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PREVALENCE OF LATENT AUTOIMMUNE DIABETES IN ADULTS: EXPERIENCE FROM A SINGLE CENTRE IN SOUTH INDIA

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ABSTRACT

Abstract: Latent autoimmune diabetes in adults (LADA) is a heterogeneous clinical entity where patients are usually diagnosed at later age and are mostly misdiagnosed as type 2 Diabetes Mellitus (T2 DM). Though they respond to oral hypoglycemic agents (OHA'S) initially, but require insulin dependent therapy more rapidly than with type 2 DM patients. Like Type 1 Diabetes mellitus (T1DM) this group of patients also express circulating beta ( ) cell autoantibodies.

Methods: This is a cross sectional study to estimate the prevalence of LADA in south Indian population conducted from 2 centre's in Hyderabad. Sixty four patients who were newly diagnosed with diabetes mellitus (aged between 15- 55 years) were recruited in to the study after careful exclusion. All subjects were screened for GAD, IAA, IA- 2 antibodies using ELISA kits provided by Aesku Diagnostics (Oakland, CA).

Results: GAD-65 auto antibodies were positive in 23.4 % (16) patients, IAA auto antibodies were positive in 4.7% (3) patients, IA-2 auto antibodies were positive in 3.1%(2) patients. Most of these subjects are younger with normal BMI and had low C-peptide levels.

Conclusion: The prevalence of LADA is 32% in this study, indicates this form of diabetes is not uncommon. So it is imperative to investigate for this form of diabetes for specific treatment from the outset of the disease, thereby it benefits the patient and the society.

INTRODUCTION:

The incidence of diabetes mellitus has been on the rise worldwide more so in India[1].The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in diabetic patients[2,3]. The etiology for this rise in diabetes mellitus in India is multi factorial, with a genetic background influenced by environmental factors like obesity, rapid urbanization, life style changes etc.

Of late the incidence of early onset diabetes is increasing rapidly among our population, along with its co-morbidities and complications. Complications due to diabetes are linked to its duration and glycemic control, making youth with diabetes more prone to these complications. The most important step to minimize these complications can be made only by right diagnosis and proper management of the disease from the outset.

The typical clinical profile of Type1Diabetes mellitus (T1DM) is rapid onset of osmotic symptoms in a span of days to weeks, weight loss, and progression to ketosis / ketoacidosis. C-peptide levels are found to be low for the corresponding blood glucose levels. Glutamic acid decarboxylase (GAD) antibodies and other auto antibodies may be positive, and other autoimmune disorders like hypothyroidism, vitiligo, or celiac disease may be present, or develop later. Whereas, Type2 Diabetes mellitus (T2DM) is marked by insidious onset, obesity, evidence of insulin resistance (acanthosis nigricans), and absence of autoimmunity. Hypertension and/or polycystic ovarian syndrome (PCOS) in girls and a strong family history of Diabetes are often present. In most patients, the distinction between these predominant two types is easier, but in some adolescents and young adults the distinction of T2DM from T1DM can be difficult at first encounter, especially in latent autoimmune diabetes of adults. (LADA)

The concept of LADA or slow onset type 1 diabetes or diabetes type 1.5, was first introduced in 1993 as a form of DM type 1 that occurs in adults because of slowly progressive auto immune isletis associated with insidious onset[4]. Adults with LADA may initially be diagnosed falsely as type 2 diabetes based on their age, particularly if they have risk factors for type 2 diabetes such as obesity and strong family history.

The diagnosis is based on the finding of high blood sugar together with the clinical impression that islet failure rather than insulin resistance is the main cause. Detection of a low C-peptide and raised antibodies against the islets of Langerhans support the diagnosis. It can only be treated with the usual oral treatments for type 2 diabetes for a certain period of time, after which insulin treatment is usually necessary, as well as long-term monitoring for complications.

Hence this study was performed to identify pancreatic islet cell autoimmune markers in young Indian diabetic patients (adolescents and young adults), thereby initiating proper treatment and directions from the early stage of the disease.

Materials and methods:

Sixty four patients who were diagnosed with diabetes mellitus

(aged between 15- 55 years), with a fasting blood sugar ≥126mg/dl and glycated haemoglobin (HbA1C) ≥ 6.5 % were recruited in to the study.

Patients with pancreatic pathology, with a history of DKA, patients on treatment with steroids and pregnancy were excluded. All patients are newly diagnosed and blood samples were drawn within a month from the diagnosis. None of these newly diabetes participants had received prior lifestyle or medication management. Patients were consecutively recruited from two centre's from Hyderabad (Krishna Institute of Medical Sciences Begumpet and Kondapur) between June 2013 to Dec 2015. Abdominal X-ray and/or ultrasound were done to rule out pancreatic calcifications. Informed consent was obtained from participants and/or parents.

