

# Fulminant Type 1 Diabetes

## A nationwide survey in Japan

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**OBJECTIVE** — To describe the clinical and immunologic characteristics of fulminant type 1 diabetes, a novel subtype of type 1 diabetes, we conducted a nationwide survey.

**RESEARCH DESIGN AND METHODS** — History and laboratory data, including islet-related autoantibodies, were examined in 222 patients with fulminant and nonfulminant type 1 diabetes in our hospitals in addition to another 118 patients with fulminant type 1 diabetes located outside our hospitals in Japan.

**RESULTS** — In our hospitals, of the 222 patients studied, 43 (19.4%) were diagnosed with fulminant type 1 diabetes, 137 (61.7%) were classified as having autoimmune type 1 diabetes, and 42 were type 1 diabetic subjects who were not fulminant and did not have anti-islet antibodies. An additional 118 fulminant patients outside our hospitals were enrolled, making a total of 161 fulminant type 1 diabetic subjects (83 male and 78 female subjects; 14 children/adolescents and 147 adults) identified from all over Japan. (In 2000, the average incidence was three cases per month.) Flu-like symptoms and pregnancy were more frequently observed in the fulminant than in the autoimmune group ( $P < 0.001$ ). In the fulminant patients, 4.8% were positive for anti-GAD antibodies and none were positive for anti-islet antigen 2 antibodies.

**CONCLUSIONS** — Fulminant type 1 diabetes is a distinct subtype and accounts for ~20% of the ketosis-onset type 1 diabetes cases in Japan. Flu-like symptoms are characteristic of disease onset. Metabolic derangement is more severe in this subtype than in autoimmune type 1 diabetes.

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**Abbreviations:** ADA, American Diabetes Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GADAb, GAD antibody; IAA, insulin autoantibody; IA-2, islet antigen 2; IA-2Ab, IA-2 antibody; ICA, islet cell antibody; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Type 1 (insulin-dependent) diabetes is characterized by insulin deficiency from the destruction of pancreatic  $\beta$ -cells. According to the recently proposed classification of diabetes by the American Diabetes Association (ADA) and the World Health Organization (WHO), type 1 diabetes is divided into two subtypes: autoimmune type 1 (immune-mediated; type 1A) diabetes and idiopathic (type 1B) diabetes (1,2).

Since 1974, when Bottazzo et al. (3) reported the presence of islet cell antibodies (ICAs) in the sera of type 1 diabetic patients, several autoantibodies to pancreatic islet cells have been recognized as a marker of type 1 diabetes. These islet-related autoantibodies are anti-GAD antibodies (GADAb), insulin autoantibodies (IAA), and anti-islet antigen 2 (IA-2)/IA-2 $\beta$  antibodies (4,5).

However, type 1 diabetic patients are not always positive for these autoantibodies, even at the onset of overt diabetes (6,7). Patients with type 1 diabetes who do not have islet autoantibodies at the time of diagnosis are classified as having idiopathic or type 1B diabetes. In Japan, several cases have been reported in which islet-related autoantibodies were negative and the onset of diabetes was acute (8–12). Imagawa and colleagues (13,14) have proposed that these cases are “non-autoimmune fulminant” type 1 diabetes. The clinical characteristics of this subtype of type 1 diabetes are 1) remarkably abrupt onset of disease; 2) very short (<1 week) duration of diabetic symptoms, such as polyuria, thirst, and body weight loss; 3) acidosis at diagnosis; 4) negative status of islet-related autoantibodies, such as ICA, GADAb, IAA, or anti-IA-2 antibodies; 5) virtually no C-peptide secretion (<10  $\mu$ g/day in urine); and 6) elevated serum pancreatic enzyme levels (13).

To clarify the more detailed clinical and immunologic characteristics of fulminant type 1 diabetic patients, we performed a multicenter study and a nationwide survey under the auspices of the Japanese Diabetes Society.

