Section: Miscellaneous

Case Report

DIAGNOSIS AND MANAGEMENT OF LADA IN A PATIENT WITH UNCONTROLLED HYPERGLYCEMIA - A CASE REPORT

Krupaa Madhu[1], Lyluma Ishfaq[2], Sravani Bhavanam[3], Abhirami Das[4], Mayank Jaitwar[5], Safa Kaleem[6], Harshada Santosh Keluskar[7], Smaran Kasireddy[8], Vishal Venugopal[9]

[1]GMERS Medical College, Gandhingar, Gujarat, India
[2]Directorate of Health Services Kashmir, Srinagar, India
[3]Sri Devaraj urs medical College, Kolar, India
[4]Rajiv Gandhi Medical College, Thane, India
[5]IGGMC, Nagpur, India
[6]Shadan Institute of Medical Sciences, Hyderabad, India
[7]Kazan State Medical University, Russia
[8]JJM Medical College, Davangere, India
[9]Bhaarath Medical College & Hospital, Chennai, India

Received : 10/04/2023
Received in revised form : 22/05/2023
Accepted : 08/06/2023

Keywords:
Endotracheal tube, Alkalized lidocaine, Cuff-related complications.

Corresponding Author:
Dr. C. Sridevi,
Email: t.sridevi32@gmail.com

DOI: 10.47009/jamp.2023.5.3.345

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 1727-1730

Abstract

LADA (latent autoimmune diabetes in adults) also known as type 1.5 diabetes is an autoimmune related diabetes in adults. This condition has also been termed as "slowly evolving immune-mediated diabetes" by the World Health Organization, under the category of hybrid forms of diabetes. It occurs in middle aged women of 35-45. It shares intermediate features of both type 1 and type 2 diabetes making clinical diagnosis quite challenging. The antibodies against beta pancreatic cells make cells functionally impaired so patients of LADA are highly insulin dependent. Accurate and early diagnosis of LADA is important as it requires different management than type 1 diabetes. Early initiation of insulin is highly advised to save the pancreatic cell function. Our article is aimed at providing the importance of diagnosis of type 1.5 diabetes and to provide consideration to overlapping symptoms for easy and early management of the disease.

INTRODUCTION

Diabetes Mellitus is a group of diseases which cause hyperglycemia due to insulin secretory dysfunction as well as insulin resistance, classifying the disease into type 1 DM and type 2 DM. A significant proportion of patients may present in adulthood, with auto-antibodies against islet cell antigens such as GADA (glutamic acid decarboxylase autoantibodies) despite having a clinical presentation similar to that of type 2 DM, and an absence of insulin dependency initially. This has come to be defined as LADA (latent autoimmune diabetes in adults). About 20% of the patients diagnosed with type 2 diabetes may have LADA.[1] Latent autoimmune diabetes in adults (LADA) is an underrecognized and understudied condition, exhibiting overlapping features between type 1 and type 2 DM. The presence of auto-antibodies suggests an autoimmune etiology similar to type 1 DM whereas the adult onset of the disease and clinical characteristics are akin to type 2 DM.[2]

Patients with LADA, compared to those of type 2 DM, are younger at diagnosis with a lower BMI, and are less likely to develop metabolic syndrome, diabetic dyslipidemia and hypertension.[3] Family history is a strong risk factor for LADA and the influence of family history may be mediated through a heritable reduction of insulin secretion.[4] They often exhibit lower residual β-cell function than DM2 patients, the severity of which is associated with the GADA titer. A high GADA titer tends to have significant β-cell impairment.[5] However, the decrease in C-peptide levels in LADA is slower compared to type 1DM.[3] LADA patients have a lower risk of microvascular complications at onset, that becomes higher due to worsening glycemic control compared with type 2 DM subjects.[6]

