

PRACTICE

Latent autoimmune diabetes of adulthood (LADA): An often misdiagnosed type of diabetes mellitus

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Abstract

Purpose: The purpose of this article is to raise awareness about a frequently misdiagnosed form of diabetes, latent autoimmune diabetes of adulthood (LADA), to describe its clinical and epidemiological characteristics, and to compare them to those of the more common and widely known types of diabetes, type 1 diabetes mellitus (DM) and type 2 DM.

Data sources: A review of the pertinent literature describing the features of LADA from 2000–2007 is summarized.

Results: LADA is a rather common and often underrecognized form of diabetes whose clinical presentation falls somewhere between that of type 1 DM and type 2 DM. From a pathophysiological perspective, it is more closely related to type 1 DM, and some have even used the term type 1.5 diabetes to refer to it; however, it is most often misdiagnosed and treated as type 2 DM.


Conclusions: Nurse practitioners (NPs) should always consider alternate diagnoses when patients with newly or previously identified adult onset diabetes mellitus do not fit the traditional stereotype of type 2 DM (i.e., overweight with signs of insulin resistance and a significant family history of diabetes). Statistically, strong consideration must be given to the diagnosis of LADA, especially in those who are of normal weight, show little evidence of insulin resistance, and have hardly any family history of diabetes.

Implications for practice: Knowing the patient’s exact diabetes type can give the NP a much greater understanding of the natural history of the patient’s disease, the changes that may occur as the patient ages, and how to optimally manage their diabetes to minimize complications. Likewise, when a patient is correctly diagnosed, they can be empowered to manage their diabetes with the appropriate therapies.

LADA is an autoimmune disorder that occurs when the body mistakes the insulin-producing beta cells of the pancreas as being foreign (Behme, Dupre, Harris, Hramiak, & Mahon, 2003; Fournalanos et al., 2005). The body responds by attacking and destroying beta cells in what seems to be an auto-allergy state, a common phenomenon in all autoimmune diseases. These patients commonly have a personal or family history of other autoimmune

diseases such as Graves’ disease, Hashimoto’s thyroiditis, pernicious anemia, vitiligo, celiac disease, Addison’s disease, premature gonadal failure, and others (Grasso et al., 2001; Notkins, 2004), but frequently lack a family history of diabetes (Anaya et al., 2006).

Because patients with LADA present with an insidious onset of hyperglycemia, and lack the tendency for acute hyperglycemic crisis (i.e., diabetes ketoacidosis [DKA]),

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patients with LADA are frequently misdiagnosed as having type 2 diabetes mellitus (DM). However, patients with LADA are typically of normal to slightly overweight body habitus compared to the tendency for class III or IV obesity more commonly found among patients with type 2 DM. Patients with LADA are much less likely to give a history of hyperglycemic crisis, such as DKA, at the time of their diagnosis or early in the disease process as compared to those with classic type 1 DM. Alternatively, patients with LADA usually lack the overt signs of insulin resistance seen in classic type 2 DM such as acanthosis nigricans (i.e., darkening of the skin in body folds) or acrochordons (i.e., skin tags) (Chiu et al., 2007; Litonjua, Pinero-Pilona, Aviles-Santa, & Raskin, 2004).

Pathophysiology

Among individuals with LADA, the autoimmune system attack against the pancreatic beta cells is much slower and more selective than in classic type 1 DM, therefore permitting the surviving beta cells to produce insulin for a longer period of time, usually several more years. Insulin is usually required in half of those with LADA within 4 years of diagnosis compared with more than 10 years in patients with frank type 2 DM (Grasso et al., 2001).

The existence of HLA-DR4-DQ8 antigens is associated with a more destructive progression of beta cells among a large percentage of patients with classic type 1 DM (Schranz et al., 2000). The fact that HLA-DR4-DQ8 antigens are more widespread among patients with classic type 1 DM than among those with LADA may offer an explanation as to why patients with LADA do not develop insulin dependence as quickly as patients with classic type 1 DM. It has also been hypothesized that immune tolerance to beta cell antigens may develop among patients with LADA, potentially offering protection from widespread destruction of beta cells. In short, the fundamental immune-mediated destruction of beta cells among patients with LADA fosters insulin dependency more promptly than in type 2 DM, but much slower than in type 1 DM (Schranz et al., 2000). The less extreme genetic and immune features associated with LADA versus type 1 DM are credited with causing an older age at onset and a slower development of insulin dependency (Furlanos et al., 2005; Grasso et al., 2001).

Diagnosis

LADA is diagnosed by demonstrating the presence of pancreatic islet autoantibodies in patients with recently diagnosed adult onset diabetes that do not immediately require insulin. Pancreatic islet autoantibodies serve to identify both the existence of LADA as well as the rate of

progression toward insulin dependency (Furlanos et al., 2006). Positive tests for glutamic acid decarboxylase autoantibodies (anti-GAD), islet cell auto-antibodies (anti-ICA), and tyrosine phosphatase auto-antibodies (anti-IA2 or anti-ICA512) have been found to be predictive of insulin dependency within 3 years (Torn et al., 2000). The occurrence of all three autoantibodies forecast insulin dependency in 100% of cases (Furlanos et al., 2006). Anti-insulin auto-antibodies are more common among patients with classic type 1 DM than in patients with LADA (Furlanos et al., 2006).

