Latent Autoimmune Diabetes in Adults

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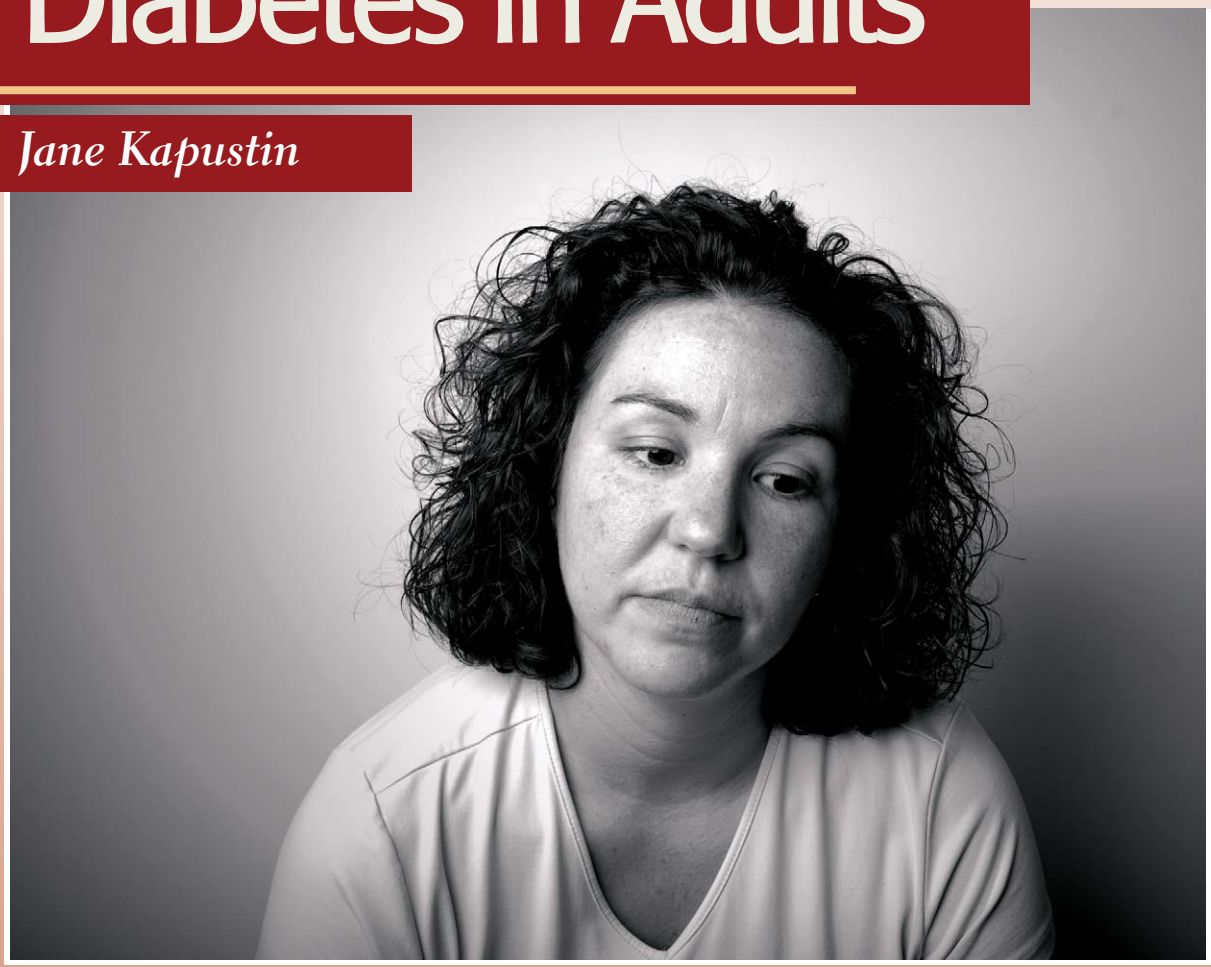

ABSTRACT

Latent autoimmune diabetes in adults (LADA) is a genetically linked, autoimmune form of type 1 diabetes mellitus that is commonly seen after age 30 in patients who often have a normal body mass index without overt signs of metabolic syndrome. They have positive circulating antibodies reflecting the autoimmune nature of beta cell destruction, and they frequently are poorly controlled on oral anti-diabetic agents. Because they are older when first symptomatic, they are often diagnosed with type 2 diabetes. However, it is important to recognize patients with LADA because they often progress quickly to insulin dependence. The characteristics of LADA, pathogenesis, diagnostic work-up, complications, and evidence-based management of the disease will be reviewed. Implications for practice will be included.