Serum samples were stored at -20^0 C before antibody testing and shipped in frozen state from the study site. IAA, GAD65, IA-2 were measured in serum using commercial ELISA kits from Aesku Diagnostics (Oakland, CA). The sensitivities and specificities of the GAD65 and IA-2 autoantibody assays based on the 2012 Islet Autoantibody Standardization Program are 82 and 82% and 78 and 67%, respectively. Sensitivities and specificities for the other autoantibody assays provided by the manufacturer are 70 and 98% for IAA. When clinical setting demands other antibody like thyroid peroxidase (TPO), thyroglobulin (TG), and tissue transglutaminase (tTG) autoantibodies were measured in the study population by using commercial ELISA kits. Statistical analysis done by using software IBM SPSS statistics for windows software (version 16 USA).

RESULTS:

In our study we have included 64 patients [out of which 48(75%) male; 16(25%) female] who were attended to our hospital. As shown in table 1 majority of patients were in 25-34 yrs age group 32(50%) followed by 14(21.8%) patients were in 35-44 yrs age group.

As shown in table 2 IAA auto antibodies were positive in 4.7% (3) patients out of which 2 patients were in 15-24yrs age group. GAD-65 auto antibodies were positive in 23.4 %(15) patients with majority of male patients (9.4%) were in 25-34 yrs age group; 4.7% female patients in 15-24yrs age group. IA-2 auto antibodies were positive in 2 patients (3.1%) in 15-24 yrs age group. we also noticed that only one patient was positive for all three islet cell auto antibodies, one patient was positive for IAA and GAD 65 auto antibodies, one patient was positive for GAD 65 and IA-2 auto antibodies, rest of the patients were positive for only one auto antibodies but not even a single patient was positive for IA-2 auto antibodies alone.

As shown in table 3 we found that 14 (21.9%) male patients had HbA1c more than 10% in 25-34 yrs age group followed by 10.9% male patient had HbA1c 8.5- 9.99% ; 6.2% female patient had HbA1c 8.5-9.99% but only 2 (3.1%) female patients had HbA1c more than 10% in 25-34 yrs age group. When compared with BMI group with gender and age group we noticed that 54.7% (35) patients were having normal BMI (18.5-22.99), 10.9 %(7) patients with BMI more than 27kg/m2. Only 4.7 %(3) patients were having BMI less than 18.5 kg/m2.

When we compare age group with C-Peptide level group we found that 35.9%(23) patients were having C-peptide levels < 0.81ng/ml in this majority of patients were in 25- 34 yrs age group[11 patients {8(12.5%) male, 3 (4.7%) female}] followed by 8 (12.5%) patients were in age group 15-24yr [5(7.8%) male, 3(44.7% female]. We compare fasting plasma Glucose at the time of presentation with age group we found that 10.9% (7) patients had FBS less than 200mg%, 34.4% (22) patients had FBS 200-249 mg%, 39.1% (25) patients had FBS 250-350mg%, 15.6%(10) patients having FBS more than 350mg%. 6.2 %(4) patients in 15-24 yrs age group had FBS more than 350 mg%. We compare HbA1c group with BMI group and found that majority of patients who were having HbA1c more than 10% were from 18.5-22.99kg/m2 BMI group [23(35.9%) patients] followed by 7 (10.9%) patients in BMI 23-26.99kg/m2 ,only 2 (3.1%) patients who had BMI less than 18.5 had HbA1c more than 10%. We compare C- peptide group with HbA1c and BMI groups and found that 14(21.9%) patients who had more than 10% HbA1c and BMI 18.5 to 22.99 were having C- peptide less than 0.81ng/ml.

We compare islet cell antibodies with BMI and found that 2 (3.1%) patients were positive for IAA auto antibodies, 11(17.2%) patients were positive for GAD 65 auto antibodies, 2(3.1%) patients were positive for IA-2 auto antibodies in 18.5-22.99kg/m2 group. We compare islet cell antibodies with C- peptide levels group and found that 3 (4.7%) patients were positive for IAA auto antibodies, 11(17.2%) patients were positive for GAD 65 auto antibodies, 2(3.1%) patients who were positive for IA-2 auto antibodies had C-peptide levels below 0.81ng/ml. We compare islet cell antibodies with FBS and found that 2 (3.1%) patients were positive for IAA auto antibodies had FBS in 200-249mg% range, 6(9.4%%) patients were positive for GAD 65 auto antibodies had FBS 250-350 mg% range followed by 5(7.8%)in 200-249mg% range, 1(1.6%) patients positive for IA-2 auto antibodies was present in 200-249mg% group and 1(1.6%) patient was present in more than 350mg% group.

