

CLINICAL VIGNETTE

LADA: Latent Autoimmune Diabetes in Adults

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Introduction

The difference between type 1 diabetes mellitus and type 2 diabetes mellitus is well established in the medical literature. Type 1 diabetes results from autoimmune β -cell destruction usually leading to absolute insulin deficiency. Type 2 diabetes results from a progressive insulin secretory defect in the setting of insulin resistance¹. Although many patients present with symptoms and signs consistent with a classic diabetes diagnosis, clinical presentation and disease progression vary considerably in both types of diabetes making diagnoses more difficult, especially in older patients. LADA, Latent Autoimmune Diabetes in Adults, is a classification of Diabetes Mellitus with phenotypic and genotypic similarities to both type 1 and type 2 diabetes. About 10% of adult patients with diabetes fall into this category².

Case Presentation

A 62-year-old woman who had no family or personal history of type 1, type 2 or gestational diabetes presented for a general physical with her primary care doctor February, 2013. For the first time in her life, she was told that her fasting blood sugar was elevated to 108 mg/dl and her cholesterol was elevated. She was started on atorvastatin nightly, but decreased the dose to every other night because she had read information regarding an increased incidence of diabetes with statins³.

In April, 2013 she was started on metformin 500 mg twice daily, but stopped after three days due to nausea and vomiting. In June, 2013 her fasting blood sugar was 142 mg/dl and HgbA1c was 6.9%. In August, 2013 she was referred to UCLA-Thousand Oaks Endocrinology for further evaluation.

Due to anxiety regarding a diagnosis of diabetes mellitus, she began to check her blood sugar levels

regularly. Self-monitoring blood glucose values ranged from 100-140 mg/dl fasting to 100-200 mg/dl post-prandial. Her review of systems was remarkable for mild fatigue and a 10 pound weight gain over the previous year (mostly in her abdomen). She had no polyuria, polydipsia, blurry vision or history of autoimmune diseases such as vitiligo, hypothyroidism, hyperthyroidism, pernicious anemia or celiac disease.

Physical exam revealed a thin female with the following vital signs: Blood pressure 98/60, Pulse 66, Temperature 98.1 F, Weight 112 pounds, Height 61" and BMI 21. Because of her thin body habitus, age at onset of progressive hyperglycemia in spite of a vegetarian/low carbohydrate diet and no evidence of ketones in her urine or blood, insulin antibodies were checked and were found to be positive as follows: glutamic acid decarboxylase 65 antibody (GADA) 30 (<1.0 u/ml), insulinoma-associated antigen antibody (IA-2A) 36.2 (<0.8 U/ml), insulin auto-antibody (IAA) 0.5 (<0.4 U/ml), C-peptide 1.36 (0.8-3.1 ng/ml). Six months after presentation of hyperglycemia, the patient was diagnosed with Latent Autoimmune Diabetes in Adults (LADA) and started on long-acting insulin injections before bed. Her HgbA1c decreased to 6.3% and the patient began to feel better emotionally because she could understand the type of diabetes she was living with.

Discussion

The evolution of the diagnosis and clinical studies of Latent Autoimmune Diabetes in Adults began almost 40 years ago. In 1974 it was noted that islet cell antibodies were common in the sera of patients with type 1 diabetes and that the β -cell lesion of type 1 diabetes was autoimmune in nature⁴. It was serendipitously noted in the same year that ~11% of patients with type 2 diabetes were also positive for islet cell antibodies and that this subset of patients with type 2 diabetes tended to fail sulfonylurea therapy and needed insulin treatment earlier than type 2 diabetes patients who were negative for islet cell antibodies⁵. In 1986, islet cell antibody (ICA) positivity identified a group of patients aged 35-75 with a latent form of type 1 diabetes⁶. In 1993, the entity known as Latent Autoimmune Diabetes in

Adults was coined in the literature as it was found that glutamic acid decarboxylase antibodies (GADA) were associated with a slowly progressive form of autoimmune diabetes that could be treated initially *without* insulin, but that ~80% of these patients eventually progressed to insulin dependence within 6 years⁷. In 1997, data from the United Kingdom Prospective Diabetes Study (the largest prospective study of patients with type 2 diabetes originally designed to provide guidelines for the management of type 2 diabetes) revealed that ~10% of adults with type 2 diabetes at diagnosis had evidence of islet cell autoimmunity and the majority of these patients progressed to insulin dependence within 6 years⁸.

By 2005, Latent Autoimmune Diabetes in Adults became the most common term describing patients with a type 2 diabetes phenotype combined with islet cell antibodies and slowly progressive β -cell failure over the age of 35. Features of Latent Autoimmune Diabetes in Adults similar to type 1 diabetes included identical pre-disposing HLA genotypes for diabetes (HLA-DR3/DR4) and the fact that multiple and higher titers of islet cell antibodies predisposed patients with LADA to a more rapidly progressive course of β -cell failure².

In 2007, a European Union Initiative, *ACTION LADA*, was started to further define the prevalence, characterize genetic, immunological and metabolic features of patients affected by Latent Autoimmune Diabetes in Adults and develop potential intervention trials with DiaPep277TM (an immune- modulating peptide that prevents the destruction of β -cells and preserves their natural function which to date has only been studied in patients with type 1 diabetes). *ACTION LADA* defined Latent Autoimmune Diabetes in Adults, for clinical and research purposes, as patients with adult-onset diabetes (ages 30-70), non-insulin requiring diabetes for a minimum of 6 months and the presence of diabetes-associated auto-antibodies (specifically glutamic acid decarboxylase antibodies)⁹. Further *ACTION LADA* studies showed similarities of Latent Autoimmune Diabetes in Adults to type 1 diabetes (higher islet cell antibody titers and thinner patients) and type 2 diabetes (lower islet cell antibody titers and the presence of metabolic syndrome)^{10,11}.

In conclusion, it has been established in the literature that β - cell autoimmunity and HLA genotypes contribute to the evolution of type 1 diabetes. It is also known that non-autoimmune β -cell dysfunction and insulin resistance contribute to the evolution of type 2 diabetes. It appears that there are three mechanisms for disease evolution in Latent

Autoimmune Diabetes in Adults including β -cell autoimmunity, non-autoimmune β -cell dysfunction and insulin resistance¹². Several studies have found that ~10% of patients with adult-onset diabetes mellitus fall into this latter category of Latent Autoimmune Diabetes in Adults with autoimmune diabetes which is non-insulin requiring at diagnosis. There is some controversy regarding the definition of Latent Autoimmune Diabetes in Adults because the diagnostic criteria can be considered biased depending on the natural history and phase of presentation of a patient. There does appear to be value in measuring glutamic acid decarboxylase antibodies in adult-onset diabetes patients to identify autoimmune disease that appears to have no absolute identifiable clinical phenotype. Knowing that adult-onset diabetic patients are glutamic acid decarboxylase antibody positive will alert clinicians to the increased likelihood of a more rapid progression to insulin therapy and the potential for other autoimmune disease processes.

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