LADA patients were more likely to have GADA and a higher frequency of N-terminal reactive GADA than type 1 DM.[7] 56.1% LADA patients were shown to require insulin as compared to 20.9% of type 2 DM patients during a seven year follow up period. Furthermore, a high GADA titer was shown to increase the risk of insulin requirement in LADA patients,[8] HLA-DQB1 and HLA-DRB are the strongest genetic factors associated with LADA. The highest risk is conferred by the HLA haplotypes HLA-DRB1*04-DQB1*0302 ("DR4") and HLA-DRB1*0301-DQB1*0201 ("DR3"). The

ISSN (O): 2687-5365; ISSN (P): 2753-6556

associations with PTPN22 and INS appear stronger for LADA with high GADA titres and for LADA characterized by multiple autoantibodies. LADA has been linked to a risk locus on the transcription factor 7-like 2 (TCF7L2) gene. TCF7L2 is the strongest genetic factor associated with type 2 DM.[9]

LADA cases are severely underreported in developing countries like India due to their phenotypic similarities to type 2 DM. The aim of this case report is to present a case of LADA, which might provide valuable insights in differentiating LADA from other types of diabetes and aid Indian physicians in identifying and treating such patients.

CASE PRESENTATION

A 42-year-old female presented to the clinic with complaints of polyuria, polydipsia, and weight loss of 7 kg since 1 year. She was diagnosed with T2DM six years ago and was initially started on metformin. Despite dietary measures and the addition of teneligliptin and pioglitazone, her glycemic control remained poor. Her medical history was otherwise unremarkable, and there was no family history of diabetes or autoimmune disorders. She had no history of alcohol or tobacco use.

On physical examination, her vital signs were stable, with a blood pressure of 120/80mmHg, pulse rate of 80 beats per minute, and respiratory rate of 16 breaths per minute. Her body mass index (BMI) was 20.2 kg/m2. There were no signs of adenopathy, peripheral neuropathy, and her fundoscopic examination was normal. There were no signs of acanthosis nigricans or skin infections. Her cardiovascular, respiratory, and abdominal examinations were unremarkable.

Her complete blood count (CBC) was within normal limits. Her fasting blood glucose (FBG) was 225.3 mg/dL, and her postprandial blood glucose (PPBG) was 329.9 mg/dL. Her HbA1c was 9.5%. She was also diagnosed with hyperthyroidism and was started on neomercazole 5 mg once daily for the same. Further investigations revealed the absence of C-peptide, indicating the presence of LADA.

The patient was diagnosed with LADA and hyperthyroidism. She was started on insulin therapy consisting of basal and bolus insulin, which improved her glycemic control. Her insulin regimen was titrated according to her blood glucose levels. She was advised 6 units of insulin Apidra (Gluisine) before each meal for maintaining bolus levels and 14 units of insulin glargine (Lantus) once a day to maintain basal insulin levels.

Table 1:

Investigations	Values	References value
Hb	11.6gm%	12-16gm %
RBC	3.64 mil/cmm	4.2-5.4mil/cmm
WBC	4100 cmm	4000-11,000/cmm
PLATELETS	219000 cmm	1.5 -4 lac/cmmm
HBA1C	9.5%	< 5 %
FBS	225 mg/dl	<150 mg/dl
PP2BS	329 mg/dl	< 200 mg/dl
C PEPTIDE	Less than 0.2ng/ml	1.1- 3.3 ng/ml
URINE KETONE	Positive	nil
URINE GLUCOSE	Positive ++++	Nil
S. Creatinine	normal	0.9- 1.2

Table 2:

Key points	Type 1 DM	Type 2 DM	LADA	Case report
Age	Usually young	Usually adulthood	>30 years	42 years
Metabolic syndrome	Uncommon	Usually present	Uncommon	Not present
Ketoacidosis	Frequent	Less common	Usually absent at diagnosis but could be present	Not present
Pancreatic autoantibodies	Positive	Negative	Positive	Not measured
Insulin Requirement	At the time of diagnosis	Usually years after the diagnosis	Usually >6 months after diagnosis	Required
Family history of Diabetes	Present or absent	Usually absent	Present or absent	absent
Personal or family history of autoimmunity	Usually present	Usually absent	Usually present	History of Hyperthyroidism
Body habitus	Non- obese	Obese	Non-obese	Non- obese