## RESEARCH DESIGN AND METHODS

### Patients

**Study 1.** Inclusion criteria for fulminant type 1 diabetes in this study were 1) ketosis or ketoacidosis within a week after the onset of hyperglycemic symptoms; 2) urinary C-peptide excretion  $<10 \mu\text{g/day}$ , fasting serum C-peptide  $<0.3 \text{ ng/ml}$  ( $0.1 \text{ nmol/l}$ ), or serum C-peptide  $<0.5 \text{ ng/ml}$  ( $0.17 \text{ nmol/l}$ ) after glucagon injection or meal load soon after disease onset; and 3)  $\text{HbA}_{1c} <8.5\%$  on the first visit. These criteria were determined based on the data from the first 11 patients diagnosed with fulminant diabetes, as reported by Imagawa et al. (13).

First, using retrospective review of patient records, we identified all patients diagnosed with type 1 diabetes who visited the Internal Medicine section or the Diabetes Center in the participating hospitals from 1991 through 2000. Participating hospitals were Osaka University Medical Hospital, Osaka Medical College Hospital, Hospital of Tokyo Women's Medical University School of Medicine, Nagasaki University Hospital, Nagasaki Genbaku Hospital, Sasebo-Central Hospital, Kosei-kai Hospital, Nijigaoka Hospital, Toranomon Hospital, Keio University Hospital, Saiseikai Central Hospital, Ehime Prefectural Central Hospital, Saitama Social Insurance Hospital, Ehime University Hospital, South-Matsuyama Hospital, Matsuyama Municipal Hospital, Central Saijo Hospital, and Matsuyama Red-Cross Hospital. Next, we identified all acute-onset type 1 diabetic patients with ketosis or ketoacidosis at onset who met nos. 1–4 or 1–3 plus 5 of the following criteria: 1) presence of ketosis or ketoacidosis at the onset of diabetes, 2) duration of hyperglycemic symptoms before insulin therapy of  $<3$  months, 3) required insulin replacement therapy at both onset and 6 months after onset, 4) presence of at least one islet-related autoantibody (GADAb, ICA, IAA, or IA-2 antibody [IA-2Ab]), and 5) decreased insulin-secreting capacity (urinary C-peptide excretion  $<20 \mu\text{g/day}$ , fasting serum C-peptide level  $<0.4 \text{ ng/ml}$  [ $0.13 \text{ nmol/l}$ ], or peak serum C-peptide level  $<1.0 \text{ ng/ml}$  [ $0.33 \text{ nmol/l}$ ] after glucagon or meal load). Of the 222 patients who were thus identified with acute-onset type 1 diabetes in our hospitals, we deter-

mined that 43 had fulminant type 1 diabetes using the criteria described above.

**Study 2.** First, we asked all members of the Japan Diabetes Society through direct mail and the *Journal of the Japan Diabetes Society* if they knew of candidates who fulfilled the criteria of fulminant type 1 diabetes, as described above. To those who responded positively, we sent a questionnaire asking for a description of the patients' clinical characteristics and autoantibody status, as described herein. The criteria used to determine fulminant type 1 diabetes were the same as those used in Study 1. Through this method, we identified 229 candidates and confirmed 118 patients among them.

The 118 patients from the Japan Diabetes Society survey and the 43 patients identified in study 1 (total 161 patients: 83 male and 78 female patients) were diagnosed with fulminant type 1 diabetes and comprised the subjects of study 2.

### Methods

**Clinical characteristics.** Clinical characteristics of all patients (age at onset, sex, BMI, date of onset of hyperglycemic symptoms, date insulin therapy was started, family history of diabetes, symptoms accompanying onset of diabetes, and diabetic complications) were recorded. In addition, dosages of daily insulin injection and the following laboratory data were determined at 0, 3, 6, and 12 months after the onset of diabetes in each hospital: plasma glucose concentration;  $\text{HbA}_{1c}$  level; urinary ketone bodies; serum ketone levels; arterial pH; serum concentrations of sodium, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, and triglyceride; daily urinary C-peptide excretion; fasting serum C-peptide level; and serum concentrations of amylase, elastase-1, and lipase. Ketosis was determined by ketonuria, elevated serum ketones, or both.

