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Fulminant type 1 diabetes as a high risk group for diabetic microangiopathy—a nationwide 5-year-study in Japan

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Abstract

Aims/hypothesis The aim of the present study was to assess the development of microangiopathy in patients with fulminant type 1 diabetes, a novel subtype of type 1B diabetes.

Materials and methods In a nationwide survey, we followed 41 patients with fulminant type 1 diabetes and 76 age- and sex-matched patients with type 1A diabetes for 5 years. The following data were recorded every 12 months after the onset of diabetes: seven-point blood glucose concentrations, HbA_{1c} level, urinary albumin excretion, serum C-peptide level, blood pressure, daily dosages of insulin, frequency of severe hypoglycaemic episodes, and neurological and fundoscopic examination.

Results The 5-year cumulative incidence of microangiopathy was 24.4% in fulminant type 1 diabetes and 2.6% in type 1A diabetes. In longitudinal studies using the Kaplan–Meier method, the cumulative incidence of each form of microangiopathy was significantly higher in fulminant type 1 diabetes than in type 1A diabetes; retinopathy was 9.8% vs 0% ($p=0.014$), nephropathy 12.2% vs 2.6% ($p=0.015$) and neuropathy 12.2% vs 1.3% ($p=0.010$), respectively. Mean HbA_{1c} levels were similar in the fulminant and type 1A diabetes groups during the follow-up periods. However, the mean M-value, mean insulin dosages and the frequency of severe hypoglycaemic episodes were significantly higher, and the mean postprandial C-peptide level was significantly lower in the fulminant type 1 diabetes group.

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Conclusions/interpretation These data suggest that patients with fulminant type 1 diabetes are a high-risk subgroup for diabetic microangiopathy associated with the lack of endogenous insulin secretion from the onset of diabetes.

Abbreviations

DCCT	Diabetes Control and Complications Trial
DISS	Diabetes Incidence Study in Sweden
GADAb	anti-GAD antibodies
IA-2Ab	anti-insulinoma-associated antigen 2 antibodies
ICA	islet-cell antibodies
NIA	nephelometric immunoassay
SDR	simple diabetic retinopathy
TIA	turbidimetric immunoassay
UAE	urinary albumin excretion

Introduction

Type 1 diabetes mellitus is characterised by an insulin deficiency resulting from the destruction of pancreatic beta cells [1, 2] and is subclassified into type 1A (autoimmune) or type 1B (idiopathic). Recently, a novel subtype of type 1B has been recorded. Referred to as 'fulminant type 1 diabetes,' this new subtype accounts for approximately 20% of Japanese ketosis-onset type 1 diabetes [3, 4]. The clinical characteristics of this subtype of type 1 diabetes are: (1) remarkably abrupt onset of the disease; (2) very short duration (usually less than 1 week) of diabetic symptoms, e.g. polyuria, thirst; (3) acidosis at the time of diagnosis; (4) negative findings for islet-related autoantibodies, such as islet-cell antibodies (ICA), anti-GAD antibodies (GADAb), insulin autoantibodies or anti-insulinoma-associated antigen 2 antibodies (IA-2Ab); (5) virtually no C-peptide secretion (less than 10 μg/day in the urine); (6) elevated serum pancreatic enzyme levels; (7) frequent flu-like symptoms around the time of disease onset; (8) association with pregnancy; and (9) strong association with *HLA-DR4-DQ4* haplotype [3–6].

We have previously reported that fulminant type 1 diabetes showed more severe metabolic acidosis at disease onset than autoimmune type 1A diabetes [3, 4]. However, little is known about chronic complications of fulminant type 1 diabetes. Due to the lack of endogenous insulin secretion from the onset, strict glycaemic control is usually difficult and blood glucose levels tend to be erratic, as in brittle diabetes, even with intensified insulin treatments. Brittle diabetes itself is one of the risk factors for microangiopathy [7]. These phenomena prompted us to hypothe-

sise that patients with fulminant type 1 diabetes may have higher risks of developing microangiopathic complications. To date, the precise clinical course of diabetic complications of fulminant type 1 diabetes has not been reported.

The aim of the present study was to assess the development of microvascular complications in fulminant type 1 diabetes of 5 years duration in comparison with acute-onset type 1A diabetes in a nationwide survey in Japan.

