Islet cell antibodies in the Japanese population and subjects with Type 1 (insulin-dependent) diabetes

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Summary. Islet cell antibodies were studied in 1,112 non-diabetic adults, 473 normal school children and 162 Type 1 (insulin-dependent) diabetic patients in a Japanese population. The prevalence of islet cell antibodies was 0.5%, 0.4% and 32%, respectively. Most islet cell antibodies positive subjects with Type 1 diabetes had short duration of the disease. No patients who had over 10 years from the onset had islet cell antibodies. Six non-diabetic adults with islet cell antibodies were followed for 4 years. Only one with Hashimoto's thyroiditis showed a diabetic pattern in her oral glucose tolerance test. However, none developed overt insulin-dependent

diabetes until 1984. Two out of these six subjects continued to be positive for both islet cell antibodies and antithyroid antibodies or antinuclear antibodies. Islet cell antibodies in the remaining four patients disappeared during the second year. It is difficult to predict the onset of Type 1 diabetes by islet cell antibodies in non-diabetic individuals because they may be transient.

Key words: Population survey, islet cell antibody, Type 1 diabetes, autoantibodies, pre-Type 1 diabetes.

In general, the prevalence of Japanese subjects with autoantibodies is smaller than in Caucasoids. For example, there are less patients with Addison's disease being positive for anti-adrenal antibodies [1]. Two hundred and eighty patients with Addison's disease were autopsied from 1946 to 1968 in Japan; however, there were no patients with autoimmune adrenalitis [2]. There are several reports concerning the prevalence of islet cell antibodies (ICA) in Caucasoids, Blacks and Pima Indians [3–9]. We compared the incidence of ICA in a Japanese population, including Type 1 diabetic patients, with Caucasoids and other races. ICA and especially complement-fixed ICA (CF-ICA) have been found to predict the onset of Type 1 diabetes [10]. However, it remains to be shown whether all non-diabetic individuals with ICA develop Type 1 diabetes. We performed a follow-up study of ICA-positive subjects for 4 years.

Subjects and methods

In 1981, a mass screening for the presence of ICA was conducted in a rural community in Japan. One thousand one hundred and twelve normal adults without overt diabetes (516 men, 596 women, age range 22–92 years, mean age 58) took part in this survey in Daiwa Village. The number of participants was approximately 75% of the entire adult population of the village. The past medical history, the family

history and any present illness of each participant were recorded. ICA and post-prandial plasma glucose levels were determined. Fifty-gram oral glucose tolerance tests were performed in adult patients with ICA in 1982 and 75-g oral glucose tolerance tests were carried out in 1984. In addition, the sera of the ICA-positive individuals were tested for the presence of four other autoantibodies (CF-ICA, anti-thyroid antibodies (MCHA), anti-nuclear antibodies (ANA) and rheumatoid factor). These patients were followed up from 1981–1984.

The prevalence of ICA in 473 normal school children and in 162 Type 1 diabetic children was also studied. Serum samples of normal school children were collected in elementary or junior high or high school in Izumo City. They were completely normal school children. The sex ratio of them was 240:233 and the age range was 7–18 (mean 10.8). Type 1 diabetic children were participants of the summer camp in the Kinki District. Seventy-one men and 91 women participated in this camp. The mean age of these childhood diabetic patients was 10.8 (range 6–20).

ICA, CF-ICA and ANA were detected by indirect immunofluorescence using cryostat sections of human pancreas of blood type O and rat livers, respectively [11–14]. Human pancreas were obtained from patients with gastric or pancreatic cancer who received pancreatectomy. We utilized normal pancreatic tissue in these patients as substrates. The serum was applied undiluted in order to screen for presence of ICA. ICA-titres were determined subsequently. The anti-human IgG conjugate were derived from Behring Institute (FRG). MCHA and rheumatoid factor were measured by the tanned red cell haemagglutination technique and the latex fixation test, respectively. CF-ICA, ANA, MCHA and rheumatoid factor were measured in adult subjects and normal children with ICA and in Type 1 diabetic children.

Table 1. Plasma glucose levels, oral glucose tolerance tests, autoantibodies and clinical findings in the six asymptomatic adults with islet cell antibodies

Patient	Age/ sex	Family history (diabetes)	Auto- immune disease	Body mass index	Plasma glucose levels. Autoantibodies (titre)				Oral glucose tolerance tests	
					(1981)	(1982)	(1983)	(1984)	50 g (1982)	75 g (1984)
1.	33 M	(-)	(-)	± 0	ICA 6.0 (5)	5.9 -	5.0 -	5.2 -	Borderline	
2.	45 F	(-)	Hashimoto's thyroiditis	+ 12	ICA 7.0 (10)	4.5 (5)	5.0 (5)	6.0 (5)	Diabetic	Diabetic
					MCHA (1024)	(1024)	(1024)	(1024)		
3.	53 F	(-)	(-)	- 11	ICA 6.8 (5)	4.7 -	5.0 -	4.0 -	Borderline	
4.	57 F	(-)	(-)	+ 6	ICA 6.6 (5)	6.1 -	not tested	5.3 -	Borderline	
5.	64 M	(-)	(-)	- 1	ICA 5.1 (5)	5.3 -	5.2 -	5.0 -	Borderline	
6.	72 M	(-)	(-)	+ 7	ICA 5.2 (5)	5.1 (1)	5.0 (1)	5.4 (1)	Borderline	Borderline
					ANA (80)	(40)	(40)	(40)		

Complement-fixing ICA and rheumatoid factor could not be detected. Patients 1, 3, 4 and 5 had neither ANA nor MCHA

Plasma glucose levels were measured by the routine examination using enzyme methods. Post-prandial plasma glucose estimations were carried out in all adult subjects in 1981. These adults had normal plasma glucose levels and were non-diabetic.