**Autoantibodies.** GADAb, ICA, and IA-2Ab were determined at the onset of diabetes. If no data were available, but serum samples stored at the time of diagnosis were available, autoantibodies were examined retrospectively. GADAbs and IA-2Abs were measured by radioimmunoassay or radioligand-binding assay (15) and ICAs were measured by the immunohistochemical methods. Thyroid anti-microsomal and anti-thyroglobulin antibodies were also investigated.

### Statistical analysis

Statistical analysis was performed with Fisher's exact probability test, the Mann-Whitney  $U$  test, and the unpaired or paired  $t$  test, as appropriate.

## RESULTS

### Study 1

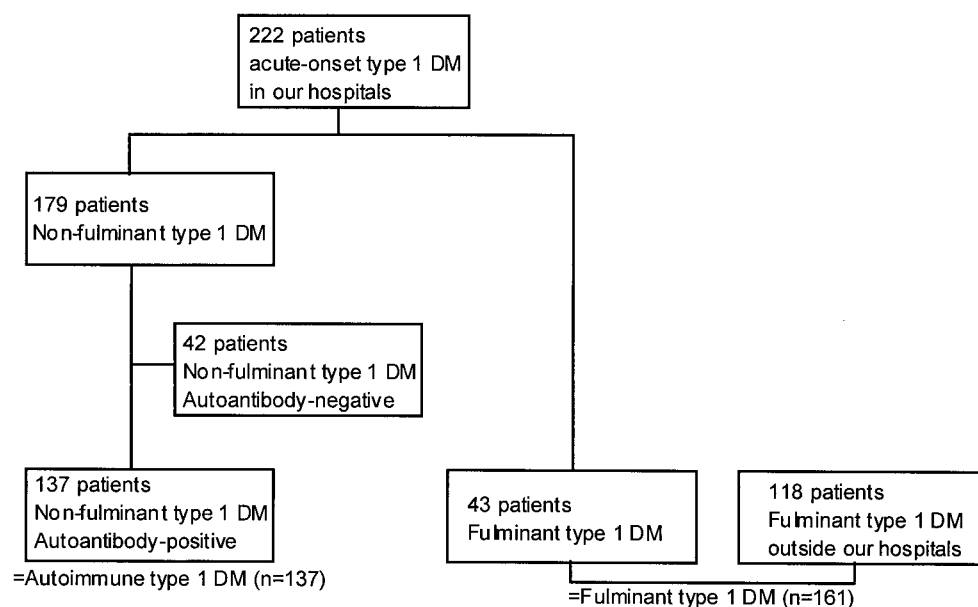
In our 18 hospitals, 222 patients (102 male and 120 female) were diagnosed with acute-onset type 1 diabetes with ketosis at disease onset. Of these 222 patients, 43 (19.4%) were diagnosed as having fulminant type 1 diabetes, including 27 male and 16 female patients. Among the remaining (nonfulminant) 179 patients, 137 (47 male and 90 female patients) were positive for at least one islet-related autoantibody. Of those 137 patients, 117 patients were positive for at least GADAb, another 17 were positive for at least ICA, and the remaining 3 were positive for at least IA-2Ab. We diagnosed these patients as having autoimmune type 1 diabetes. There was a significant difference by sex between fulminant and autoimmune type ( $P = 0.001$ ); 62.8% of fulminant diabetic patients were male vs. only 34.3% of autoimmune diabetic patients. The final 42 patients (28 male and 14 female) were diagnosed with type 1 diabetes, but were negative for islet-related autoantibodies and did not fulfill the criteria for fulminant type 1 diabetes (Fig. 1). In all, 4.7% of fulminant patients and 72.6% of nonfulminant patients ( $P < 0.0001$ ) were positive for GADAb. The distribution of  $\text{HbA}_{1c}$  level with or without GADAb at the onset of type 1 diabetes in our hospitals is shown in Fig. 2.

