

Recognizing and Appropriately Treating Latent Autoimmune Diabetes in Adults

Katherine S. O'Neal,¹ Jeremy L. Johnson,² and Rebekah L. Panak¹

Latent autoimmune diabetes in adults (LADA) is considered a subgroup of type 1 diabetes and is often misdiagnosed because of a lack of both awareness and standardized diagnostic criteria (1–3). LADA is characterized by adult-onset diabetes and circulating autoimmune antibodies; thus, patients may present clinically with characteristics of both type 1 and type 2 diabetes (2–5). Typically, the clinical features of type 1 diabetes seen in LADA include a lower BMI compared to what is typical in type 2 diabetes and autoimmunity against one or more of the following antibodies: islet cell autoantibodies (ICA), autoantibodies to glutamic acid decarboxylase (GAD), tyrosine phosphatase–related islet antigen 2 (IA-2), and insulin autoantibodies (IAA) (4,5). The characteristics of type 2 diabetes that may present in LADA include older age at onset and insulin resistance or deficiency. Characteristics of LADA tend to include an intermediate level of β -cell dysfunction between those in type 1 and type 2 diabetes, faster decline of C-peptide compared to type 2 diabetes, and a level of insulin resistance that is comparable to type 1 diabetes (4). β -Cell decline is variable in LADA, as measured by C-peptide levels (5–7).

Although it has a closer pathophysiological relationship to type 1 diabetes, LADA is often misdiagnosed and treated as type 2 diabetes (2–5). This results in insufficient glycemic control and harm to patients.

It is imperative to establish distinct practice guidelines for the diagnosis and treatment of LADA and for providers to recognize this clinical scenario as one that requires special testing to establish a proper diagnosis and thus improve patient safety and treatment efficacy.

The similarities between type 1 diabetes, type 2 diabetes, and LADA can make diagnosis difficult (Table 1). There are, however, other characteristics for this population that may prompt diagnostic screenings and help to distinguish LADA from type 1 or type 2 diabetes (4,5). In type 1 diabetes, the typical age of onset is <35 years, the response to lifestyle modification and oral agents is poor, patients are generally lean from unintentional weight loss, and they have positive titers for at least one autoantibody (4). Conversely, in type 2 diabetes, the typical age of onset is >35 years, response to lifestyle modifications and oral agents is good, patients are often overweight or obese, and they test negative for autoantibodies. LADA has a typical age of onset that is more characteristic of type 2 diabetes, and patients respond initially to lifestyle modifications and oral agents, but their response then declines as β -cell function deteriorates (5). Patients with LADA also test positive for at least one autoantibody.

In addition to a full antibody panel, C-peptide is often measured as a marker to differentiate the types of diabetes (4,5,8) C-peptide levels are

¹University of Oklahoma College of Pharmacy, Tulsa, OK

²Southwestern Oklahoma State University College of Pharmacy, Tulsa, OK

Corresponding author: Katherine S. O'Neal, katherine-oneal@ouhsc.edu

DOI: 10.2337/ds15-0047

©2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0> for details.

TABLE 1. Characteristics of Type 1 Diabetes, Type 2 Diabetes, and LADA

| | Type 1 Diabetes | Type 2 Diabetes | LADA |
|---------------------------|-------------------|-------------------------|----------------------------|
| Age (years) | <35 | >35 | ≥30 |
| C-peptide | Very low | Normal to high | Low |
| ICA | Often positive | Negative | Can be positive |
| GAD65 | Often positive | Negative | Can be positive |
| IA-2 | Often positive | Negative | Can be positive |
| IAA | Often positive | Negative | Can be positive |
| Circulating insulin | Rapidly deficient | Excessive and resistant | Gradually deficient |
| Time to requiring insulin | At onset | Can be many years | Within 6 months (variable) |

often undetectable in type 1 diabetes and normal to high in type 2 diabetes, whereas patients with LADA tend to have low to normal initial C-peptide levels. However, patients with type 1 diabetes can have some residual C-peptide up to 5 years after diagnosis, especially those who are diagnosed after the age of 18 years, making this a less distinct marker for diagnosis (8). Recognizing that testing for specific autoantibodies may not always be practical because of high testing costs, standardization, and results that can be difficult to interpret, evaluating C-peptide levels may be more cost-effective.

