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Clinical Study

Occurrence of Type 1 Diabetes in Graves' Disease Patients Who Are Positive for Antiglutamic Acid Decarboxylase Antibodies: An 8-Year Followup Study

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Glutamic acid decarboxylase antibodies (GADAs) are one of the markers of islet cell autoimmunity and are sometimes present before the onset of type 1 diabetes (T1D). GADA can be present in Graves' patients without diabetes; however, the outcome of GADA-positive Graves' patients is not fully understood, and the predictive value of GADA for the development of T1D in Graves' patients remains to be clarified. We investigated the prevalence of GADA in 158 patients with Graves' disease and detected GADA in 10 patients. They were followed up to discover whether or not T1D developed. In the course of eight years, 2 patients with high titers of GADA developed T1D, both had long-standing antithyroid drug-resistant Graves' disease. Thus, Graves' disease with high GADA titer seems to be at high risk for T1D.

1. Introduction

Autoimmune type 1 diabetes (type 1A diabetes) is an organ-specific autoimmune endocrine disease, which is caused by immune destruction of pancreatic β cells [1]. Antibodies to islet-related antigens including glutamic acid decarboxylase antibodies (GADAs) and insulinoma-associated antigen 2 (IA-2) antibodies are markers for autoimmunity to islet cells [2, 3]. When these antibodies are positive, the patient's diabetes is usually considered to be type 1 even if they are not insulin dependent [4–6]. Antibodies to islet-related antigens are present before the onset of type 1 diabetes (T1D) [7], and their predictive value for the development of T1D has been repeatedly investigated in close relatives of T1D patients and the general population [7–12].

Graves' disease, which is also an organ-specific autoimmune endocrine disease, is frequently associated with T1D [13]. In these patients, titers of GADA tend to be high [14], which may indicate powerful ability of producing autoimmune process to islet antigens. On the other hand, GADA is sometimes positive in Graves' patients without diabetes [15–17]. In these patients, GADA may exist independently from β-cell destruction. However, the fate of Graves' patients who are positive for GADA is obscure, and the predictive value of GADA for the development of T1D in Graves' patients remains to be clarified. We examined GADA in patients with Graves' disease and followed up patients who were positive for GADA for 8 years.

2. Patients and Methods

GADA was measured by a highly sensitive ligand-binding assay in 158 patients with Graves' disease (50 untreated, 108 treated) who had not been diagnosed to have diabetes. The patients were randomly collected by one physician at Ito

Thyroid Clinic. Most patients other than new patients were under the treatment with antithyroid drugs. In the patients who were positive for GADA by ligand-binding assay (positive when detected), GADA was again measured by radioimmunoassay (Cosmic Corporation, standard value was <1.5 U/ml), and antibodies to Islet Cell Antibodies (ICAs) 512/IA-2 were measured by a ligand-binding assay (positive when detected). Details of the ligand-binding assay for GADA and antibodies to ICA512/IA-2 have been described elsewhere [18, 19]. Glucose intolerance was assessed by either oral glucose tolerance test or HbA1c (reference range: 4.3–5.8%) within a half year after the detection of GADA. Diabetes was diagnosed by criteria of American Diabetes Association. In the cases in which only HbA1c was measured for the detection of glucose intolerance, less than 5.8% was considered to be normal glucose tolerance. Patients positive for GADA by ligand-binding assay were followed up whether or not type 1 diabetes developed. In seven patients whose GADA titers by ligand-binding assay were relatively high and GADA by RIA were positive, HbA1c and occasional plasma glucose were measured at least every two years for eight years. GADA was occasionally measured by radioimmunoassay. In other three patients who were negative for GADA by RIA, physicians inquired whether or not diabetes developed at every visiting to the outpatient clinic. One patient was dropped out three years after the initial workup. The patients who were negative for GADA at the start of the study were not followed up.