### Study 2

In addition to the 43 patients diagnosed with fulminant diabetes in our hospitals, we also identified 118 patients outside our hospitals with this same diagnosis. In all, we identified 161 patients with fulminant type 1 diabetes.

**Regional, seasonal, and chronological changes of incidence.** Fulminant type 1 diabetic patients were reported from all over Japan, from Hokkaido Island to Kyushu Island. Fulminant type 1 diabetic patients were accumulated in crowded areas, but not in a specific region by prefecture in Japan.

The annual number of newly diagnosed patients with fulminant diabetes was 0–7 from 1990 to 2000, and has not



**Figure 1**—Study design. DM, diabetes.

increased in our hospitals over the past 10 years. As to seasonal changes, 20 patients were diagnosed with fulminant type 1 diabetes in May, whereas 6–13 patients were diagnosed in the other 11 months. In 2000, 39 cases of newly diagnosed fulminant type 1 diabetes were reported, and the average incidence was 3 cases per month all over Japan. In May and July of 2000, eight and six cases of newly diagnosed fulminant diabetes were reported, respectively; one to four cases were reported monthly in the other 10 months.

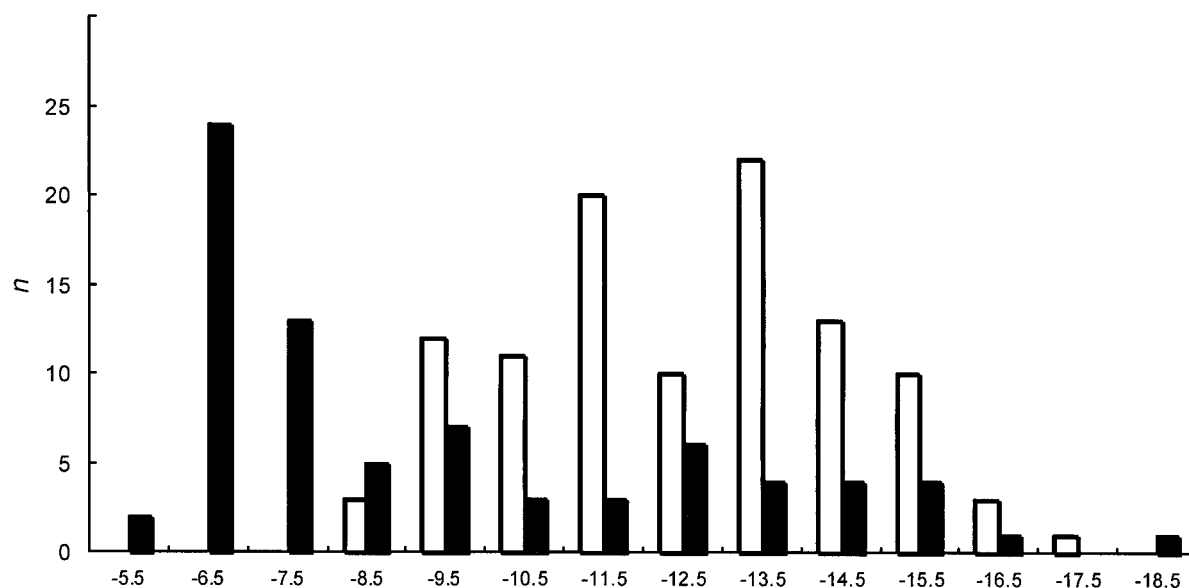
In the following analysis, two groups

of patients were compared: 161 patients with fulminant type 1 diabetes recruited from studies 1 and 2, and the 137 patients with autoimmune type 1 diabetes recruited from study 1.

