Latent Autoimmune Diabetes in Adults (LADA)

Not all cases of late onset diabetes are type 2. Because of the similarity in clinical presentation, latent autoimmune diabetes in adults (LADA) is frequently confused with type 2 diabetes. A characteristic of LADA is the presence of anti-glutamic acid decarboxylase (GAD) antibodies so a definitive diagnosis of LADA can be established through GAD testing. However, some type 2 patients also have high anti-GAD levels (as do non-diabetics). GAD testing can therefore be more cost-effective if it is preceded by another screening test to identify such patients. For this, C-peptide can be used, which is initially higher than normal in subjects with type 2 diabetes. If C-peptide levels are normal or low, an anti-GAD antibody test is indicated. In subjects with LADA, the use of standard oral anti-diabetic agents should be complemented by insulin treatment to slow the rate of decline in beta cell function. Thiazolidinediones may also be protective in such patients, whereas secretagogues should be avoided because they stimulate beta cell function which could accelerate their destruction through autoimmune attack.

At least one-third of patients diagnosed with autoimmune diabetes are diagnosed after the age of 35. As many as 10%-15% of adult onset diabetes may be autoimmune in origin. Whether LADA is a late-onset slowly progressive form of type 1 diabetes or a separate clinical entity (type 1 1/2) is disputed. What is not disputed is that LADA has genetic, autoimmune and clinical features that are different from those of early onset type 1 diabetes.

Subjects with LADA have lower frequencies of the high risk HLA alleles (DR3/DQ*6201 and DR4/DQ*0302). LADA patients also have lower levels of islet cell and insulin antibodies but have varying titres of glutamic acid decarboxylase (GAD) antibodies. Clinically LADA usually presents in an insidious way which may be indistinguishable from the presentation of type 2 diabetes.

**LADA and anti-GAD antibodies**

The hallmark of LADA is the presence of anti-GAD antibodies. However, one per cent of the non-diabetic population have anti-GAD antibodies simply because reference laboratories fix their upper limit of normal at that level. Therefore, 1 in 100 patients who do have type 2 diabetes will have detectable anti-GAD antibodies [Figure 1]. However, at least early in the course of type 2 diabetes this will be accompanied by high normal or even elevated C-peptide levels (a measure of endogenous insulin production) whereas with the LADA patient the C-peptide levels will be low or low-normal.

In the United Kingdom Prospective Diabetes Study (UKPDS) of 3,762 white subjects with recently diagnosed type 2 diabetes (based on clinical criteria) 10% had anti-GAD antibodies at the time of diagnosis. A Tasmanian study of 1,232 patients with adult-onset diabetes reported that 36% of the men and 34% of the women were GAD antibody positive. Another study looked at Finns with an onset of diabetes after the age of 35, who were assumed to have type 2 diabetes and who were therefore not treated with insulin. In 102 such individuals GAD antibodies were associated with subsequent early insulin deficiency and the need to utilise insulin therapy. In those requiring insulin, 75% were GAD antibody positive compared with 12% in those who did not need insulin. A similar Swedish study showed that 70 of 97 patients assumed to have type 2 diabetes at onset required insulin after 6 years. GAD antibodies were present in 60% of these patients compared with 7% in those who did not require insulin.

Although studies of European populations have generally shown that 10%-20% of late onset diabetes is GAD positive, the presence of GAD antibodies is rare in Filipinos and subjects of African origin. Conversely, 16% of late-onset diabetes in Chinese subjects is GAD positive.

While LADAs in general have lower frequencies of the high risk HLA alleles which are present in early onset type 1 diabetes, a study in Finland has shown a strong correlation between these alleles and GAD antibodies. Furthermore, pancreatic T lymphocytes, the pathological hallmark of autoimmune diabetes, were observed in a biopsy specimen of a GAD positive 65 year old with late onset diabetes and retained endogenous insulin production.

**The clinical presentation and clinical course of the LADA patient**

In the UKPDS, the presence of GAD antibodies at onset was predictive of the need for insulin therapy after six years. In a New Zealand study of 1,148 subjects with what was presumed to be type 2 diabetes, 14.4% were GAD positive within one year of diagnosis and of these 83% required insulin within a year of diagnosis. In Sweden, if GAD antibodies were positive in those with a typical type 2 presentation, 60% required insulin within 12 months.

Although most patients with LADA are thin, the disease can occur in patients of any body weight. Furthermore, because of the slower destruction of the beta cells, excellent glycaemic control can be maintained for some time in patients with LADA via lifestyle changes (diet, exercise and weight loss) and/or oral anti-diabetic therapies. For example, a group of Finnish women with LADA were maintained with reasonable glycaemic control for as long as 10 years before they required insulin.

Furthermore, as in the type 2 diabetic patient, the slow destruction of the beta cells means that acute symptoms such as polyuria, polydipsia and weight loss are rare. Therefore, diabetes may be present for several months or years before it is diagnosed. A common symptom in early diabetes is reactive hypoglycaemia due to the loss of the first phase insulin response, hyperglycaemia and delayed excessive insulin production. As with type 2 diabetes, recurrent or calcific yeast vaginitis may be a presenting feature. Realisation of previous ill health, and improved well being, almost invariably occur with gly-
caemic control.

Thus it can be seen that the clinical presentation of LADA is in most cases indistinguishable from that of type 2 diabetes. However, an acute onset, especially in a non-obese subject, should lead to the suspicion that the diagnosis is LADA rather than type 2 diabetes.

