Fulminant type 1 diabetes mellitus in Japanese children and adolescents: multi-institutional joint research of the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes

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Abstract. Fulminant type 1 diabetes mellitus (FT1DM) is a subtype of type 1 diabetes mellitus characterized by a remarkably abrupt onset. In Japan, FT1DM accounts for approximately 20% of acute-onset adult type 1 diabetes mellitus cases; however, reports of pediatric-onset FT1DM are rare. We aimed to determine the frequency and clinical characteristics of FT1DM in Japanese children and adolescents by conducting a 2-phase questionnaire survey among the members of the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (JSGIT) regarding their clinical experience with FT1DM. Responses were obtained from 54 of the 79 participating hospitals (68.4%). Of these, 8 hospitals managed a total of 15 pediatric patients with FT1DM (4 patients in each of 2 hospitals, 2 patients in 1 hospital, and 1 patient in each of 5 hospitals). The distribution of patient age was biphasic, with peaks in children younger than 5 years and older than 8 years of age. The clinical characteristics of FT1DM in this population (such as the duration from onset of symptoms to diagnosis, severity of symptoms, preceding flu-like episodes, and abnormal laboratory data) did not differ from those of patients with adult-onset FT1DM. The frequency of pediatric-onset FT1DM is low compared with that of adult-onset FT1DM. The genetic background and susceptibility patterns of pediatric patients with FT1DM may differ from those typical of adults with FT1DM, but both age groups share similar clinical characteristics.

Key words: Fulminant type 1 diabetes mellitus, Pediatric-onset diabetes mellitus, Child, Adolescent

IN JAPAN, patients with type 1 diabetes mellitus (T1DM) form a clinically heterogeneous group; the condition is divided into the following 3 subtypes: acute-onset, fulminant, and slowly progressive [1-3]. Imagawa et al. were the first to report on fulminant type 1 diabetes mellitus (FT1DM) in Japan [4]. The clinical characteristics of FT1DM are defined as follows: Occurrence of diabetic ketosis or ketoacidosis soon (within approximately 7 days) after the onset of hyperglycemic symptoms; plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and glycated hemoglobin (HbA1c) level <8.5% (based on the Japan Diabetes Society [JDS] criteria) at first visit; and urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucose (or after meal) load at onset [5]. In addition, FT1DM has the following characteristics: Islet cell-related autoantibodies such as anti-glutamic acid decarboxylase
antibodies (GADA) are absent in most cases; serum pancreatic enzyme levels (amylase, lipase, or elastase-1) are elevated in 98% of patients; and preceding flu-like symptoms (fever and upper respiratory symptoms, among others) or gastrointestinal symptoms (upper abdominal pain and nausea and/or vomiting, among others) are observed in 70% of patients [5].

The incidence of T1DM is not as high in Asian countries as it is in European countries and the US. In contrast, the incidence of FT1DM is higher in Asian than in European countries [6-10]. In Japan, FT1DM accounts for approximately 20% of acute-onset adult T1DM cases with ketosis at disease onset [6], but few reports have described cases of FT1DM in pediatric patients [10, 11], even though T1DM is more common among children and adolescents than among adults. This study aimed to clarify the frequency of FT1DM and its characteristics in Japanese children and adolescents.

**Materials and Methods**

**Respondents and patient cohort**

A 2-phase questionnaire survey was sent to the members of the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (JSGIT), established in 1994 [12]. This group now comprises pediatric diabetologists from 79 institutions (current chairman: Sugihara S.) and is the largest group studying pediatric T1DM in Japan. The 4th research cohort of JSGIT has been underway since 2013, and 1,076 patients are registered in this cohort.

**Questionnaires**

In this 2-phase survey, the first questionnaire aimed to confirm whether the pediatric diabetologist had treated a case of FT1DM with an age of diagnosis below 16 years. The diagnosis of FT1DM was based on the diagnostic criteria described by the JDS in 2012 [5].