**Clinical and immunological status at onset.** As shown in Table 1, the mean duration from the onset of hyperglycemic symptoms to the start of insulin therapy was 4.4 days, and the mean value of HbA<sub>1c</sub> levels, daily urinary C-peptide excretion, and fasting serum C-peptide concentration was 6.4%, 4.3 μg, and 0.3 ng/ml (0.10 nmol/l), respectively, at the

onset of fulminant diabetes. The duration of disease was significantly shorter and HbA<sub>1c</sub> levels, urinary C-peptide excretion, and the serum C-peptide concentration were significantly lower in fulminant than in autoimmune type 1 diabetes.

The mean age at onset of type 1 diabetes was 39.1 years in fulminant type 1 diabetic patients and was significantly older than age at onset in autoimmune type 1 diabetic patients. The age at onset of male fulminant patients was 42.8 ± 14.8 years (mean ± SD) and significantly higher than that of female fulminant pa-



**Figure 2**—Distribution of HbA<sub>1c</sub> at onset of newly diagnosed type 1 diabetes in patients with (□) or without (■) GADAb. n = number of patients.

Table 1—Profiles of fulminant and autoimmune type 1 diabetic patients

	Fulminant	Autoimmune
<i>n</i>	161	137
Clinical characteristics		
Duration of symptoms (days)	4.4 ± 3.1	36.4 ± 25.1
Age (years)	39.1 ± 15.7	30.1 ± 16.2
BMI (kg/m <sup>2</sup> )	20.7 ± 3.9	18.8 ± 2.8
Family history of type 1 diabetes	1/160	2/135
Family history of type 2 diabetes	25/119	33/102
Other autoimmune disease	9/85	17/51
Laboratory data 1		
HbA <sub>1c</sub> (%)	6.4 ± 0.9	12.2 ± 2.2
Urinary C-peptide (μg/day)	4.3 ± 4.0	21.0 ± 14.8
Fasting serum C-peptide (nmol/l)	0.10 ± 0.07	0.23 ± 0.13
Peak serum C-peptide (nmol/l)	0.10 ± 0.10	0.40 ± 0.26
Increment of serum C-peptide (nmol/l)	0.03 ± 0.03	0.20 ± 0.20
Accompanying symptoms		
Thirst	93.7	93.3
Body weight loss (kg)	3.5 ± 2.7	5.5 ± 3.7
Flu-like symptoms (total)	71.7	26.9
Fever	60.0	ND
Headache	11.5	ND
Sore throat	25.2	ND
Cough	12.0	ND
Rhinorrhea	7.9	ND
Joint pain	5.5	ND
Abdominal symptoms (total)	72.5	7.5
Nausea, Vomiting	65.4	ND
Upper abdominal pain	39.2	ND
Lower abdominal pain	11.0	ND
Diarrhea	5.5	ND
Drowsiness	45.2	5.3
Pregnancy†	21.0	1.5
Laboratory data 2		
Plasma glucose level (mmol/l)	44.4 ± 20.0	24.1 ± 11.8
Arterial pH	7.125 ± 0.125	7.309 ± 0.124
Serum exocrine pancreatic enzyme level	98/2	17/26
Amylase	74/54	11/81
Elastase-1	54/9	1/37
Lipase	50/9	5/38
Serum sodium level (mEq/l)	131 ± 9	137 ± 4
Serum potassium level (mEq/l)	5.5 ± 1.2	4.3 ± 0.8
Serum chloride level (mEq/l)	94 ± 10	101 ± 5
Serum AST level (IU/l)	49 ± 83	22 ± 17
Serum ALT level (IU/l)	44 ± 51	26 ± 33
Serum total cholesterol level (mmol/l)	5.1 ± 1.6	5.5 ± 1.7
Serum triglycerides (mmol/l)	2.0 ± 1.8	1.3 ± 1.0
Autoantibodies		
Anti-GAD antibody	7/138	114/14
Anti-IA-2 antibody	0/43	31/24
Anti-thyroglobulin antibody	5/63	13/64
Anti-thyroid microsomal antibody	6/59	24/64

