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Latent Autoimmune Diabetes in Adults (LADA): A Case Series

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ABSTRACT

An adult presenting with diabetes is usually assumed to have type 2 diabetes. Since the 1980s, type 2 diabetic subjects who had failed sulphonylurea therapy soon after diagnosis have been thought to be actually slowly progressive type 1 patients. This diabetes sub-type is currently referred to as latent autoimmune diabetes in adults (LADA). Early recognition of such patients has important clinical implications.

To assist local doctors in the recognition of such patients, we performed a retrospective study to profile and highlight distinctive features of thirteen LADA patients. We found that these patients were mostly females with a mean body mass index of 17.2 kg/m^2, diagnosed with type 2 diabetes in their fourth decade of life and becoming insulin dependent after a mean of 2.5 years.

Keywords: latent autoimmune diabetes in adults, anti-GAD antibodies

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INTRODUCTION

An adult presenting with diabetes is usually assumed to have type 2 diabetes. Since the early 1980s, doctors have come to recognise that type 1 diabetes is more frequent in adults than formerly believed. Groop et al reported a high frequency of islet cell antibodies in adult Finnish patients with what was thought to be type 2 diabetes but was later termed as latent type 1 diabetes[1]. Zimmet et al later termed this group of diabetics as having latent autoimmune diabetes in adults (LADA)[2]. Early identification of LADA is relevant to avoid a delay in insulin treatment and prolonged exposure to the deleterious effects of hyperglycaemia.

To assist local doctors in the recognition of such patients, we performed a retrospective study to profile and highlight distinctive features of thirteen LADA patients, characterising mainly the clinical, immunological and metabolic features of these patients.

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RESEARCH DESIGN AND METHODS

The Diabetes Centre in the Singapore General Hospital sees about 1,000 to 1,300 cases per month. The majority of these cases are referred from primary care physicians, intra-hospital referrals or in-patient follow-up. Over the past two years, we have been collecting a database of anti-glutamic acid decarboxylase (GAD) positive patients on review at the centre. To date, we have 34 patients in our database.

Thirteen patients from this database were identified as LADA as they fulfilled the following criteria[3]:

1. initial diagnosis and treatment as for Type 2 diabetes for at least six months
2. presence of anti-GAD antibodies

We proceeded to study these patients and analyse the data for ethnic distribution, characteristics of clinical presentation, evidence of diabetic ketoacidosis or ketonuria, biochemical indices, age, sex, age of onset of diabetes, body mass index (BMI), family history of diabetes, C-peptide levels and presence of other autoimmune disease or markers.

Presence of anti-GAD was confirmed if the level of antibodies detected was higher than the normal range provided by our laboratory. The GAD-antibodies were measured by a radioligand binding assay (^{125}I-labelled human recombinant GAD 65, RSR Limited). The normal range provided by our laboratory is 0.32 - 0.74 U/ml. The coefficients of variation (CV) for inter-assay and intra-assay replicates for high positive control serum (mean 27.2U) were 5.1% (n = 11) and 2.9% (n = 19).

Islet cell antibodies (ICAs) were detected using indirect immunofluorescence, using primate pancreas as standard substrate (Euroimmun laboratory). A titre of 1:10 or higher was regarded as positive.

Ketonuria was defined as urinary ketones $\geq$ 1+. DKA was defined as an arterial pH <7.3, a bicarbonate value <15 mmol/l and a glucose level >14 mmol/l with ketonuria.

RESULTS

Clinical features

The clinical characteristics of the thirteen LADA patients are tabulated in Table I. Of the thirteen patients,

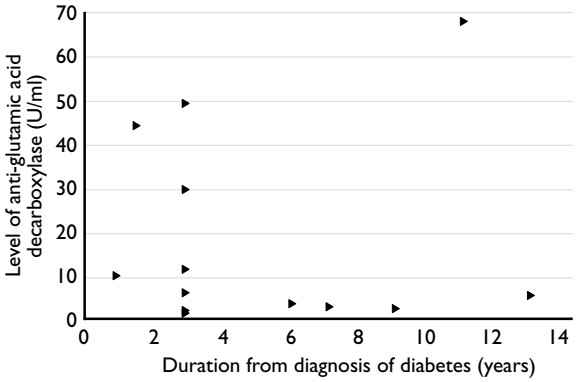
Table I. Clinical characteristics of the 13 LADA patients.