The second questionnaire was sent to those members who had clinical experience of managing FT1DM in pediatric patients. It included questions regarding the following aspects: patient’s sex, age at FT1DM onset, body weight and height, duration from the onset of symptoms to diagnosis, symptoms at the time of onset, family history of diabetes, precursor symptoms (i.e., upper respiratory symptoms and/or gastrointestinal symptoms), blood glucose and HbA1c values at onset, existence of ketosis and/or ketoacidosis, blood and/or urine C-peptide immunoactivity (CPR) values, presence of islet cell-related autoantibodies, concentrations of exocrine pancreatic enzymes, and human leukocyte antigen (HLA) class II typing.

**Data collection and measurements**

The clinical examination of each patient was conducted by the attending clinician at each institution. All values are presented as the mean ± SD. JDS-based HbA1c values were converted to the HbA1c values recommended by the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry (IFCC) using the following equations: NGSP (%) = 1.02 × JDS (%) + 0.25 [13], and IFCC (mmol/mol) = (10.93 × NGSP) – 23.50 [14], respectively.

Questionnaire response forms were collected by facsimile or e-mail, and were kept by the JSGIT secretariat. All data were analyzed by the authors.

**Ethical approval**

This study was approved by the review board of each participating institution in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. Written consent was obtained from all patients or their legal guardians.

**Results**

**Data collection**

Responses to the questionnaires were obtained from 54 of 79 hospitals (68.4%). Overall, 8 hospitals had treated a total of 15 pediatric patients with FT1DM (4 patients in each of 2 hospitals, 2 patients in 1 hospital, and 1 patient in each of 5 hospitals).

**Clinical characteristics of the patients**

The clinical characteristics of the patients are shown in Table 1. The 15 patients included 6 boys and 9 girls, aged 9.2 ± 5.1 (range: 0.9–15.7) years. Six (40.0%) patients (1 with T1DM and 5 with type 2 diabetes mellitus) each had a family history of diabetes. The mean interval from the onset of symptoms to diagnosis was 3.2 ± 1.5 (range: 2–7) days. At the onset of the disease, 9 (60.0%) patients showed disturbances of consciousness, and 13 (86.7%) experienced at least one symptom of upper respiratory tract infection or gastroenteritis preceding the onset of hyperglycemic symptoms.

The age at onset appeared to have a biphasic distribution, with 1 group including 5 younger children aged <5
years and the other comprising 10 older children and adolescents aged >8 years (Fig. 1).

Laboratory data at onset

The laboratory data of all 15 patients are shown in Table 2. The mean blood glucose level at onset was 797.0 ± 297.0 (range: 409–1,134) mg/dL and the mean HbA1c value was 6.7 ± 0.8 (range: 5.6–8.3) % [49.8 ± 9.3 (range: 37.7–67.2) mmol/mol]. The mean serum and urine CPR levels were 0.20 ± 0.13 (range: 0.02–0.39) ng/mL and 4.4 ± 3.4 (range: 0.3–9.0) μg/day, respectively. The mean serum levels of exocrine pancreatic enzymes were elevated in all 8 patients who had such measurements performed: Amylase, 413.4 ± 326.2 IU/L (range: 94–879 IU/L); lipase, 119.3 ± 98.0 IU/L (range: 16–219 IU/L); and elastase-1, 792.7 ± 888.6 ng/dL (range: 168–1,810 ng/dL). The results of radioimmunoassay testing for GADA were positive (≥1.5 U/mL) in 4 (26.7%) cases, but the mean titer was relatively low at 5.5 ± 3.6 (range: 3.0–9.7) U/mL.

HLA type was analyzed in 12 patients. The HLA class II haplotype was identified in 8 of these 12 patients; 4 had DRB1*04:05-DQB1*04:01 and 3 had DRB1*09:01-DQB1*03:03. Overall, 6 of 8 patients had HLA DRB1*04:05-DQB1*04:01 and/or DRB1*09:01-DQB1*03:03 (Table 3).