Data are means ± SD, %, or *n* (positive/negative). Family history of type 1 or type 2 diabetes given for first-degree relatives. Pregnancy indicates percent female subjects ages 13–49 years who had type 1 diabetes during or after pregnancy in this study (13 of 62 fulminant diabetic subjects and 1 of 68 autoimmune diabetic subjects). Data for serum enzyme levels give number of patients with elevated value of at least one of the three enzymes/patients with no elevated value of the three enzymes. ND, not determined.

tients (35.1 ± 15.8) (*P* = 0.002). The age at onset of fulminant diabetes ranged from 1 year to 80 years. Childhood/adolescent onset of fulminant diabetes (onset before age 20 years) was seen in 14 patients (3 male and 11 female), whereas adult onset was observed in the remaining 147 patients.

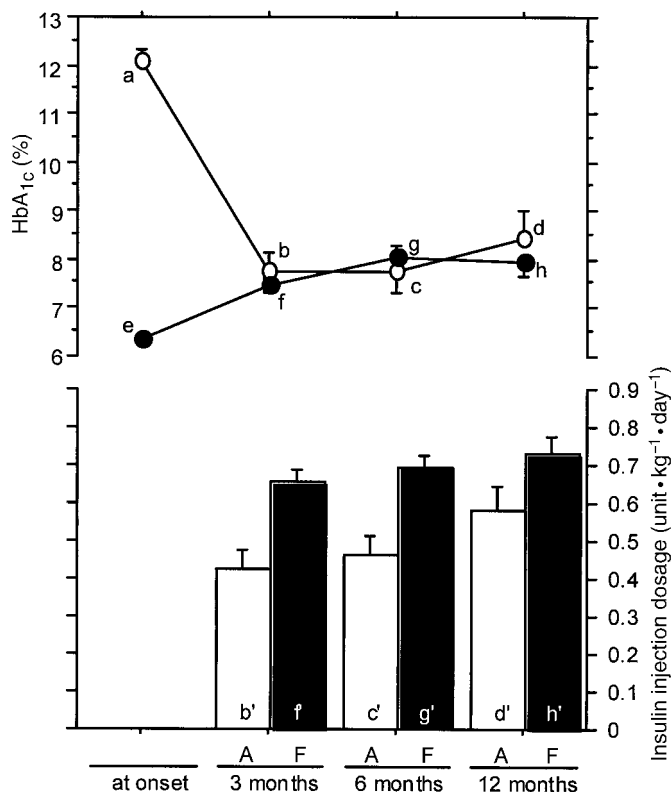
The mean BMI at onset of type 1 diabetes was 20.7 in fulminant type 1 diabetic patients, which was significantly higher than that in autoimmune type 1 diabetic patients. There was no significant difference in the presence of family history of type 1 and type 2 diabetes in first-degree relatives between fulminant and autoimmune diabetes, but autoimmune diseases other than type 1 diabetes were more frequently observed in autoimmune diabetes than in fulminant diabetes (Table 1).

Thirst was the most common symptom accompanying the onset of diabetes and was observed in ~90% of both fulminant and autoimmune type 1 diabetic patients. Lower body weight loss was observed in fulminant diabetes than in autoimmune diabetes.

Flu-like symptoms, abdominal symptoms, and drowsiness were more frequently observed in the fulminant group than in the autoimmune group at disease onset (*P* < 0.0001) (Table 1). Among the flu-like symptoms, fever was the most common and was observed in 60.0% of patients. Nausea, vomiting, or both were also frequent and were observed in 65.4% of patients.

Of the 14 patients who had type 1 diabetes during or after pregnancy in this study, 13 belonged to fulminant subtype (Table 1). Their onset was the 19th week in one patient, the 22nd week in one patient, the 26th week in one patient, the 29th week in one patient, the 30th week in three patients, the 31st week in one patient, the 35th week in one patient, the 36th week in two patients, and the 2nd week after delivery in two patients.