**Diagnosing LADA**

The most sensitive test for the diagnosis of LADA is the presence of anti-GAD antibodies. This test should therefore ideally be carried out in all subjects with adult onset diabetes. However, anti-GAD antibody testing is expensive. If another, cheaper screening test could be utilised this would be of great benefit and would also be cost-effective.

Our group has found that a serum C-peptide level is an excellent screening test. C-peptide is a fragment of the proinsulin molecule that remains when the alpha and beta chains of the insulin molecule separate. Because of its longer half-life, it is a better measure of endogenous insulin production than straightforward serum insulin levels. On measuring C-peptide levels we found that in GAD antibody positive subjects, i.e. LADAs, C-peptide levels were low or in the normal range. Type 2 patients, i.e. GAD antibody negative, had C-peptide levels that were normal or high. Therefore a high C-peptide level, which often occurs in type 2 diabetes at onset, rules out LADA and anti-GAD antibody level assays need not be performed. However, if the C-peptide level is low or in the normal range, the anti-GAD antibody level should be measured.

Another test that may be helpful is the HDL to triglyceride ratio. If this ratio exceeds 4 then the patient is likely to be insulin resistant and therefore less likely to have LADA. It has been shown that insulin resistance is lower in LADA, similar to that found in long-term type 1 diabetes and lower than that found in type 2 diabetes.

**Procedure after diagnosis of LADA**

If diagnosing LADA only resulted in the knowledge that insulin therapy would be needed at an earlier time than in the type 2 patient irrespective of the therapy utilised, then its diagnosis could be merely an academic exercise. However, diagnosing LADA could be of the utmost importance if therapies could be initiated to specifically slow down the rate of decline in beta cell function. For example, if early utilisation of insulin were to result in preservation of the insulin-secreting pancreatic beta cells, better glycaemic control would be achieved with fewer diabetic complications.

The autoimmune attack on the pancreatic beta cells is only directed at the insulin-producing cells. If the function of these cells is taken over by injecting exogenous insulin, endogenous insulin production declines or ceases to protect the beta cells from the autoimmune “attack”. Alternatively, if secretagogues, the most common therapy for type 2 diabetes, are utilised, the stimulated beta cells will be the subject of a more intense “autoimmune attack”, thus the progress towards total destruction will occur more rapidly. Therefore, with secretagogues insulin will not only be needed at an earlier stage, but glycaemic control will worsen resulting in earlier and more severe diabetic complications.

The protective effect of insulin and the detrimental effect of secretagogues can be explained by the theory that only active beta cells are attacked and destroyed by the immune system. Animal studies have shown that stimulating insulin secretion results in the release of insulin-containing secretory granules which have antigenic properties. In animal models of autoimmune diabetes (NOD mice and BB rats) administration of oral or subcutaneous insulin has been shown to prevent diabetes. In islet cell antibody positive diabetic subjects with the clinical features of type 2 diabetes, it was shown that islet cell destruction was slowed by daily administration of small doses of subcutaneous insulin. Early insulin administration may also be protective because of the immunomodulatory properties of insulin which could increase the production of TH2 cytokines thus protecting the beta cell from autoimmune damage.

However, the evidence that insulin administration can suppress autoimmune destruction of beta cells in humans is far from complete and the theory far from proven. In the Diabetes Prevention Trial it was found that insulin therapy did not prevent or even delay the clinical onset of type 1 diabetes in antibody-positive and endogenous insulin-deficient relatives of type 1 diabetic patients (a high risk group). However, with type 1 diabetes there is a more intense and rapid autoimmune destruction of the pancreatic beta cells than that which occurs with LADA. Therefore, the failure of insulin therapy to prevent type 1 diabetes does not necessarily mean that insulin therapy will not avoid or delay the onset of complete beta cell destruction in the LADA patient.

Currently my own strategy, which will only be modified if further data suggest that this is necessary or prudent, is to screen for LADA and if diagnosed to utilise insulin and avoid secretagogues in these "at risk" patients. In addition, I utilise in all of these subjects thiazolidinediones (TZDs), the oral agent of choice for the LADA patient, in combination with insulin. While it is well recognised that in type 2 diabetes TZDs preserve or even rejuvenate pancreatic beta cells, the evidence for this protective effect is lacking in type 1 diabetes. TZDs’ protective effect on type 2 diabetic beta cells is thought to be mediated through the lowering of free fatty acid levels and their metabolites within the beta cell, which results in decreased production of nitric oxide and suppression of the accelerated beta cell apoptosis. However, TZDs are also anti-inflammatory and therefore in the LADA patient could also potentially alter the course of beta cell damage. Recently a small placebo-controlled trial reported beta cell preservation with the TZD drug rosiglitazone in subjects with LADA. Therefore, the LADA patient may benefit from the anti-inflammatory effect as well as the decreased beta cell free fatty acid content when TZDs are utilised.

In conclusion, LADA is associated with the presence of anti-GAD antibodies and a lower endogenous insulin production than is seen in type 2 diabetes, though the clinical features are more similar. Screening for LADA should be carried out by measuring C-peptide level in later onset diabetes, which if normal or low should trigger measurement of the GAD antibody level. When LADA is diagnosed in the diabetic patient insulin therapy and TZD utilisation should result in a better outcome, and secretagoue therapy should be avoided.

**Further reading**

1) Bell DSH. Should anti-glutamic acid decarboxylase antibody levels be determined in new onset diabetes? Endocrine Practice 2000; 6(2): 214-216.
2) Bell DSH, Ovalle F. The role of C-peptide levels in screening for Latent Autoimmune Diabetes in Adult. Amer J Ther 2004; 11: 308-311.

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