Characteristics of a Fulminant Onset Form of Idiopathic Type 1 Diabetes Mellitus in Japanese Children

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Abstract. We studied the clinical characteristics of Japanese children with idiopathic type 1 diabetes who had had a remarkably rapid onset, severe metabolic disorder and absolute insulin deficiency at diagnosis. In 85 Japanese children with type 1 diabetes, 14 (16.5%) were classified as idiopathic type 1 diabetes mellitus with no evidence of anti-islet autoantibodies. Among the 14 patients with the idiopathic form, three were identified as having a fulminant onset form. These three patients had had a remarkably rapid onset with a short symptomatic period of less than seven days prior to the onset of overt diabetes. They exhibited severe ketoacidosis and had low levels of HbA1c despite high concentrations of blood glucose at diagnosis. Their initial serum C-peptide levels were extremely low or undetectable. Most of the patients experienced viral infections prior to the onset of the disease. These findings suggest that the non-autoimmune, fulminant onset form of type 1 diabetes may be not rare in the Japanese population. This form is characterized by a remarkably rapid onset with severe metabolic disorder and absolute deficiency of insulin secretion at onset. Viral infections may be associated with the rapid destruction of beta-cells without an autoimmune mechanism.

Key words: idiopathic type 1 diabetes, fulminant onset, severe metabolic disorder, absolute insulin deficiency, viral infection

Introduction

Several studies have demonstrated that autoimmunity is not the only cause of beta-cell destruction. At least 10 to 15 percent of patients with newly diagnosed type 1 diabetes do not show evidence of beta-cell autoimmunity, including the existence of diabetes-related autoantibodies (1, 2). Such cases are classified as idiopathic type 1 diabetes (3, 4). Idiopathic type 1 diabetes has no known etiologies. Although only a minority of patients with type 1 diabetes fall into this category, it has been reported that the majority are non-Europids, African or Asian origin. Individuals with this form of diabetes are considered to be heterogeneous in the clinical features (3, 4) (Table 1).

Imagawa et al. (5) reported a novel subtype of type 1 diabetes characterized by a fulminant onset and the absence of beta-cell autoimmunity in Japanese adults. In the fulminant onset form of type 1 diabetes characterized by the absence of both insulitis and diabetes-related autoantibodies,
the onset of overt diabetes was remarkably rapid and the beta-cell function had deteriorated completely from the onset of the disease.

We studied the clinical characteristics of Japanese children with idiopathic type 1 diabetes who had a remarkably abrupt onset, severe metabolic disorder and absolute insulin deficiency at the time of diagnosis.

**Subjects**

The study subjects were 85 Japanese children, 34 males and 51 females, with type 1 diabetes of rapidly progressive form (4). They were diagnosed as having diabetes on the basis of the World Health Organization criteria established in 1980 (6), between 1974 and 1998. The patients initially showed typical symptoms of hyperglycemia and 51.8% of them presented ketoacidosis or impaired consciousness as the first manifestation of the disease. All of the patients required insulin replacement therapy for survival or to achieve adequate glycemic control from the time of the initial diagnosis.

The subjects were divided into two subgroups with respect to the presence or absence of anti-islet autoantibodies. Patients were diagnosed as having immune-mediated type 1 diabetes (type 1A diabetes) when they had at least one of the following autoantibodies: islet-cell cytoplasmic antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD) antibodies, or tyrosine phosphatase-like protein (IA-2) antibodies. They were classified as having idiopathic type 1 diabetes (type 1B diabetes) when they had no evidence of these autoantibodies with beta-cell destruction. We did not perform a biopsy of the pancreas for confirming insulitis on any patient.

**Laboratory evaluation**

ICA were detected by an indirect immunofluorescence method using blood type O human pancreas (positive: more than 5 JDF units). IAA were examined using a RIA method. Antibodies to GAD and IA-2 were measured by RIA kits employing recombinant human GAD and IA-2 (positive: anti-GAD antibodies, more than 1.5 units/ml; anti-IA-2 antibodies, more than 0.4 units/ml; Cosmic, Tokyo, Japan). HLA-DR typing was performed using a standard microcytotoxicity test. Serum C-peptide was measured by RIA using two antibodies. HbA1c was measured by a HPLC method (normal: 3.3–5.8%).

**Statistical analysis**

The results were expressed as the mean value ± SD. To detect differences between the groups, a nonparametric test for unpaired data (Mann-Whitney U test) was used. Analysis of the frequency was performed using Fisher’s exact probability test. Analysis of the correlation was performed using Pearson and Spearman correlation coefficients. P<0.05 was considered significant.

**Table 1** Clinical characteristics of Type 1B diabetes

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<th>Characteristic</th>
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<tr>
<td>1. Permanent insulinopenia</td>
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<td>2. Ketosis-prone (Episodic ketoacidosis)</td>
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<td>3. Non-Europids (African or Asian origin)</td>
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<td>4. Varying degrees of insulin deficiency between episodes</td>
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<td>5. An absolute requirement for insulin replacement in future</td>
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<td>6. Strongly inherited (Not HLA associated)</td>
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<td>7. Lack of immunological evidence for β-cell autoimmunity</td>
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Results

Frequency and clinical features of patients with type 1A and type 1B diabetes at the time of onset

Table 2 shows the frequency and clinical features of the patients with type 1A and type 1B diabetes at the time of onset. While the frequency of type 1A diabetes was 83.5%, that of type 1B diabetes was 16.5%. There was no significant difference in gender between the two types of diabetes. With regard to the age at onset, the mean age of patients with type 1B diabetes was significantly lower than that of patients with type 1A diabetes ($6.9 \pm 4.5$ vs. $8.9 \pm 4.5$ years, $p<0.05$). Diabetic ketoacidosis at onset was significantly more common in type 1B diabetes than in type 1A diabetes ($78.6$ vs. $46.5\%$, $p<0.05$). Viral infection prior to the onset of the disease was significantly more frequent in type 1B diabetes than in type 1A diabetes ($53.8$ vs. $26.8\%$, $p<0.05$).