N	Sex	Ethnic group	Age $_{at\ diagnosis}$ (years)	Age $_{at\ presentation}$ (years)	BMI (kg/m^2)	HbA_{1c} $_{at\ presentation}$ (%)
1	F	Chinese	21	23	17.75	12.9
2	M	Chinese	19	23	18.50	11.5
3	M	Chinese	24	25	17.01	19.3
4	F	Indian	29	32	16.30	10.8
5	M	Chinese	41	43	16.53	14.5
6	F	Chinese	41	43	14.03	13.2
7	F	Chinese	41	44	18.71	11.3
8	F	Chinese	40	43	18.82	12.2
9	F	Chinese	48	51	15.27	21.6
10	F	Chinese	56	59	18.43	14.0
11	F	Malay	70	72	14.38	19.3
12	F	Chinese	36	37	17.41	12.9
13	F	Chinese	41	44	20.70	13.5
Mean ± SD			39.0 ± 14	41.3 ± 14	17.2 ± 1.9	14.3 ± 3.5

F: Female M: Male BMI: Body Mass Index

there are only three males and the majority are Chinese (85%). The median age of diagnosis of diabetes mellitus was 39 ± 14 years, ranging from 19 to 70 years of age. The median age of presentation to the hospital was 43 ± 14 years. The mean body mass index (BMI) was 17.2 ± 1.9 kg/m^2, ranging from 14.03 to 20.70 kg/m^2. All except one patient were non-smokers and had no history of chronic alcohol consumption. These patients were previously on oral hypoglycaemic agents for a duration of one to four years (mean 2.5 ± 0.9 years). Of the seven patients who gave a positive family history of diabetes, only four of them had affected first degree relation of which only one had a son with Type 1 diabetes. The other relations were all Type 2 diabetics.

Graph 1. Scatterplot of level of anti-GAD antibodies against the duration from onset of diabetes.



Clinical presentation

Half of these patients were seen at the Accident & Emergency (A&E) department, while the other half were referred directly to our Diabetes Centre. Referrals to the hospital came mainly from general practitioners and the government clinics. All those seen at the A&E were admitted while half of those seen at the centre were managed as outpatients. Most of them had presented to the hospital with complaints pertaining to uncontrolled diabetes, namely loss of weight, polyuria and polydipsia. The other complaints were for right hand cramps and diarrhoea. Of those admitted, a diagnosis of diabetic ketoacidosis was made for only three patients; the rest were admitted on a diagnosis of uncontrolled diabetes.

Clinical and Biochemical parameters

All the patients were clinically stable; only one had septicaemia proven by blood culture. Their mean HbA_{1c} was 14.3 ± 3.45% and their mean random blood glucose at presentation was 25.4 ± 13.3 mmol/l. Urine ketones were positive for all except four patients; of the latter, ketonuria was not sought for. Based on the diagnostic criteria for DKA, only two patients had presented with diabetic ketoacidosis; both did not have any identifiable precipitating factor.

At the time of presentation, two patients were found to have all the three major microvascular complications of diabetics (retinopathy, nephropathy and neuropathy). One has had diabetes for only three years while the other had been diabetic for nine years. There were no complications detected in the rest of the cohort.

Graph I shows the scatterplot of the level of anti-GAD antibodies against the duration from time of diagnosis of diabetes mellitus. The anti-GAD assays done for these patients were from one to 13 years from

diagnosis of diabetes. Their levels ranged from 1.03 to 67.48 U/ml, with a median of 7.9 U/ml.