Discussion

In Japan, a nation-wide survey showed that FT1DM was diagnosed in 19.4% of patients with acute-onset adult T1DM with ketosis at disease onset. The mean age at onset was 39.1 years while the proportion aged younger than 20 years at onset was less than 10%; however, the frequency of FT1DM among pediatric patients was unclear [6]. Recent studies suggest that FT1DM is common in eastern Asian countries such as Japan, Korea, and China. In these countries, most FT1DM patients are adults [8-10]; few reports have focused on FT1DM in the pediatric population [10, 11].

In the present study, 16 patients aged <16 years fulfilled the diagnostic criteria for FT1DM. The 4th research cohort of the JSGIT has been under way since 2013. Currently, 1,076 patients, including 450 boys and 629 girls aged 6.5 ± 3.8 years (range: 0.1–18.3 years), are registered in this cohort. A sizeable proportion of pediatric FT1DM cases in Japan were, thus, included in the present study. The time of onset was not restricted in this
**Fig. 1** Age distribution of children with fulminant type 1 diabetes mellitus

The age at onset was distributed biphasically: One group comprised younger children <5 years of age, the other comprised children and adolescents >8 years of age.

**Table 2** The laboratory data of all patients with fulminant type 1 diabetes mellitus

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Glucose (mg/dL)</th>
<th>HbA1c (%)</th>
<th>HbA1c (mmol/mol)</th>
<th>S-CPR (ng/mL)</th>
<th>U-CPR (μg/day)</th>
<th>GADA</th>
<th>Elevation of pancreatic enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>679</td>
<td>8.3</td>
<td>67.2</td>
<td>0.36</td>
<td>3.8</td>
<td>(+); 3.0</td>
<td>(+)</td>
</tr>
<tr>
<td>2</td>
<td>565</td>
<td>7.9</td>
<td>64.8</td>
<td>&lt;0.3</td>
<td>n.e.</td>
<td>(–)</td>
<td>n.e.</td>
</tr>
<tr>
<td>3</td>
<td>409</td>
<td>7</td>
<td>53</td>
<td>0.2</td>
<td>3.9</td>
<td>(+)</td>
<td>n.e.</td>
</tr>
<tr>
<td>4</td>
<td>772</td>
<td>8</td>
<td>63.9</td>
<td>&lt;0.3</td>
<td>7</td>
<td>(–)</td>
<td>n.e.</td>
</tr>
<tr>
<td>5</td>
<td>618</td>
<td>5.9</td>
<td>41</td>
<td>0.17</td>
<td>n.e.</td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td>6</td>
<td>749</td>
<td>6.3</td>
<td>45.4</td>
<td>0.1</td>
<td>4.6</td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td>7</td>
<td>626</td>
<td>5.9</td>
<td>41</td>
<td>&lt;0.5</td>
<td>0.6</td>
<td>(+); 9.7</td>
<td>n.e.</td>
</tr>
<tr>
<td>8</td>
<td>843</td>
<td>6.8</td>
<td>50.8</td>
<td>0.3</td>
<td>n.e.</td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td>9</td>
<td>949</td>
<td>6.7</td>
<td>49.7</td>
<td>&lt;0.2</td>
<td>6.1</td>
<td>(+); 3.8</td>
<td>n.e.</td>
</tr>
<tr>
<td>10</td>
<td>&gt;500</td>
<td>5.6</td>
<td>37.7</td>
<td>&lt;0.02</td>
<td>0.1</td>
<td>(–)</td>
<td>n.e.</td>
</tr>
<tr>
<td>11</td>
<td>708</td>
<td>7</td>
<td>53</td>
<td>&lt;0.3</td>
<td>9</td>
<td>(–)</td>
<td>n.e.</td>
</tr>
<tr>
<td>12</td>
<td>1,540</td>
<td>6</td>
<td>42.1</td>
<td>0.09</td>
<td>0.3</td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td>13</td>
<td>1,070</td>
<td>6.6</td>
<td>48.6</td>
<td>0.02</td>
<td>n.e.</td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td>14</td>
<td>496</td>
<td>6.5</td>
<td>47.5</td>
<td>0.39</td>
<td>9</td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td>15</td>
<td>1,134</td>
<td>5.9</td>
<td>41</td>
<td>0.06</td>
<td>n.e.</td>
<td>(–)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