The most sensitive antibody marker among patients with LADA is anti-GAD, with a sensitivity of approximately 85%. Even in the absence of anti-GAD antibodies, however, some patients may test positive for other islet cell auto-antibodies (Falorni & Calcinaro, 2002); therefore, although anti-GAD is the best test to screen for LADA, when the test is negative but the suspicion of LADA remains high, the measurement of other pancreatic islet auto-antibodies may assist in confirming the diagnosis (i.e., anti-ICA or anti-IA2) (Furlanos et al., 2006).

Although the diagnosis of LADA depends on demonstrating the presence of one of the above-mentioned markers of antipancreatic islet autoimmunity, the use of these antibodies as a screening tool for LADA in all patients with adult onset diabetes mellitus cannot be advised because of the lack of demonstrated cost-effectiveness. It may be practical, however, to measure C-peptide levels as a marker of beta cell function to screen patients with adult onset diabetes and identify those with significant pancreatic beta cell dysfunction (which would be very unusual in patients with recent onset type 2 DM) who would benefit from antipancreatic islet antibody screening (Bell & Ovalle, 2004). Measurements of C-peptide levels assist in determining the extent of beta cell dysfunction (Palmer et al., 2004). The following scenarios should prompt the clinician to measure C-peptide levels: an adult patient with relatively new onset diabetes who does not manifest features of metabolic syndrome; significant weight loss at presentation; a patient whose glucose remains uncontrolled despite the use of oral medications early in their disease process; and a patient who has a personal or family history of other autoimmune diseases. In any of those clinical scenarios, a low or normal C-peptide level in the presence of hyperglycemia should prompt the measurement of antipancreatic islet cell antibodies, at least anti-GAD antibodies (Bell & Ovalle, 2004).

Management

Controlling hyperglycemia and preventing complications are the primary focus of management for all types of diabetes mellitus. In management of a patient with LADA, it is

important to note there is often an opportunity to preserve beta cell function. The slower rate of beta cell destruction among patients with LADA, compared to that in classical type 1 DM, may allow for such interventions. Optimizing beta cell function among patients with LADA with insulin therapy has been associated with better glycemic control and less proliferative retinopathy (Maruyama et al., 2003).

Patients with LADA may manifest insulin resistance to a variable degree, which is primarily fostered by an overweight to mildly obese body mass index (BMI) (Behme et al., 2003). Management with metformin may be advantageous because inhibiting hepatic gluconeogenesis increases the liver's sensitivity to insulin and, therefore, decreases the need for insulin secretion. Similarly, although the thiazolidinediones mainly reduce insulin resistance in peripheral tissues, muscle, and fat, there is some evidence demonstrating that they might improve the secretory function of the beta cells, perhaps through an anti-inflammatory action and may be able to help slow the immune destruction of beta cells (Beales & Pozzilli, 2002).

Because of the nature of the slow beta cell destruction among patient with LADA, insulin is not usually required at the time of diagnosis. At first, patients with LADA may be managed with changes in lifestyle and by adding oral agents. Alternatively, some investigators feel that insulin should be started as soon as possible rather than using sulfonylureas or other oral agents for initial management (Maruyama et al., 2003); however, it remains to be determined whether early insulin therapy contributes to the preservation of beta cell

function. In addition, further research is needed to determine the role of agents like the TZDs, DPP-4 inhibitors, and the GLP-1 agonists in the preservation, regeneration, and/or improvement of beta cell function in patients with diabetes mellitus, including those with LADA.

Summary

LADA is a rather common and underrecognized form of diabetes that is usually misdiagnosed and treated as type 2 DM. The clinical characteristics of LADA fall somewhere between those of type 1 and type 2 DM. Consequently some have used the term type 1.5 diabetes to refer to it. Nurse practitioners (NPs) should always consider alternative diagnoses when patients with newly or previously diagnosed adult onset DM do not fit the traditional stereotype of type 2 DM (i.e., overweight with signs of insulin resistance and a significant family history of diabetes). Statistically, strong consideration must be given to the diagnosis of LADA. Knowing the patient's exact type of diabetes can give the practitioner a better understanding of the changes that may occur as they age, the natural history of the disease, and the best management strategies that will minimize complications for that individual.

It is important that patients who have LADA are educated about how this form of diabetes may differ from frank type 2 DM. NPs should explain that LADA is closer to type 1 diabetes and an appropriate strategy for its management is insulin therapy. Otherwise, patients with LADA may see the addition of insulin therapy as their failure to effectively manage their diabetes rather than an expected step in the progression of the disease.

Table 1. Comparison of the characteristics of type 1 and type 2 diabetes mellitus to those of LADA

Characteristic	Type 1	Type 2	LADA (Type 1.5)
Typical age of onset	<35	>35	>35
Speed of onset	Rapid	Slow	Slow
Response to lifestyle modification or oral agents	Poor	Good	Initially acceptable, but worsens in time
Frequency of DKA	High	Low	Low
Family history of DM	Uncommon	Common	Uncommon
Personal or family history of other autoimmune diseases	Common	Uncommon	Common
Body habitus	Fit or lean	Overweight to obese with "apple shape"	Normal to overweight
Acanthosis nigricans or acrochordons	No	Yes	No
Metabolic syndrome or components	No	Yes	No
C-peptide level	Undetectable/low	Normal/high	Low/normal
Anti-GAD/ Anti-ICA/ Anti-IA2	Positive	Negative	Positive

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