Keywords: GAD antibodies, insulin, LADA, metabolic syndrome, type 1 diabetes mellitus

Latent autoimmune diabetes in adults (LADA) is a genetically linked, autoimmune form of type 1 diabetes mellitus that is manifested in adult populations, typically over the age of 30.[1] Because many of the affected patients have poor glycemic control and are older when first symptomatic, they are often diagnosed with type 2 diabetes. However, many do not have the typical characteristics of type 2 diabetics such as obesity and insulin resistance.[2]

Confusion regarding the diagnosis and categorization of LADA exists because patients share symptoms of both types 1 and 2 diabetes, and it is usually diagnosed in adulthood. It has been referred to as "late-onset autoimmune diabetes of adulthood," "slow onset type 1 diabetes," and "type 1.5 diabetes."[3] Officially, LADA is classified as type 1 diabetes by the World Health Organization.

The frequency of LADA is underestimated and may range as high as 6% to 50% among type 2 diabetics. Its prevalence is increased among younger patients.[4] Given its frequency among the population, it is important to recognize LADA because these patients are at particular high risk for developing insulin dependence. They may require a rapid escalation of oral medications and it may result in multiple medication failure. At that point, they will become insulin dependent earlier than antibody-negative patients.[5]

The characteristics of LADA, pathogenesis, diagnostic work-up, complications, and evidence-based management of the disease will be reviewed. Emphasis on the clinical signs and symptoms that may prompt a more detailed work-up will be included.

BACKGROUND AND INCIDENCE

LADA is associated with circulating antibodies to islet cells and most commonly to glutamic acid decarboxylase (GAD). Because they appear to have a more insidious form of autoimmune beta cell destruction, the patients affected with LADA do not require insulin initially. Eventually, however, most patients with LADA will require insulin within 3 years as beta cell function declines. In particular, those patients with LADA who have positive islet cell antibodies are more likely to experience accelerated beta cell failure.[6-8]

Patients with LADA have several characteristics of type 1 and type 2 diabetes (Table 1). The accurate diagnosis of LADA is usually based on 3 criteria: (1) adult onset, typically over the age of 30, (2) presence of circulating antibodies, and (3) requiring insulin no sooner than 6 months after diagnosis.[1,6,7] This type of diabetes is etiologically associated with environmental and heritable predispositions.[7]

Patients with LADA usually present with low C-peptide levels consistent with the autodestruction of islet cells, thus reducing the amount of insulin produced. Patients with type 2 diabetes usually have normal to high levels of C-peptides. Eventually, as the disease progresses, the patient with LADA will require insulin. Of note, the need for insulin occurs much more rapidly for patients with LADA than for typical type 2 diabetics.[7-9] In essence, patients with LADA tend to be more insulin *deficient*, not insulin resistant. Like patients with type 2 diabetes, patients with LADA may not require insulin initially but some may have some degree of insulin resistance. Unlike type 2 diabetes, there is often an absence of family history of type 2 diabetes in a LADA patient's family.[10]

Based on the findings from the United Kingdom Prospective Diabetes Study (UKPDS),[11] approximately 10% of adults with diabetes tested positive for GAD antibodies and were determined to have LADA. This can be inferred to represent approximately 375,000 people in the United States.

RISK FACTORS

The risk factors associated with LADA are important to recognize so that health care providers can appropriately conduct antibody testing for proper diagnosis. Because antibody testing is not indicated for every patient with diabetes, other clues can assist with identification.[12] Clinical features include age of onset < 50 (typically < 35), acute symptoms of diabetes, BMI < 25 kg/m^2, personal history of autoimmune diseases such as autoimmune thyroid disease, and family history of autoimmune disease. LADA should be suspected when a younger adult with uncontrolled hyperglycemia presents without signs of metabolic syndrome, has poor response to oral agents, and has evidence of other autoimmune diseases such as Grave's disease, Hashimoto's thyroiditis, or pernicious anemia.[12,13]

Because it is not practical or economical to test all diabetics for LADA, Fourlanos et al[14] developed a screening tool to assist with distinguishing patients at high risk for developing LADA from those with type 2 diabetics. In their retrospective study, the authors dis-