GADA, glutamic acid decarboxylase antibodies; HbA1c, glycated hemoglobin; n.e. not examined; S-CPR, serum C-peptide immunoreactivity; U-CPR, urine C-peptide immunoreactivity.
study; therefore, patients not registered in the 4th research cohort were also included. Because it was difficult to determine what denominator to use, we could not calculate the exact prevalence and incidence of pediatric-onset FT1DM. Nevertheless, the frequency of FT1DM is estimated to be considerably lower in children and adolescents than in adults. One reason why pediatric-onset FT1DM is considered rare may be that it is unfamiliar to pediatricians; hence, some cases of FT1DM may not be identified.

With regard to patient age at disease onset, the distribution seems to be biphasic, with 1 group comprising younger children (<5 years old) and the other comprising older children and adolescents (>8 years old). Although all patients met the diagnostic criteria for FT1DM, younger patients had relatively higher HbA1c levels and lower body mass index-standard deviation scores than older patients.

The currently used diagnostic criteria for FT1DM are mainly based on adult data [5], wherein proof of an abrupt onset depends on the lack of a substantial elevation in the value of HbA1c. However, in infant patients, the percentage of fetal hemoglobin (HbF) in the blood is estimated to be high, and a higher percentage of non-HbA1c, such as HbF, is associated with a lower level of HbA1c [15]. Therefore, in the present study, the true duration of high blood glucose status may have been underestimated by the relatively low HbA1c values. Moreover, it may be more difficult to establish the diagnosis of FT1DM in younger patients.

The mean serum and urine CPR levels observed in the present study were both at an extremely low level, indicating very low secretion of endogenous insulin. The exact pathophysiology resulting in the onset of FT1DM is unknown. The sudden and complete destruction of pancreatic β-cells is thought to be a cause of this disease, but the precise mechanisms of such cell destruction remain unclear. It has been suggested that viral infections, such as reactivation of human herpes virus-6, Epstein-Barr virus, cytomegalovirus, coxsackievirus, mumps virus, and influenza type B virus, are related to the onset of FT1DM [16-22]. In this study, 86.7% of patients presented with signs suggestive of a preceding viral infection. Urakami et al. reported that patients with type 1B diabetes mellitus were significantly younger at the time of diagnosis and had a higher frequency of a preceding viral infection than those with type 1A diabetes mellitus [23]. One possible mechanism underlying FT1DM is that in some susceptible individuals, viral infection initiates an abnormal immune response that triggers abrupt and total β-cell destruction [24-26]. Immunologic immaturity against viral infection may also be associated with the onset of FT1DM in these populations. Because of the absence of insulitis and islet-related autoantibodies, FT1DM was first reported as a subtype of idiopathic (type 1B) diabetes mellitus [4]. However, recent studies show that T-cells, macrophages, and dendritic cells infiltrate into the islets or exocrine tissues around the islets soon after the onset of the disease. Enterovirus capsid protein 1 and enterovirus RNA has been detected in islet cells and exocrine tissues [27, 28]. Enterovirus infection of islet cells and exocrine tissues [27, 28]. Enterovirus infection of islet cells might induce innate immunity [29, 30]. Interferon-α and β, expressed in islet cells and infiltrating mononuclear cells, produce autoimmunity to islet cells including β- and α-cells; this leads to rapid and complete destruction of islet cells in patients.