3. Results

Ten patients out of 158 (6.3%) were positive for GADA by the ligand-binding assay. Eight of these patients were treated with antithyroid drugs (ATDs) and 2 were untreated (treatment naive). The overall prevalence of positivity for GADA among treated and untreated patients was 7.4% and 4.0%, respectively (Table 1). GADA was again investigated by standard radioimmunoassay (RIA) in 9 of the 10 patients, and 6 were positive (Table 2). In 4 patients, titers by RIA were over 20 U/ml. ICA512/IA-2 antibodies were weakly positive in 2 patients. An oral glucose tolerance test was performed in 5 of the 10 GADA-positive patients. Of these, one patient showed a diabetic pattern and another had impaired glucose tolerance (this patient dropped out from study 3 years after the initial workup). BMI of these patients was 19.9 and 21.0, respectively. The other 3 patients had normal GTT. HbA1c levels of the other 5 patients were within the normal range. During the 8-year followup period, T1D developed with marked hyperglycemia and ketosis in two patients whose Graves' disease was long standing and uncontrollable by antithyroid drug. One of them showed diabetic pattern in GTT at the initial work up, but HbA1c was within a normal range (Section 3.1 and Table 2).

3.1. Case Reports. Patient 1 was a 44-year-old man (at the diagnosis of T1D), in whom Graves' disease developed at age 21. He took an antithyroid drug (ATD), but 10–20 mg of methimazole was needed to maintain euthyroid. At age 42, GADA was detected. His oral glucose tolerance test the next year showed a diabetic pattern (FPG 7.8 mmol/L (141 mg/dL), 2 hours 14.3 mmol/L (257 mg/dL)). HbA1c was 5.7%. His insulin response to oral glucose was very low (insulinogenic index, 0.08). GADA by RIA was as high as 6090 U/ml. Calorie restriction was recommended, but symptoms of severe hyperglycemia including thirst and polyuria developed the following year. Plasma glucose was 29.6 mmol/L (534 mg/dL), and urine ketone bodies were 2+. Blood gas analysis did not demonstrate acidosis (pH 7.385). Insulin therapy was started, and the requirement of insulin was reduced to 2 units/day but increased to 34 to 40 units thereafter. Postprandial C-peptide reactivity (CPR) was 0.23 nmol/L at 3 years after the onset of diabetic ketosis. Finally, the patient received semitotal thyroidectomy after the exacerbation of thyrotoxicosis.

Table 1: Prevalence of GAD antibodies in Graves' patients who had not been diagnosed with diabetes at the study start.

	Patient number	GADA(+)	(%)
Graves' disease	158	10	6.3
untreated	50	2	4.0
treated	108	8	7.4

Difference of prevalence is not statistically significant.

Patient 2 is a 34-year-old woman (at the diagnosis of T1D). Her grandmother had type 2 diabetes. Graves' disease developed at age 14. After ATD therapy, she had remission at age 19, but Graves' disease relapsed at age 21. At age 26, Graves' disease was exacerbated 9 months after delivery. GADA was detected next year. Postprandial glucose was 5.3 mmol/L (95 mg/dL), and HbA1c was 5.0%. GADA by RIA was 855 U/ml. Three years later, Graves' disease was exacerbated again after her second delivery. She needed 60 mg methimazole to maintain euthyroid and she took radioisotope therapy, but an antithyroid drug was continued as she was still thyrotoxic. One year after RI therapy, her postprandial plasma glucose was 123 mg/dL and HbA1c was 5.6%. GADA by RIA was increased to 1440 U/ml. Next year T1D developed with the manifestations of hyperglycemia such as thirst, polydipsia, polyuria, and weight loss. On the laboratory examinations, plasma glucose was 34.6 mmol/L (623 mg/dL), HbA1c was 14.1%, urine ketone bodies were positive, and arterial blood pH was 7.41. After initial therapy for hyperglycemia, she took 24 units of insulin daily, and her CPR before lunch was 0.18 nmol/L.