Whereas type 1 diabetes often develops rapidly, LADA is not as rapid and presents like a slowly progressing form of type 1 diabetes. Because β -cell function is lost more gradually than in type 1 diabetes but more rapidly than in type 2 diabetes, patients may initially respond to noninsulin glucose-lowering agents. However, once β -cell function declines, their response to these agents will diminish.

Patients with LADA who are incorrectly diagnosed with type 2 diabetes often will be started down a path of various oral treatment options, potentially delaying effective treatment. Although, as noted, LADA patients may initially respond to oral medications, they often require insulin therapy within 5 years of diagnosis. Providers may spend several months titrating oral medications, suspecting nonadherence,

and enforcing further lifestyle modifications when, in actuality, these patients are in need of insulin therapy. Medications that preserve β -cell function may be useful for LADA as well, given its relatively more rapid progression of β -cell loss compared to type 2 diabetes (4). Incorrect diagnosis can delay proper treatment, exposing patients to potential adverse effects from ineffective drugs, slowing progress toward normoglycemia, and ultimately increasing the risk of long-term complications.

In an effort to build on the groundwork for establishing guidelines, the Immunology of Diabetes Society (IDS) has proposed three criteria to standardize the definition of LADA: 1) age usually ≥ 30 years, 2) positive titer for at least one of the four autoantibodies, and 3) has not been treated with insulin within the first 6 months after diagnosis (4,5).

Although it has been demonstrated that GAD and ICA are the more dominant antibodies in LADA, the presence of other antibodies is also indicative of an underlying autoimmune process (1,8–10). In fact, Tiberti et al. (10) have proposed, based on their study of 177 patients with LADA, that the specific IA-2 construct 256-760 may be more frequent in LADA than has been reported previously.

The following case presentation highlights the diagnosis and management of a patient who closely met the IDS criteria for LADA but was initially diagnosed with type 2 diabetes.

Case Presentation

A 36-year-old man presented to an internal medicine clinic’s pharmacotherapy diabetes service as a new patient. He had been diagnosed with type 2 diabetes 2 years previously and was started on metformin, with the later addition of glyburide.

At the initial visit with the new service, the patient reported no improvement from current oral medications, feelings of frustration and defeat about his current glycemic control, and unintentional weight loss of >20 lb in the past year. His A1C was 9.3%. In addition to diabetes, the patient was prehypertensive and had total and LDL cholesterol levels that were not meeting standard goals of the time.

Because of the A1C >9% and suspicion of LADA, the patient was instructed to discontinue oral agents and was started on insulin glargine 25 units daily. Antibody tests were ordered with the following results: C-peptide 0.34 ng/mL (normal 0.8–3.0 ng/mL), GAD65 <1 U/mL (normal <1 U/mL), and IA-2 3.4 U/mL (normal <0.8 U/mL, specific construct level detail not available). The patient was also started on pravastatin 20 mg daily.

The patient was diagnosed with LADA and subsequently also started on 2 units of insulin aspart with meals. Two months later, his A1C had improved to 5.9%. At this visit, he was educated about counting carbohydrates to further match insulin doses to carbohydrate intake using an

insulin-to-carbohydrate ratio of 1:15 for breakfast and 1:10 for lunch and dinner. Four months later, the patient continued to maintain good glycemic control with an A1C of 5.6%. After the adjustment in drug therapy, he demonstrated good glycemic control and had improvements in blood pressure and total and LDL cholesterol. With insulin use, he also returned to his "normal" weight, regaining almost 20 lb. The patient reported adherence to his insulin regimen and carbohydrate counting at meals, and his glucose remained controlled throughout the next year.