### Table 3 Results of HLA typing

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>HLA typing</th>
<th>GADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9</td>
<td>DRB1<em>04:05-DQB1</em>04:01/DRB1<em>09:01-DQB1</em>03:03 (+)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>DRB1<em>01:01-DQB1</em>05:01/DRB1<em>09:01-DQB1</em>03:03 (+)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>DRB1<em>04:05-DQB1</em>04:01/DRB1<em>16:02-DQB1</em>05:02 (+)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9.4</td>
<td>DRB1<em>03:01-DQB1</em>02:01/DRB1<em>16:02-DQB1</em>05:02 (+)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>11.5</td>
<td>DRB1<em>15:02-DQB1</em>06:01/DRB1<em>09:01-DQB1</em>03:03 (+)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>13.4</td>
<td>DRB1<em>04:05-DQB1</em>04:01/DRB1<em>08:02-DQB1</em>04:02 (+)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>14.8</td>
<td>DRB1<em>11:01-DQB1</em>03:01/DRB1<em>14:05-DQB1</em>05:03 (+)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>15.7</td>
<td>DRB1<em>04:05-DQB1</em>04:01/DRB1<em>04:05-DQB1</em>04:01 (+)</td>
<td></td>
</tr>
</tbody>
</table>

*The HLA class II haplotype was identified in 8 patients.
GADA, glutamic acid decarboxylase antibodies; HLA, human leukocyte antigen.
with FT1DM [27, 31].

Individual susceptibility may be defined by various potential factors, including genetic factors, especially HLA class II [32-35]. With regard to HLA class II typing, among the 8 patients in whom the HLA class II haplotype was evaluated, DRB1*04:05-DQB1*04:01 was identified in 4 cases and DRB1*09:01-DQB1*03:03 was identified in 3 cases. Both DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03 are related to both acute onset and slowly progressive T1DM. In particular, DRB1*09:01-DQB1*03:03 is more strongly associated with GADA-positive T1DM, while DRB1*04:05-DQB1*04:01 is more strongly associated with FT1DM. High frequency of homozygous haplotype of DRB1*04:05-DQB1*04:01 is reported in adult-onset FT1DM, which may induce greater genetic effect on the destruction of β-cells, and is supposed to play an important role in the development of FT1DM [31-33]. In this study, only one patient had homozygous haplotype of DRB1*04:05-DQB1*04:01. The number of patients who underwent HLA typing was too small for appropriate evaluation, so it is unclear whether the frequency of homozygous haplotype of DRB1*04:05-DQB1*04:01 is actually low in young-onset FT1DM.

On the other hand, a high frequency of DRB1*09:01-DQB1*03:03 haplotype, which is typically associated with autoimmune T1DM, has also been demonstrated in pregnancy-associated FT1DM [36]. Moreover, recent studies have indicated an association between DRB1*09:01-DQB1*03:03 and FT1DM [35].

Islet-cell related autoantibodies, such as GADA, are generally undetectable in patients with FT1DM. However, a nation-wide survey showed that approximately 5% of patients with FT1DM test positive for GADA, although in most of such cases, the titer is low and transient [6, 37]. In the present study, 4 cases (26.7%) yielded positive results for GADA. This percentage seems relatively high compared with findings from previous reports of adult patients [6]. However, the mean GADA titer was relatively low (5.5 ± 3.6 U/mL), similar to that in adult patients. In this study 2 of 4 GADA-positive patients had the DRB1*09:01-DQB1*03:03 HLA class II haplotype; both were <3 years of age. It seems that autoimmune mechanisms, rather than genetic mechanisms, may play an important role in such patients. In pediatric patients, particularly in younger children, although the clinical course of FT1DM is similar to that seen in adults, the genetic background and mechanisms underlying susceptibility to FT1DM may be different.

The present study has some limitations. It was a retrospective, multi-institutional joint research project and clinical examinations were conducted individually in each institution; therefore, all data at onset were not necessarily provided. Because the number of FT1DM patients in this study was so small, we could not perform a statistically meaningful analysis; the accumulation of cases and further investigations are warranted.

In conclusion, this study demonstrates that the estimated frequency of FT1DM is considerably lower in pediatric than in adult patients. Although the genetic background and susceptibility patterns of childhood-onset FT1DM may differ from those typical of adult-onset FT1DM, the clinical characteristics of FT1DM are similar in both pediatric and adult patients. Pediatricians should recognize the existence of FT1DM as it is a life-threatening metabolic state for which an accurate diagnosis, made as early as possible, and provision of appropriate therapy, are crucial, especially in pediatric patients.

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Disclosure

The authors declare no conflicts of interest concerning this manuscript.

References


