



## LADA or KETOSIS PRONE Type 2 Diabetes Mellitus? – A Case Report

### KEYWORDS

Latent autoimmune diabetes in adults (LADA), Type 1 diabetes mellitus –DM 1, Type 2 diabetes mellitus – DM 2, Glutamic acid decarboxylase autoantibodies (GADs)

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**ABSTRACT** *Latent Autoimmune Diabetes in Adults (LADA), an increasingly recognized form of type 1 diabetes mellitus (DM 1). Usually presented in adulthood has slower progression towards an absolute insulin requirement. In comparison to type 1 diabetes mellitus, in spite of presence of pancreatic islet autoantibodies, the progression to beta cell insufficiency is slow. It is often confused and misdiagnosed as ketosis prone diabetes mellitus (KPD) and treated with oral hypoglycaemic drugs causing rapid fall in beta cell reserve than KPD. Hence early initiation of insulin therapy is a must in LADA to delay rapid islet cell failure. LADA is diagnosis based on the presence of glutamic acid decarboxylase autoantibodies (GADs). We here in report a case of 33 – year – old male presented with hyperglycemia and ketosis – LADA or Ketosis prone diabetes mellitus?*

### INTRODUCTION

Latent Autoimmune Diabetes in Adults (LADA) is an autoimmune form of type 1 diabetes mellitus that is manifested in adult populations, typically over the age of 30 years<sup>1</sup>. It is often misdiagnosed as type 2 diabetes mellitus because of its late onset of symptoms. Incidence of LADA may be as high as 6 – 50% among patients with type 2 diabetes. However, many do not have the typical characteristics of type 2 diabetes like obesity and insulin resistance. LADA is also known as type 1.5 diabetes as it shares symptoms of both type 1 and type 2 diabetes<sup>2</sup>. Diagnosis is based on presence of autoantibody to glutamic acid decarboxylase (GAD 65) is the most sensitive and specific marker for this subgroup of diabetes and in cases of positivity, patients generally progress to insulin dependency with in three years, though some do not<sup>3,4</sup>.

The Presence of circulating islet cell autoantibodies (at least one) should be necessary for the diagnosis of LADA. Autoantibodies to insulin (IAA), tyrosine phosphatase like insulinoma-associated protein 2 (IA2), have been reported to be rather infrequent, the diagnosis basically relies on identifying glutamic acid decarboxylase autoantibodies (GADs), is the best single marker for screening.<sup>14</sup>

There are numerous areas to be elucidated regarding the pathogenesis of LADA, although several factors that have been related to develop this kind of diabetes are shown in (table 1)<sup>5</sup>. The genetics of LADA is not well defined. LADA is associated with increased frequencies of genetic markers (HLA DR3, DR4 and DR3/4) that are also commonly seen in DM1. However, HLA DR4 DQ8 antigen commonly associated with rapid beta cell destruction in DM1, less common in LADA. This explains why patients with LADA do not require insulin as early as DM 1. Ketosis prone diabetes mellitus is a subset of diabetes patients who presents in acute form, negative GAD antibodies. It is necessary to differentiate between these two as LADA always requires insulin therapy but some KPD patients can be managed with OAD.

### CASE REPORT

A 33 year old male with Body mass index 16.1Kg/m<sup>2</sup>, non hypertensive presented to general medicine as an out patient with complaints of pain, swelling over glans penis and nose from one month. On enquiry he is a known case of diabetes from four years, initially on oral hypoglycaemic drugs for four months later switched to insulin (mixtard – regular 30, isophane 70) 40 units before breakfast and 35 units before dinner. No history of fever, ulcer, discharge over glans penis. History of pulmonary tuberculosis in past and took Anti tuberculosis treatment for 6 months. No family history of diabetes. Non smoker, occasional alcoholic. Vitals at the time of presentation are temp 99° F, pulse 86/min, blood pressure 110/60 mm of Hg, respiratory rate 16/min. His random blood glucose noted as 542 mg/dl. Urine sugar 4+, ketone test by ketostix was positive. Arterial blood gas analysis was within normal limits. Haemogram, urine microscopy, serum electrolytes, renal function tests and liver function tests were normal. ECG was normal. Patient was kept on regular insulin three times daily along with glargine at bed time. C-peptide levels 2.3ng/ml (1.1 – .44 ng/ml). HBA1c is 12.5. GAD antibodies were sent. Thyroid function tests were within normal limits. He was screened for nephropathy and retinopathy, no changes were seen.

Paraphimosis was treated with antibiotics and circumcision was done. After stabilization of glycemic status, his general condition improved.