Discussion

The patient in this case closely fits the proposed IDS criteria for diagnosing LADA. He was >30 years of age, and although he did not test positive to one of the more commonly seen antibodies (GAD), he had high titers of IA-2 (meeting the criterion of testing positive to at least one antibody), and he was not treated with insulin within the first 6 months after diagnosis. Additionally, he had a low C-peptide level.

In addition to meeting these criteria, his course of disease progression resembled that of a misdiagnosed LADA patient. The patient was initially treated with oral medications, as would be a patient with type 2 diabetes. However, despite adherence, these medications made an insufficient impact, achieving an A1C of 9.3% by the time he was first seen at the clinic. The patient also continued to lose weight, much like a patient with type 1 diabetes.

Within these guidelines, an accurate diagnosis was made and treatment was appropriately changed to basal and bolus insulin to gain consistent glycemic control.

Conclusion

Correctly diagnosing LADA is essential to choosing a proper treatment regimen that will attain and maintain glycemic control. In a review by Laugesen et al. (11), patients with LADA were found to have worse gly-

cemic control with higher A1C levels and progress toward needing insulin therapy much more rapidly than those with type 2 diabetes. Given the high prevalence of type 2 diabetes in adults, it can be easy to miss a LADA diagnosis.

Ironically, the prevalence of LADA may actually be even higher than that of type 1 diabetes. Hawa et al. (12) studied 6,156 patients who were within 5 years of diabetes diagnosis and between the ages of 30 and 70 years. Similar to previous reports in the literature, they found that 9.7% of the patients had characteristics of LADA, which included 1) age 30–70 years, 2) presence of diabetes-associated antibodies (68.6% GAD only, 5% IA-2A only, 2.3% ZnT8A only, and 24.1% with two antibodies), and 3) no insulin requirement within 6 months of diagnosis. Additionally, among the patients in this study, more were classified with LADA ($n = 377$) than with type 1 diabetes ($n = 114$) (odds ratio 3.3).

Patients are often misdiagnosed due to the use of arbitrary screening criteria such as age. In addition to the IDS proposal of testing positive to at least one antibody, this case highlights the potential benefit of also adding C-peptide measurement for screening purposes. Additionally, using the IDS criteria, the LADA China Study (13) found that the prevalence of LADA in their cohort was 5.9% and observed that the patients with LADA had lower fasting C-peptide levels. C-peptide levels are generally lower in LADA than in type 2 diabetes and are not as reliable for the diagnosis of type 1 diabetes (4,5,13).

Health care providers must learn to recognize the characteristics associated with LADA and to order the proper diagnostic tests to make a differentiation (11–13). Because there are no distinct clinical features for LADA, the only way to identify it is by antibody testing. Doing so may lead to better treatment options and earlier glycemic control, potentially

decreasing the risk of long-term complications associated with poor glycemic control.

In addition to insulin, other therapy options that preserve β -cell function, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists, and thiazolidinediones, could be considered for patients with LADA. Conversely, therapy options such as sulfonylureas that increase the rate of deterioration of C-peptide secretion, further depleting insulin levels, should be avoided (14–20).

By recognizing that a patient has LADA, we can ensure that the patient is also screened for other autoimmune diseases in a timely manner. Thyroid disease, for example, was found to be more prevalent in patients with LADA compared to those with type 2 diabetes (14).