DISCUSSION

Latent autoimmune diabetes of adults is also called Type 1.5 Diabetes is an autoimmune disorder that shares many similarities with type 1 diabetes, such as the presence of islet autoantibodies and a gradual loss of beta-cell function. However, LADA also has clinical manifestations that resemble type 2 diabetes, such as insulin resistance and a later onset of the disease. LADA typically occurs in adults over the age of 30, but the onset can range from early adulthood to later in life.[10] Type 1 diabetes is characterized by the autoimmune destruction of beta cells in the pancreas, which is confirmed by the presence of islet-cell autoantibodies or low levels of c-peptide. In contrast, LADA patients do not experience an immediate loss of beta cell function

ISSN (O): 2687-5365; ISSN (P): 2753-6556

and therefore have a clinical presentation that resembles more closely that of type 2 diabetes.[11]

To standardize the definition of LADA, the Immunology of Diabetes Society (IDS) has proposed three criteria. These include age of onset of 35 years or older, the presence of at least one of four autoantibodies common in type 1 diabetes, and not requiring insulin therapy in the first six months after diagnosis.[12] These criteria are used to differentiate LADA from other forms of diabetes, especially type 2 diabetes which is more common in older adults but does not show autoimmune markers. It is important to keep in mind that the diagnosis of LADA should be based on various factors including the patient's response to therapy over time and that some patients with LADA may not meet all three criteria. LADA patients may have sufficient beta-cell function in the early stages of the disease and can manage their blood sugar levels with dietary modifications and oral antidiabetic medications. However, as the disease progresses, they experience a decline in insulin production and thus may require insulin therapy. LADA patients typically require insulin treatment earlier and more frequently than patients with type 2 diabetes.[13]

In this case, the patient exhibited classic symptoms of diabetes including weight loss, polyuria, and polydipsia. Additionally, hyperthyroidism was identified in the patient, which could indicate an underlying autoimmune cause. A C-peptide test was performed and revealed a low level. However, the patient was not tested for islet cell and glutamic acid decarboxylase antibodies. The patient met two of the requirements for LADA diagnosis, which include onset age over 30 years and the persistence of symptoms despite oral antihyperglycemic agents, diet and need for insulin therapy. Due to the initial clinical symptoms, LADA patients may receive treatment with oral hypoglycemic medications, such as sulphonylureas and biguanides. These drugs may produce a noticeable improvement in blood sugar levels initially, but LADA patients tend to become resistant to the medications quickly. As a result, insulin therapy may be necessary soon after the initial diagnosis.[14]

Insulin therapy is highly beneficial for patients with LADA as it improves beta-cell function, reduces HbA1c levels, autoantibody concentration, and glucose toxicity.[15] It is important to recognize LADA as a distinct subtype of diabetes and to initiate insulin therapy early in the disease process to optimize outcomes. Patients with LADA have a higher prevalence of other autoimmune diseases, especially thyroid disease.[16]

CONCLUSION

The heterogeneity of LADA showcased in its etio-pathogenesis- a blend of auto-immunity and lifestyle factors, explains the various difficulties faced in the therapeutic management of LADA. Despite the prevalence of LADA equaling that of type 1 DM globally, insufficient data exists on the definitive screening and management of LADA. Many patients in India are misdiagnosed with type 2 DM which delays efficient treatment of LADA, leading to further autoimmune destruction of β-cells. LADA patients have at least a few functioning β-cells when they're diagnosed (indicated by lack of insulin dependency at diagnosis). This highlights the importance of early diagnosis and implementing strategies to not only improve metabolic control, but preserve and improve remaining secretory function. Our patient was promptly started on insulin therapy at diagnosis due to poor glycemic control. Our case report hopes to highlight the need for screening proper diagnostic criteria in a country like India, which has a high prevalence of diabetes mellitus in its population.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556