4. Discussion

Type 1 diabetes (T1D) and Graves' disease, both endocrine organ-specific autoimmune diseases, frequently coexist and in combination are classified as autoimmune polyglandular syndrome type III [13]. There are common genetic backgrounds for both diseases [20] such as the CTLA-4 gene [21–23] and PTPN-22 gene [24–27]. In Japanese adults, the two diseases often develop simultaneously or Graves' disease proceeds to T1D [28]. Thus, Graves' disease is a risk factor for T1D, as seen in the present study in which two out

Table 2: Baseline characteristics of the patients with positive GAD antibodies including their antibody titers.

Case		Age at entry	Sex	duration (yr)	GADA (LBA) 0	GADA (RIA) u/ml <1.5	IA-2Ab 0	TRAb (%) <10.0	TGHA (X) <400	MCHA (X) <400	HbA1c (%) 4.3–5.8	GTT
1	*	42	M	21	>1.300	6090	0.024	63.5		400000	5.7	DM
2		21	F	0	>1.128	>256	neg			400		normal
3	*	27	F	13	0.928	855	neg	21.5		400000	5.0	
4		50	F	11	0.790	21.4	neg	7.2	400	100000		IGT
5		26	F	0	0.192	2.6	neg	6.7	1600	25600		normal
6		23	F	5	0.076		neg	24.2		100000		
7		25	F	4	0.073	3.3	neg	29.5		400000	4.4	normal
8		42	F	2	0.062	0.5	neg	21.1			4.9	
9		25	M	6	0.047	<0.4	0.083	7.0		6400	3.9	
10		42	F	12	0.027	<0.4	neg	12.5			4.8	

Figures at the bottom of the items are reference values.
*Cases 1 and 3 developed T1D.
neg: negative.
Age: age at examination of GAD antibodies.
TRAb: TSH receptor antibodies, TGHA: thyroglobulin hemagglutination, MCHA: microsome hemoagglutination.

of 158 patients with Graves' disease developed T1D during the course of 8 years.

In this study, the prevalence of GADA in Graves' patients without previously diagnosed diabetes was high, similar to those in previous reports [15–17]. Furthermore, the prevalence was high in the treated patients but the difference of the prevalence between treated patients and treatment-naïve patients was not statistically significant. Among the patients positive for GADA, T1D developed in two patients with long-standing Graves' disease who were not easily controlled by antithyroid drug (ATD) therapy. One needed a 10 to 20 mg methimazole for control of the disease and finally had a thyroidectomy after exacerbation. The other frequently relapsed and finally had radioiodine therapy. Their titers of GADA both by ligand-binding assay and radioimmunoassay were very high. It is conceivable that autoimmune reaction to islet antigens is strong in the Graves' patients with high titer of GADA, and that those patients are susceptible to T1D.

Antibodies to islet antigens are present before the onset of type 1 diabetes [7]. On the other hand, many individuals positive for antibodies to islet antigens do not develop T1D. In Finland, where the incidence of T1D is very high, it was reported that T1D developed only in 26% of GADA-positive young subjects from general population over 25 years [29]. In the same study, only 0.26% of GADA-negative subjects developed T1D. Previous studies have revealed that positivity for more than 2 kinds of islet-associated antibodies, especially the combination of GADA and IA-2 antibodies, has predictive value [2]. Of the patients in the present study who developed T1D, one had IA-2 antibodies and the other did not. On the contrary, one patient who had both antibodies in low titers did not develop T1D during the followup period. The number of patients was small and we could not obtain conclusive results, but the presence of both GADA and IA-2 antibodies seems to indicate a high risk also in Graves' patients. Screening of GADA followed by examination of IA-2 antibodies may allow detecting those patients at greater risk for development of T1D, and careful followup may provide earlier detection of the onset of T1D in these patients.

5. Conclusions

We show preliminarily that Graves' patients with long duration and high titers of GADA are at high risk for developing T1D. To clarify what factors are involved in the susceptibility to T1D in Graves' disease, greater numbers of patients need to be followed up intensively over a long period of time.

Abbreviations

GADA: Glutamic acid decarboxylase antibodies
T1D: Type 1 diabetes
IA-2: Insulinoma-associated antigen 2
CPR: C-peptide reactivity
ICA: Islet cell antibodies
ATD: Antithyroid drug
RIA: Radioimmunoassay.

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