This case highlights the importance of developing standardized guidelines for LADA to improve diagnostic and treatment quality, help providers become more aware of LADA, and decrease the risk of harm to patients from inadequate treatment.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Tuomi T, Groop LC, Zimmet PZ, et al. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes* 1993;42:359–362
2. Lutgens M, Meijer M, Peeters B, et al. Easily obtainable clinical features increase the diagnostic accuracy for latent autoimmune diabetes in adults: an evidence-based report. *Prim Care Diabetes* 2008;2:207–211
3. Appel SJ, Wadas TM, Rosenthal RS, Ovalle F. Latent autoimmune diabetes of adulthood (LADA): an often misdiagnosed type of diabetes mellitus. *J Am Acad Nurse Pract* 2009;21:156–159
4. Naik RG, Brooks-Worrell BM, Palmer JP. Latent autoimmune diabetes in adults. *J Clin Endocrinol Metab* 2009;94:4635–4644
5. Pipi E, Marketou M, Tsirogianni A. Distinct clinical and laboratory characteristics of latent autoimmune diabetes in

- adults in relation to type 1 and type 2 diabetes mellitus. *World J Diabetes* 2014;5:505–510
6. Fourlanos S, Dotta F, Greebuam CJ, et al. Latent autoimmune diabetes in adults (LADA) should be less latent. *Diabetologia* 2005;48:2206–2212
 7. Hawa M, Buchan AP, Ola T, et al. LADA and CARDS: a prospective study of clinical outcome in established adult-onset autoimmune diabetes. *Diabetes Care* 2014;37:1643–1649
 8. Davis AK, DuBose SN, Haller MJ, et al. Prevalence of detectable C-peptide according to age at diagnosis and duration of type 1 diabetes. *Diabetes Care* 2015;38:476–481
 9. Hosszufalusi N, Vatay A, Rajczy K, et al. Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. *Diabetes Care* 2003;26:452–457
 10. Tiberti C, Giordano C, Locatelli M, et al. Identification of tyrosine phosphatase 2 (256-760) construct as a new, sensitive marker for the detection of islet autoimmunity in type 2 diabetic patients. *Diabetes* 2008;57:1276–1283
 11. Laugesen E, Ostergaard JA, Leslie RDG, et al. Latent autoimmune diabetes of the adult: current knowledge and uncertainty. *Diabet Med* 2015;32:843–852
 12. Hawa MI, Kolb H, Schloot N, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype. *Diabetes Care* 2013;36:908–913
 13. Zhou Z, Xiang Y, Linong J, et al. Frequency, immunogenetics, and clinical characteristics of latent autoimmune diabetes in China (LADA China Study): a nationwide, multicenter, clinic-based cross-sectional study. *Diabetes* 2013;62:543–550
 14. Murao S, Kondo S, Ohashi J, et al. Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict β cell failure in patients with latent autoimmune diabetes in adults (LADA): a 5-year follow-up of the Ehime study. *Diabetes Res Clin Pract* 2008;80:114–121
 15. Zhao Y, Yang L, Xiang Y, et al. Dipeptidyl peptidase 4 inhibitor sitagliptin maintains beta-cell function in patients with recent-onset latent autoimmune diabetes in adults: a one year prospective study. *J Clin Endocrinol Metab* 2014;99:E876–E880
 16. Johansen OE, Boehm BO, Grill V, et al. C-peptide levels in latent autoimmune diabetes in adults treated with linagliptin versus glimepiride: exploratory results from a 2-year double-blind, randomized, controlled study. *Diabetes Care* 2014;37:E11–E12
 17. Yang Z, Zhou Z, Li X, et al. Rosiglitazone preserves islet beta-cell function of adult-onset latent autoimmune diabetes in 3 year follow-up study. *Diabetes Res Clin Pract* 2009;83:54–60
 18. Kobayashi T, Nakanishi K, Murase T, et al. Small doses of subcutaneous insulin as a strategy for preventing slowly progressive beta-cell failure in islet cell antibody-positive patients with clinical features of NIDDM. *Diabetes* 1996;45:622–626
 19. Maruyama T, Tanaka S, Shimada A, et al. Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus. *J Clin Endocrinol Metab* 2008;93:2115–2121
 20. Brophy S, Davies H, Mannan S, et al. Interventions for latent autoimmune diabetes (LADA) in adults. *Cochrane Database Syst Rev* 2011;9:CD006165