C-peptide levels were only available for nine patients: fasting C-peptide ranged from 0.10 to 1.90 ug/ml while intravenous glucagon stimulated C-peptide varied from 0.20 to 3.40 ug/ml. Islet cell antibodies done in nine patients were all negative. Only one patient had a history of thyrotoxicosis and that had occurred prior to the onset of diabetes.

Upon the institution of insulin therapy, the mean HbA_{1c} decreased to 9.0 ± 2.0% (ranging from 6.3 - 12.2%) and the patients also had a mean weight gain of 6.4 ± 2.9 kg.

DISCUSSION

Our study demonstrated that LADA patients are not infrequently seen amongst our diabetic population. These patients have distinctive features that may differentiate them from type 2 diabetics. From this cohort, we found that these patients usually presented in the fourth decade of life, are mainly females and would have been treated as for type 2 diabetes for an average of 2.5 years. At presentation, they were phenotypically similar to classical type 1 diabetics as their mean BMI was only 17.2 kg/m^2. According to our 1992 National Health Survey, the mean BMI of diabetics in Singapore was 22.28 ± 3.8 kg/m^2 in males and 21.29 ± 3.63 kg/m^2 in females[4]. These observations are in concordance with those made by previous authors. They were usually described as being "25 years or older and non-obese, presenting with what clinically appears to be type 2 diabetes, which is often maintained in good metabolic control on diet or oral hypoglycaemic therapy for up to several years before insulin dependency"[5].

All these patients were diagnosed based on the presence of anti-glutamic acid decarboxylase antibodies that was assayed several years after the diagnosis of diabetes. In Singapore, Thai et al[6] had previously determined the frequency of anti-GAD in a group of 134 type 1 and 168 type 2 Chinese diabetic patients: their results showed that 39.6% type 1 and 16.1% type 2 diabetic had anti-GAD whilst 20.1% and 4.8% respectively had detectable ICAs. They did not, however, find any distinctive differences in clinical characteristics between the anti-GAD positive and seronegative type 2 diabetics and had concluded that anti-GAD might not be useful to identify the LADA group of patients amongst Asians. The negative results in this study may have been attributed to the inclusion of patients with variable duration of the disease and various body weights.

Recently the UKPDS and other studies[7,8] have added weight to data available that the measurement of anti-GAD is a useful marker for classifying individuals with adult onset diabetes, even more so than traditional characteristics such as BMI and age at diagnosis. From the data gathered from our study, we wish to concur, as these antibodies were present and were still detectable even after 13 years from diagnosis.

From a clinical perspective, it is important that adults with atypical diabetes have their type of diabetes identified. Earlier treatment of diabetes with insulin may improve their immediate well-being and moreover, it provides a chance of preserving remaining β-cell function and thereby lessening the risks of long-term microvascular complications of diabetes. Failure to commence insulin treatment in LADA individuals may mean that several months of unnecessarily poor control may ensue.

As in the case of our patients, they had poorly controlled diabetes prior to their admission as reflected by their HbA_{1c} at presentation (14.3%). Two of these patients already had multiple diabetic complications due to poorly controlled diabetes by the time they presented to the hospital. Early identification of LADA is therefore relevant to avoid delayed insulin treatment and prolonged exposure to the deleterious effects of hyperglycaemia. From the referral patterns, we also realised that most physicians are not familiar yet with the possibility of dealing with a slow progressive type 1 diabetic. Most have failed to take note of the ketonuria that was present in almost all the patients on presentation to our hospital.

Etiological classification of each patient is also mandatory for conducting early prevention trials of diabetes. Data suggesting that prompt insulin therapy may preserve β-cell function in newly-diagnosed type 1 diabetes[9] is currently available. Should the results of Diabetes Prevention Trial - Type 1 confirm this, a reliable indicator of autoimmune etiology in adult-onset diabetes becomes very important for early diagnosis. The early use of insulin in LADA could then possibly be aligned with "postprimary" intervention with immunotherapy.

CONCLUSIONS

Physicians should consider immunological screening in adult diabetics who are clearly underweight and appear clinically atypical of type 2 diabetes.

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