distinct form of autoimmune diabetes compared with classic childhood type 1 diabetes? Phenotypically there are at least three separate populations of autoimmune diabetes in adults: LADA, adult-onset type 1 diabetes, and obese phenotypic type 2 diabetes in patients who are antibody positive.

In this issue of *Diabetes Care*, Hosszúfalusi et al. (4) compared patients with LADA with patients presenting with classic type 1 diabetes at older ages. These populations were also compared with a control group of patients with type 2 diabetes. Clinical parameters (lipid levels, frequency of hypertension, BMI, and waist-to-hip ratio) were similar in the LADA group and the adult-onset type 1 patients and there were no differences in the prevalence of predisposing HLA genotypes between these two groups. But, the LADA patients were more commonly positive for only one autoantibody compared with a higher frequency of multiple autoantibodies in the adult-onset type 1 diabetic patients, and the group with LADA had a slower reduction of C-peptide levels than the group with adult-onset type 1 diabetes. Unfortunately, they did not study antibody-positive type 2 diabetes.

Genetically HLA DR3 and -4 and their associated DQβ1 alleles 0201 and 0302 predispose to childhood type 1 diabetes, and these alleles are also increased in adult patients with autoimmune diabetes. DR2 and DQβ1*0602 are strongly protective against childhood type 1 diabetes and consequently are very rarely found in these patients. In contrast, DR2 DQβ1*0602 occurs relatively commonly in LADA (5); therefore, it is hypothesized that whatever mechanism accounts for HLA DR2 DQβ1*0602 protection against childhood type 1 diabetes is far less effective in protecting against autoimmune diabetes in adults. In general agreement with this paradigm, Hosszúfalusi et al. found increased DR3 DQβ1*0201 and increased DR4 DQβ1*0302 in LADA and adult-onset type 1 diabetes compared with control subjects. Unfortunately, data on the protective allele DR2 DQβ1*0602 were not presented.

Metabolically, it is commonly assumed that loss of β-cell function is slower in autoimmune diabetes in adults than in childhood type 1 diabetes but faster than in classic adult-onset type 2 diabetes. This presumably accounts for the nearly universally observed earlier need for insulin therapy in these patients compared with adult-onset type 2 diabetic patients. But some studies have shown comparable declines in β-cell function in autoimmune diabetes in adults and type 1 diabetes over the initial 2–3 years postdiagnosis (6). Other factors that may complicate the interpretation of β-cell function data include the observations that β-cell dysfunction tends to be more severe at diagnosis in younger children with type 1 diabetes, that intensive metabolic control slows the decline in β-cell dysfunction in type 1 diabetes (7), and that older more obese patients would be more insulin resistant and consequently would present with hyperglycemia with less β-cell dysfunction. The LADA and adult type 1 diabetic patients reported by Hosszúfalusi et al. had similar phenotypes and hence probably similar insulin sensitivity to explain their similar C-peptide levels at diagnosis. But the adult type 1 diabetic patients showed a more rapid decline postdiagnosis compared with the LADA patients, suggesting a more aggressive autoimmune attack against β-cells.

Autoantibodies against islet antigens allow us to clearly distinguish autoimmune diabetes in adults from antibody-negative type 2 diabetes and provide the strongest evidence that all three subgroups of autoimmune diabetes in adults are autoimmune disorders. But, immune markers also provide the strongest evidence for potentially important differences in the underlying disease process in autoimmune diabetes in adults versus childhood type 1 diabetes. ICA and autoantibodies against GAD, insulin, and IA-2 are all very common in childhood type 1 diabetes. ICA and GAD antibodies are also common in autoimmune diabetes in adults, whereas we and most other investigators (8) find IA-2 antibodies and insulin autoantibodies to be far less prevalent in these patients. Other observations also suggest antigenic differences between LADA and type 1 diabetes.

A larger proportion of childhood type 1 diabetic patients is positive for multiple autoantibodies. Seissler et al. (9) observed that most of the ICA signal could be blocked by the addition of GAD and IA-2 in sera from type 1 diabetes but not from LADA patients, suggesting that antibodies to antigens other than GAD and IA-2 are more prevalent in LADA patients. In collaboration with Hampe and Lernmark (10), we have recently found a difference in the epitope specificity of GAD antibodies from newly diagnosed autoimmune diabetes in adults versus childhood type 1 diabetic patients. The NH_2-terminus of GAD 65 was recognized by a significantly larger proportion of autoimmune diabetes in adults than in type 1 diabetic patients (10). In collaboration with Japanese investigators, Dr. Lernmark has also found similar difference in epitope specificity of GAD antibodies from LADA vs. type 1 diabetic patients from Japan (A. Lernmark, personal communication). We have also noted differences between autoimmune diabetes in adults and type 1 diabetes in T-cell reactivity to islet proteins (11).

Spreading of the immune response to more and more antigens of the target organ as the disease process progresses is a well-recognized component of autoimmune diseases and occurs at both the intramolecular and intermolecular levels. This probably explains the presence of antibodies to multiple islet antigens in type 1 diabetes, and we have observed antigen spreading of T-cell responses to islet antigens in the preclinical period of human type 1 diabetes (12). Based on the apparent antigenic differences between LADA and type 1 diabetes that we and others, including Hosszúfalusi, have observed, we have hypothesized that antigen spreading is more restricted in autoimmune diabetes in adults than in childhood type 1 diabetes. Or stated another way, childhood type 1 diabetic patients are more likely to lose tolerance to more islet antigens than patients with autoimmune diabetes in adults. Consequently, the autoimmune attack against the β-cells may be more aggressive in childhood type 1 diabetes than in autoimmune diabetes in adults. If this hypothesis is true, it may have important implications for future immunomodulatory therapy to block the autoimmune diabetes disease process. It is also possible that treatment with some antigens might be efficacious in both autoimmune diabetes in adults and in childhood type 1 diabetes, whereas other antigens might be selectively effective in childhood type 1 diabetes or LADA or another subset of autoimmune diabetes. That is, one would not be able to assume that any antigen-based therapy efficacious in type 1 diabetes would also be efficacious in all patients with autoimmune diabetes. As just one example, a heat-shock protein peptide (DiaPep277) has recently been reported to preserve β-cell function in newly diagnosed type 1 diabetes (13), and a trial to test its effectiveness in autoimmune diabetes in adults has just begun.

While many questions remain, we propose standardizing the nomenclature for the classification of autoimmune diabetes. Childhood-onset patients with type 1 diabetes, like the adult subjects in the Hosszúfalusi study with classic type 1 diabetes, would continue to be classified as having type 1 diabetes. The antibody-positive patients diagnosed over the age of 35 years who do not initially require insulin would continue to be classified as LADA. Importantly, these patients are generally nonobese. On the other hand, the antibody-positive patients with phenotypic type 2 diabetes (usually obese and insulin resistant) (14) would be classified as type 1.5 diabetes as opposed to "obese LADA" or LADA-type 2.

Although this proposed nomenclature will allow more homogeneous grouping of patients, we realize that it will not be completely satisfactory because it is based on clinical phenotype. When we know whether there are etiological differences between any of the subsets of autoimmune diabetes, we will be able to decide whether all autoimmune diabetes should be called type 1 diabetes or whether one or more subsets really deserves its own name.

What's in a name? We would argue, quite a bit.

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