Compared to autoimmune type 1 patients, fulminant type 1 patients showed markedly higher plasma glucose concentrations and significantly lower arterial pH at the first visit (Table 1). At least one of three serum exocrine pancreatic enzyme levels—amylase, elastase-1, or lipase—was increased over the normal range in 98 patients. In the fulminant diabetes group, only 2 patients had normal levels of all these enzymes, whereas in the autoimmune diabetes group, 17 pa-



**Figure 3**—Changes in HbA<sub>1c</sub> levels and insulin injection dosages in fulminant (F) and autoimmune (A) type 1 diabetes during 12 months after the onset. ■, ●, fulminant patients; □, ○, autoimmune patients.  $P < 0.05$  for a vs. b, c, d, and e; b vs. d; e vs. f, g, and h; f vs. g; b' vs. d' and f'; c' vs. d' and g'; d' vs. h'; and f' vs. h'.

tients showed elevated serum levels of at least one of these enzymes and 26 patients showed normal levels of all these enzymes.

As shown in Table 1, fulminant patients had significantly lower serum sodium and chloride levels and significantly higher serum potassium levels than autoimmune patients. Serum ALT and AST levels were significantly higher in the fulminant than in the autoimmune group. Serum triglyceride levels were significantly higher in the fulminant than in the autoimmune patients, but the serum cholesterol level was not significantly different between the two groups.

In the fulminant diabetes group, 4.8% were positive for GADAb, but all were negative for IA-2Ab. Thyroid antimicrobial antibodies were seen significantly more frequently in autoimmune diabetes than in fulminant diabetes patients (Table 1).

**Prognosis.** A patient with fulminant type 1 diabetes died and another patient suffered from cardiac and respiratory arrest at onset. The former patient had been

reported previously (16). None of the autoimmune type 1 diabetic patients suffered from such episodes. The other fulminant and autoimmune type 1 diabetes patients survived the metabolic disorder at onset.

Mean HbA<sub>1c</sub> levels were not significantly different between fulminant and autoimmune type 1 diabetic patients at 3, 6, or 12 months after the onset of overt diabetes. Insulin injection dosages were significantly higher in fulminant than in autoimmune diabetic patients 3, 6, and 12 months after the onset (Fig. 3).

**CONCLUSIONS**— Our present study confirmed 161 cases of fulminant type 1 diabetes distributed all over Japan, and clearly showed that fulminant type 1 diabetes is a distinct subtype within type 1 diabetes judging from the clinical characteristics, such as autoantibody status. Several new findings regarding fulminant type 1 diabetes were also confirmed by this nationwide survey: 1) fulminant diabetes accounted for ~20% of Japanese type 1 diabetes with ketosis or ketoacido-

sis at onset; 2) few patients were children or adolescents, and >90% of patients were adults; 3) male patients accounted for ~50% of all cases; 4) flu-like symptoms, especially fever, were frequently observed at onset; and 5) almost all female patients who developed type 1 diabetes during pregnancy had the fulminant type.

This nationwide survey indicated that fulminant type 1 diabetes is a major subtype in Japan. Several cases similar to fulminant type 1 diabetes have been reported in Japan after (16–23) and even before (8–12) Imagawa et al. proposed this novel subtype. However, few cases have been reported from Western countries (24–27). The number of fulminant type 1 diabetes in Caucasians might be relatively small, and therefore this subtype might have been disregarded among the majority of autoimmune type diabetes cases; however, the fulminant subtype does not appear to be rare, at least in the Japanese population.