DISCUSSION:

Though the incidence of T2 DM is increasing in younger age group[5,6] there is very little data is available from India. Because of different methodology in these studies there is significant discrepancy in the frequency of LADA has been observed which is ranging from 2.6% to 58 %[7]. In part, such heterogeneity in the results also could be attributed to the regional diversity. Based on this data it is estimated that more than 50% of these patients diagnosed as having type 2 diabetes may actually have LADA. So it is imperative that measurement of islet cell autoimmune markers namely Glutamic acid decarboxylase autoantibody (GAD), islet cell autoantibody (ICA), insulinoma-associated (IA-2) autoantibody, and zinc transporter autoantibody (ZnT8) testing should be performed on all adults who are not obese who are diagnosed with diabetes in this group[8].

The prevalence of LADA is 32% in this study, indicates this form of diabetes is not uncommon, likewise in other studies GAD is the most frequent autoantibodies in this study with 25% stake[9,10]. Among GADA negative patients, only small proportion of patients are positive for other autoantibodies (IAA 4.7% and IA-2A 3.1%). So in a resource limited settings GAD antibody can be used to screen patients with suspected LADA. Our study is not similar to others, where in some studies the prevalence of GAD antibodies were more than our study[11,12] and less in some other studies[13,14], this discordance is possibly due to the genetic heterogeneity in different regions of India or methodological problems related to various studies.(like sample size, focussing only a sub group etc)

Prevalence of LADA in our subjects was highest 17.2 % in individuals aged15-24 years followed by 10.93% in 25-34 years age group this is in accordance to large Chinese and European studies[15], where there is decreasing trend of LADA prevalence with increasing age. But in contrast to the highest prevalence of 13.9% in patients aged 50-59 years in a small Chinese cohort.[16]

C-peptide is co secreted with insulin at equimolar concentrations and is not degraded as rapidly as insulin. So quantification of C-peptide levels is a valuable test to quantify insulin and therefore to evaluate -cell function. The results of the C-peptide determination showed significantly low levels of C-peptide in LADA patients (<0.81ng/ml), majority of whom are in the younger age group (15-34 yrs), as expected the blood sugar levels higher in this group. This is in correlation with other studies suggested that LADA has lower C-peptide levels than patients with type 2 diabetes.[17,18,19]

Most of our subjects (71.4%) displayed normal BMI values, suggesting that the gradual -cell destruction in LADA is insufficient to cause significant weight loss. This observation is similar to reports which suggest that BMI values are lower in LADA patients compared to patients with type 2 diabetes.[20,21]

On the basis of the observations made in our study, the young diabetics are a heterogeneous in nature from the point of view of etiology, presentation of symptoms, and proneness to ketoacidosis.

In conclusion, clinicians should screen islet autoimmune markers in young and lean diabetic population and in any suspicious diabetes (even at later age) for the proper diagnosis, which in turn facilitates right treatment from the outset of the disease thereby it benefits the patient and the society.

Our study is following limitations we have not done auto antibodies to Zinc transporter-8 (ZnT8A) as this facility not available at the laboratory so some of the LADA patients might have been missed. Even though we screened our patients for pancreatic pathology, we could not screen them for MODY. Being a tertiary care centre it is possible that we screened subgroup of patients who were young, non obese & with high HbA1c at diagnosis means with high probability of LADA in this study, so we cannot extrapolate this prevalence with the true prevalence of LADA in Indian population.

TABLES

Table 1: Baseline characteristics

Parameters	Values
Number of cases	64
Age (years ± SD)	30.70± 8.05
Sex (%)	
Male	48 (75%)
Female	16 (25%)

Table 2 : Age and Sex wise distribution

Age groups	Male	Female	Total
15-24 yrs	9	4	13
25-34 yrs	26	6	32
35-44 yrs	10	4	14
46 yrs and above	3	2	5

Table 3 Frequency of positivity for all auto antibodies in age groups

Age groups	GAD-65 Ab		IAA Ab		IA-2Ab	
	Positive	negative	Positive	negative	Positive	negative
15-24 yrs	7	06	2	11	2	11
25-34 yrs	7	25	0	32	0	32
35-44 yrs	1	13	0	14	0	14
> 45 yrs	1	04	1	04	0	05
	16(25%)		3(4.7%)		2(3.1%)	

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