Results

The prevalence of ICA in the normal adults without diabetes, the normal school children and the Type 1 diabetic children was 0.5%, 0.4% and 32%, respectively. The highest prevalence of ICA, 63%, and CF-ICA, 41%, was observed in Type 1 diabetic children during a period of less than 1 year after disease manifestation decreasing with duration, 29% and 11% at 1-5 years, 19% and 3% at 6-10 years and 0% in both antibodies at 10 years after disease manifestation. In these patients with Type 1 diabetes, the prevalence of ANA, MCHA and rheumatoid factor was 8%, 13% and 1%, respectively. Two normal children with ICA had ANA; however, other autoantibodies were negative.

Post-prandial plasma glucose levels, patterns of oral glucose tolerance tests, titres of autoantibodies and clinical findings in the six adult patients with ICA are shown in Table 1. None had a family history of diabetes. During 1981-1984 the post-prandial plasma glucose levels were below 7.8 mmol/l. Only patient 2 showed a diabetic pattern in both 50-g (1982) and 75-g (1984) oral glucose tolerance tests. This patient had Hashimoto's goitrous thyroiditis and was slightly obese. Her thyroid function, however, was normal. The remaining five subjects had no symptom of autoimmune disorders, nor did they develop Type 1 diabetes or Type 2 (non-insulin-dependent) diabetes.

In patients 1, 3, 4 and 5 ICA had disappeared by 1982. In patient 2 with Hashimoto's thyroiditis both

ICA and MCHA persisted from 1981 to 1984. Patient 6 has been positive for both ICA and ANA; however, the titres of ICA, MCHA and ANA in these six patients were low. They had neither CF-ICA nor rheumatoid factor.

Discussion

The prevalence of ICA in non-diabetic individuals in several surveys ranged from 0% to 1.7% [3-9]. Six patients (0.5%) out of 1,112 adults, and two (0.4%) out of 473 normal children, were positive for ICA. These frequencies are comparable to the values in Caucasoids. The prevalence of ICA in Type 1 diabetic patients with short duration of the disease has been found to be 33% in Blacks and 85% in the USA [3, 9]. The proportion of Japanese ICA-positive Type 1 diabetic patients with short duration was about the same as in Caucasoids. However, it was higher than in Blacks and Pima Indians [7, 9]. In this study, none of the Type 1 diabetic patients with duration longer than ten years from onset had ICA. In most ICA-positive patients with Type 1 diabetes, the antibodies are transient over a period of months to a few years, while in the minority the antibodies persist for many years and there are a few subjects who have a strong association with organ-specific autoimmune disease and HLA-B8 [4]. These patients were classified into "subclass a", in which the presence of ICA was usually persistent and there was a close association with organ-specific autoimmune disease or autoimmune phenomenon [15]. From our results, the proportion of Japanese Type 1 diabetic patients classified into "subtype a" may be much smaller such as Addison's disease with anti-adrenal antibodies. There was no correlation between ICA-positive Type 1 diabetes

and HLA-typing in Japanese subjects [16]. There may be differences in the pathogenesis of Type 1 diabetes between Japanese and Caucasoids. Most Type 1 diabetic patients in Japan may be viral induced or "subclass c".

It is beneficial to predict the onset of Type 1 diabetes. In asymptomatic autoimmune thyroiditis, several patients with circulating thyroid antibodies suffer from hypothyroidism [17]. In Type 1 diabetes, it remains unclear whether there is asymptomatic autoimmune insulinitis in man. It is said that all patients with circulating thyroid autoantibodies have inflammatory cells infiltration to their own thyroid gland [18]. However, there are no studies concerning ICA and mononuclear cells infiltration to the pancreatic islets in pre-Type 1 diabetes or in potential abnormality of glucose tolerance. Irvine et al. [19] and Gorsuch et al. [20] showed that several asymptomatic individuals with ICA later developed Type 1 diabetes. From our results, ICA in patients without other autoantibodies disappeared without episodes of severe glucose intolerance. It is suspected that CF-ICA are more specific markers of islet cell damage [10]. Six adults with ICA were negative for CF-ICA in this study. From these results, none of them seem to develop Type 1 diabetes; however, it is doubtful that every patient with CF-ICA develops Type 1 diabetes. Spencer et al. showed that CF-ICA in non-diabetic patients disappeared without developing Type 1 diabetes [21]. Helmke et al. reported that none of the ICA-positive children with mumps infection had acquired diabetic metabolism [22]. We suspect that the four subjects without other autoantibodies in our survey have suffered from viral infection such as mumps and ICA therefore, have been transient. Thus, it is difficult to recognise prediabetic patients by ICA because of their transient nature. It is doubtful to treat non-diabetic ICA-positive patients with immunosuppressive agents, especially in Japan, because the proportion of subjects being classified into "subclass a" may be much smaller.

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