Subtype of remarkably rapid onset with severe metabolic disorder and absolute insulin deficiency in type 1B patients

Among 14 patients with type 1B diabetes, we identified three showing a subtype of remarkably rapid onset with severe metabolic disorder and absolute insulin deficiency at diagnosis. Table 3 shows the characteristics of the three patients at the onset of diabetes. They consisted of three females, aged 3.6, 1.9 and 12.6 years at the time of onset. All the patients had suffered viral illness before the onset of the disease (Coxsackie B, mumps and unknown origin). The duration of hyperglycemic symptoms prior to the onset of overt diabetes was less than seven days in all of the three patients (7, 5 and 5 days). All had ketoacidosis with bicarbonate levels of under 20 mmol/L at onset. Although all the patients showed high concentrations of plasma glucose with a severe metabolic disorder, they displayed low HbA1c values of less than 8.0%. They exhibited low or undetectable levels of serum C-peptide. No patient had either type 1 or type 2 diabetes in among first degree-relatives. All the patients had high-risk HLA typing for type 1 diabetes including either HLA-DR4 or HLA-DR9. From these findings, this form of diabetes was considered to be a subtype of a fulminant onset of type 1B patients.

Discussion

Type 1 diabetes is caused by loss of insulin-
secretion capacity due to selective autoimmune destruction of the pancreatic beta-cells. Insulitis is the direct result of the autoimmune process. Anti-islet autoantibodies are considered to be good markers of beta-cell autoimmunity. On the other hand, several lines of evidence have indicated that the immune mechanism is not the only cause of beta-cell destruction. The etiology of some forms of type 1 diabetes has not been elucidated. It has been reported that the minority of patients with newly diagnosed type 1 diabetes show no evidence of beta-cell autoimmunity including the presence of anti-islet autoantibodies. This type is classified as idiopathic type 1 (type 1B) diabetes. In the present study, among 85 Japanese children who had type 1 diabetes, we found the frequency of type 1B diabetes to be 16.5%. This frequency almost corresponds with that in previous Caucasian studies (1, 2).

Imagawa et al. (5) reported a novel subtype of type 1B diabetes characterized by remarkably rapid onset and the absence of insulin-secreting capacity at diagnosis in Japanese adults. In the fulminant form, the onset of overt diabetes is markedly abrupt and the mean symptomatic period before diagnosis was only four days. In the majority of the cases, the beta-cell function had drastically deteriorated and the initial metabolic disorder was severe. In our study, three cases in the 14 patients with type 1B diabetes had a short symptomatic period of less than seven days before diagnosis. This suggests that the onset of overt diabetes and the progression of the disease in these patients were remarkably rapid. Although all the patients showed high plasma glucose levels, they had low HbA1c values of less than 8.0% at diagnosis. This suggests that the short symptomatic period before the onset of overt diabetes might be reflected by the low HbA1c values. All the patients experienced severe ketoacidosis and had low or undetectable values of serum C-peptide at onset. This implies that a severe metabolic derangement occurred soon after the onset of hyperglycemic symptoms and that the beta-cells had been completely destroyed without an autoimmune mechanism from the onset. These cases were classified as a subtype of type 1B diabetes characterized by remarkably rapid onset with severe metabolic disorder and absolute insulin deficiency. We consider these cases to be similar to the fulminant form of type 1B diabetes described by Imagawa et al. (5).

We found a high incidence of viral infections before onset among patients with type 1B diabetes, especially in the fulminant onset cases. Several reports hypothesize that viral infection initiates beta-cell autoimmunity which leads to the onset of type 1 diabetes. Infectious agents might activate autoimmunity by molecular mimicry, in which the immune response to a viral antigen might cross-react with a beta-cell antigen (7, 8). With regard to patients with nonautoimmune type 1 diabetes, it is likely that some viruses directly invade pancreatic islets and induce beta-cell destruction without an autoimmune mechanism (9). Direct viral damage of beta-cells may be a candidate for the cause of type 1B diabetes, especially in the fulminant onset form.

Type 1B diabetes is reported to be strongly inherited and not associated with HLA susceptibility (3, 4). In the present study, however, family histories for both type 1 and type 2 diabetes were not found, and high-risk typing of either HLA-DR4 or HLA-DR9 was common in the fulminant onset form. Therefore, patients with the fulminant onset form of type 1B diabetes are considered to have HLA-defined genetic susceptibility for type 1 diabetes, which is similar to type 1A diabetes. More studies are necessary to elucidate HLA defined genetic susceptibility for the fulminant onset form of type 1 diabetes.

In conclusion, a nonautoimmune, fulminant onset form of type 1 diabetes may be not rare in the Japanese population including children as well as adults. This form is characterized by remarkably rapid onset with a severe metabolic disorder and absolute deficiency of insulin secretion at the onset. Viral infection may be associated with the
rapid destruction of beta-cells without an autoimmune mechanism.

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References