Presumptive diagnosis of LADA was confirmed by measurement of GAD65 antibody, level was 2000 IU (normal <10 IU). Islet cell antibody level was normal.

He was discharged with insulin (mixtard – regular 30, isophane 70) 40 units (30 min before breakfast) and 16 units (30 min before dinner), Metformin 500mg BD, with an advice to take low saturated fat diet, limited intake of simple sugar, high fibre diet.

His insulin requirements gradually increased overtime but no acute hyperglycemic episodes till now.

**DISCUSSION**

Latent Autoimmune diabetes in Adults (LADA) accounts for 2%-12% of all cases of diabetes and the term Latent autoimmune diabetes of adults (LADA) was given by Zimmet et al<sup>8,9</sup>. This subset of adult patients who were initially categorized as type 2 diabetes mellitus phenotype but were found to be positive for islet cell autoantibodies, a hallmark of  $\beta$  cell destruction.<sup>9,10</sup> Presence of circulating autoantibodies as well as the early requirement of insulin suggest that LADA is basically a spectrum of type 1 diabetes mellitus but with a much slower progression.<sup>4</sup>

Regarding clinical parameters or laboratory criteria for LADA screening, no current consensus is available till now. However, in a retrospective study by Fournalos et al<sup>6</sup>, five clinical parameters were found to be more frequent in LADA than in type 2 DM: (1) Age of onset <50 years; (2) Acute symptoms of hyperglycemia (polyuria / polydipsia / weightloss); (3) Body Mass Index (BMI) < 25Kg/m<sup>2</sup>; (4) personal history of other autoimmune diseases; and (5) Family history of autoimmune diseases. The five point LADA clinical risk score had a sensitivity and specificity of 90% and 70% respectively, in identifying LADA patients, with the presence of at least two of the above five clinical features.

The Immunology of Diabetes Society has led three criteria to discriminate LADA from type 1 and type 2 diabetes mellitus: (1) Adult age of onset (>30 years of age); (2) Presence of atleast one circulating autoantibody (GAD65/ ICA/IAA/IA-2); and (3) Insulin dependency no sooner than 6 months after diagnosis.<sup>7</sup>

Evidences show advantages of the early initiation of insulin therapy in patients with LADA. Japanese studies suggest that patients with LADA must receive insulin within the first year of diagnosis to maintain the glycemic levels normal, or atleast close to normal. In patients with LADA insulin therapy improves C-peptide secretion (due to better beta cell function with a higher natural insulin production), reduces HbA1c level and islet cell autoantibodies concentration.<sup>11</sup>

Clinical characteristics of patients with LADA are similar to those with type 1 and type 2 diabetes mellitus (Table 2).<sup>12</sup> when patients with LADA and type 1 diabetes mellitus are compared, the patients with LADA are older and have higher BMI as well as higher plasma C-peptide levels, and they do not require immediate insulin therapy. In a similar way, comparison of the patients with type 2 diabetes mellitus with the patients with LADA are younger and have lower BMI and lower plasma C-peptide levels.<sup>13</sup> On the other hand, insulin resistance is much lower in LADA as compared to type 2 diabetes mellitus. This is why the frequency of obesity, hypertension, dyslipidemia and CHD are found to be lower in LADA than in type 2 diabetes mellitus though microvascular complications are comparable.

With recognition of LADA, numerous works have been documented with respect to its pathophysiology, genetics, diagnostic criteria, classification and therapy. However, LADA still remains a diagnostic challenge owing to the heterogeneity in its immunological, genetic and metabolic features

Ketosis-prone diabetes or KPD is an intermediate form of diabetes that has some characteristics of type 1 and some of type 2 diabetes. However, it is distinct from latent autoimmune diabetes. KPD comes in four forms depending upon the presence or absence of  $\beta$ -cell autoantibodies (A+ or A-) and  $\beta$ -cell functional reserve ( $\beta+$  or  $\beta-$ ).<sup>15</sup> A+ $\beta-$  KPD is synonymous with classic, early onset autoimmune type 1 diabetes; A+ $\beta+$  KPD usually overlap with LADA. However, there are differences between LADA, as recently defined by the Immunology of Diabetes Society, the definition of LADA ex-

cludes patients who require insulin within the first 6 months after diagnosis, whereas the majority (90%) of A+ $\beta+$  KPD patients present with DKA as the first manifestation of diabetes and therefore require insulin at the start but later can be managed with OAD. Our patient who required insulin after 4 months of diagnosis is fitting to A+ $\beta+$  KPD ! but the GAD antibody is positive and he presented with DKA after 4 years of diagnosis. Whatever may be the diagnosis in view of presence GAD antibody our patients managed with insulin.