Second, >90% of fulminant type 1 diabetic patients were adults and no sex difference was observed among cases. The incidence of type 1 diabetes in Japanese children is 0.8 people/10,000 person-years and lower than the incidence in European countries (28); however, type 1 diabetes is not a rare disease. Nonetheless, few cases of fulminant diabetes were reported in the Japanese children or adolescents in this study. These findings suggested that fulminant type 1 diabetes is most likely an adult-onset disease. Female sex was predominant in autoimmune type diabetes.

Third, flu-like symptoms were significantly more frequent in fulminant type than in autoimmune type diabetes. Fever was the most common among such symptoms. In addition to the markedly acute clinical course at onset, this finding suggests that fulminant diabetes may be associated with viral infection. On the other hand, other frequent symptoms such as nausea, vomiting, and drowsiness could be attributable to severe metabolic acidosis in fulminant diabetes at onset. Another important finding was that fulminant diabetes accompanied pregnancy in 21.0% of females ages 13–49 years, and the incidence clearly increased in the third trimester of pregnancy. This finding was compatible with the fact that the incidence of type 1 was tripled in the third trimester (29).

In addition, the present study also

confirmed the basic characteristics of fulminant type 1 diabetes proposed by Imagawa et al. (13): 1) markedly acute onset of diabetes, 2) severe metabolic disorder, and 3) elevated levels of serum pancreatic enzymes. The plasma glucose concentration in fulminant patients was 800 mg/dl, higher than that of autoimmune patients, whereas HbA<sub>1c</sub> levels of fulminant patients were only slightly higher than the upper limit of normal range. More severe derangement of serum electrolytes was observed in fulminant patients. Loss of consciousness was more frequently observed in fulminant diabetic patients. Lower body weight loss and higher BMI of fulminant patients would indicate shorter duration of hyperglycemic period. The elevation of serum pancreatic enzyme levels was also characteristic of fulminant type 1 diabetes, although these levels can be raised as a consequence of ketoacidosis.

It was also shown that islet-related autoantibodies were seldom positive in fulminant diabetes. In this study, we recruited patients irrespective of the presence or absence of autoantibodies, and it turned out that only 4.8% of fulminant diabetes patients were positive for GADAb and none were positive for ICA and IA-2Ab. Therefore, fulminant type 1 diabetes would be classified as one subtype of idiopathic (type 1B) diabetes, according to the ADA/WHO classification.

Whether or not the pathogenesis of fulminant type 1 diabetes is associated with autoimmunity is still unknown. Tanaka et al. (16) have reported insulinitis in an autopsy case of fulminant type 1 diabetes, who died soon after the onset of the disease. Shimada and colleagues reported a fulminant diabetic patient with elevated serum interferon- $\gamma$ -inducible protein levels (19) and another patient with increased prevalence of GAD-reactive peripheral T-cells (23). These findings suggest that fulminant type 1 diabetes is autoimmune related. However, the prevalence of islet-related autoantibodies in fulminant diabetes was extremely low in the present study. The original report of Imagawa et al. (13) showed neither insulinitis nor hyperexpression of MHC class I antigens in islets in all three patients. These findings suggest that fulminant type 1 diabetes is not caused by autoimmunity. Another candidate for the pathogenesis of fulminant diabetes would be viral infection. A frequent flu-like symptom, especially fever at onset in ful-

minant diabetes, was observed in this study. Two case reports described fulminant diabetes that developed after the reactivation of human herpes virus-6 or the infection of herpes simplex virus (17,22). These findings suggest an association of viral infection to fulminant diabetes.

In conclusion, fulminant type 1 diabetes accounts for ~20% of the ketosis-onset type 1 diabetic patients in Japan. Flu-like symptoms, especially fever, are characteristic features around the onset of the disease. Metabolic derangement is more severe in this subtype than in autoimmune type 1 diabetes. The mechanism of  $\beta$ -cell death in fulminant type 1 diabetes should be further investigated, with special attention given to viral infection and autoimmunity. Even a single case report of fulminant type 1 diabetes in other countries would help improve the understanding of this subtype. A worldwide survey should be carried out in the future.

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