**CONCLUSION**

In conclusion, LADA is an autoimmune diabetes with overlapping features of type 1 and type 2 diabetes. Diagnosis is based on the presence of glutamic acid decarboxylase autoantibodies (GADs). KPD which is again 4 types depending upon the presence or absence of insulin and  $\beta$ -cell autoantibodies, the A+ $\beta+$  KPD usually confused with LADA. It needs a clear classification system to deal with this problem. Whatever may be the diagnosis but timely initiation of insulin therapy can help to protect the residual islet beta cells and thereby reduces the occurrence of ketosis as well as microvascular complications.

**Tables**

**Table 1. Factors involved in LADA diabetes pathogenesis.**

1. Lesser genetic predisposition than Type 1DM.
2. Qualitative/quantitative reduction of environmental factors related with  $\beta$ -cell destruction.
3. Possible contribution of protective genes against  $\beta$ -cell dysfunction.
4. Immune tolerant induction once autoimmune process has begun.
5. Partial  $\beta$ -cell regeneration.

**Table 2: Features and treatment of Type 2 DM, LADA and Type 1 DM**

Features	Type 2 DM	LADA	Type 1 DM
Metabolic syndrome components	Frequently present	Usually absent	Less frequent
Ketoacidosis	Less common	Usually absent at diagnosis, but could be present	Frequently
Cardiovascular complications	Increased	Same as in Type 2 DM	Increased
Microvascular complications	Increased	Same as in Type 2 DM	Increased
Pancreatic autoantibodies	Absent	Positive	Positive
Treatment	Might need insulin, but at the end stage of disease	Requires insulin in a much earlier phase than Type 2 DM	Insulin at diagnosis

**REFERENCE**

1. Stenstrom G, Gottsater A, Bakhtadze E, Berger B, Sundkvist G. Latent autoimmune | diabetes in adults: definition, prevalence, beta-cell function, and treatment. *Diabetes* | 2005;54: S68–S72. | 2. Landin-Olsson M. Latent autoimmune diabetes in adults. *Ann N Y Acad Sci* | 2002;958:112–6. | 3. Kasuga A, Maruyama T, Nakamoto S, Ozawa Y, Suzuki Y, Saruta T. High-titer | autoantibodies against glutamic acid decarboxylase plus autoantibodies against insulin | and IA-2 predicts insulin requirement in adult diabetic patients. *J Autoimmun* 1999;12:131–135. | 4. Lohmann, T, Kellner K, Verlohren HJ, Krug J, Steindorf J, Scherbaum WA, et al. Titre | and combination of ICA and autoantibodies to glutamic acid decarboxylase discriminate | two clinically distinct types of latent autoimmune diabetes in adults (LADA). | *Diabetologia* 2001; 44:1005–10. | 5. Pozzilli P, Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (latent | autoimmune diabetes of the adult): definition, characterization, and potential prevention. | *Diabetes Care* 2001;24:1460–7. | 6. Fournalos S, Perry C, Stein MS, Stankovich J, Harrison LC, Colman PG. A clinical | screening tool identifies autoimmune diabetes in adults. *Diabetes Care* 2006;29:970–5. | 7. Palmer JP, Hampe CS, Chiu H, Goel A, Brooks-Worrell BM. Is latent autoimmune | diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age? | *Diabetes* 2005;54:S62-7. | 8. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, et al. | Immunogenetic and clinical characterisation of slowly progressive IDDM. *Diabetes Care* | 1993;16:780-8. | 9. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, et al. UKPDS 25: | autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of | insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. | *Lancet* 1997;350:1288-93. | 10. Nambam B, Aggarwal S, Jain A. Latent autoimmune diabetes in adults: A distinct but | heterogeneous clinical entity. *World J Diabetes* 2010;1:111-5. | 11. Fielding AM, Brophy S, Davies H, Williams R. Latent autoimmune diabetes in adults: | increased awareness will aid diagnosis. *Ann Clin Biochem* 2007;44:321-3. | 12. Nabhan F, Emanuele MA, Emanuele N. Latent autoimmune diabetes of adulthood. | 13. Unique features that distinguish it from types 1 and 2. *Postgrad Med* 2005;117:7-12. | 14. Falorini A, Brozzetti A. Diabetes-related antibodies in adult diabetic patients. *Best Pract Res Clin Endocrinol Metab* 2005;19:119-133 | 15. Nalini, Ramaswami et al. (2008). "HLA class II alleles specify phenotypes of ketosis- | prone diabetes". *Diabetes Care* 31 (6): 1195–1200 |