Subjects and methods

Subjects We examined 41 patients with fulminant type 1 diabetes. These patients were diagnosed between 1989 and 2001, and had been followed for 5 years since the disease onset [4]. This study was conducted in accordance with the agreed standardised protocol of the centres involved. Inclusion criteria for fulminant type 1 diabetes in this study were: (1) ketosis or ketoacidosis at the onset of diabetes; (2) duration of hyperglycaemic symptoms before the diagnosis of diabetes <7 days; (3) insulin dependence, both at the onset and 6 months later; (4) absence of GADAb, ICA or IA-2Ab; (5) HbA$_{1c}$ <8.5% on the first visit; and (6) fasting serum C-peptide <0.1 nmol/l or serum C-peptide <0.17 nmol/l after glucagon injection or meal load soon after disease onset [3, 4].

As control subjects with type 1A diabetes, we asked 22 hospital doctors at the participating centres to recruit type 1A diabetic patients whose age and sex were matched to each patient with fulminant type 1 diabetes. The patients with classical acute-onset type 1A diabetes were diagnosed between 1981 and 2001 and had been followed for 5 years. Inclusion criteria for classical acute-onset type 1A diabetes were: (1) presence of ketoacidosis at the onset of diabetes; (2) duration of hyperglycaemic symptoms before insulin therapy of <3 months; (3) insulin replacement therapy required throughout the study period; and (4) presence of at least one islet-related autoantibody (GADAb, ICA or IA-2Ab). Patients with slowly progressive type 1 diabetes or latent autoimmune diabetes of adults were excluded from this study.

All patients except three with type 1A diabetes were receiving intensive insulin injection therapy. Intensive insulin injection therapy was defined as multiple daily injections with preprandial insulin regular, lispro or aspart, and with once- or twice-daily insulin NPH or glargine. All patients were instructed on self-monitoring of blood glucose. Patients were usually followed every month and insulin doses were adjusted to target near normal blood glucose levels (<7 mmol/l before meals, <10 mmol/l 2-h postprandial). No patient had hypertension or took antihypertensive drugs, including angiotensin receptor blockers or ACE inhibitors.

The following data were examined and recorded every 12 months after the onset of diabetes in each hospital: seven-point (preprandial and 120-min postprandial for each meal and bedtime) capillary blood glucose concentrations, HbA_{1c} level, urinary albumin excretion (UAE), serum C-peptide level (fasting or postprandial), body weight, blood pressure and status of diabetic complications. Seven-point blood glucose concentrations and postprandial serum C-peptide levels were available in 28 and 22 of 41 fulminant type 1 diabetic subjects and in 42 and 38 of 76 type 1A subjects, respectively. Daily dosages of insulin injections and frequency of severe hypoglycaemic episodes in the previous 12 months were also recorded. Severe hypoglycaemic episodes were defined as events with severe neurological dysfunction such as seizure or loss of consciousness and/or events that required the assistance of someone other than the patient for treatment. Data were analysed as mean of 5 years' measurements of the patients.

This study was approved by the ethics committee of the Japan Diabetes Society, and informed consent was obtained from all subjects.

Complication assessment Fundoscopic examinations were performed through dilated pupils by ophthalmologists in each hospital and classified as: (1) no evidence of diabetic retinopathy; (2) simple diabetic retinopathy (SDR); and (3) pre-proliferative retinopathy or proliferative retinopathy [8]. This classification corresponds to levels 10, 21/10 to 31/31, 41/<41 to 51/51 and 60+/<60+ to 60+/60+, as defined in the Wisconsin study [9–11]. Retinopathy was defined as the appearance of SDR or more severe grade in one eye. Normo-, micro- and macroalbuminuria were defined as having UAE <30 mg/g creatinine, 30 to 299 mg/g creatinine and ≥300 mg/g creatinine, respectively [12]. Nephropathy was defined as a UAE equal to or greater than 30 mg/g creatinine from consecutive random sterile samples in the absence of both urinary tract infection and/or haematuria. Neuropathy was defined as the presence of decreased or absent Achilles' tendon reflex.

Laboratory measurements HbA_{1c} levels were measured by high-performance liquid chromatography, which was standardised across the centres using the Tosoh and Kyoto Daiichi calibration methods (inter-laboratory CVs: <5%; normal range: 4.3–5.8%) [13]. GADAb, ICA and IA-2Ab were determined at the onset of diabetes and serum C-peptide levels were measured, as previously described [3–5]. Urinary albumin concentrations were determined by turbidimetric immunoassay (TIA) or nephelometric immunoassay (NIA) using commercial kits. TIA was used in 19 hospitals and NIA in the other three hospitals. These two assays for measuring UAE have been reported to be well correlated ($r \geq 0.97$) [14], although a direct comparison

between them was not performed in this study. These assays were not centralised; however, all laboratories have participated in quality control procedures using commercially available kits (TIA kit: Wako Pure Chemical, Mitsubishi Chemical or Nittobo, Tokyo, Japan; NIA kit: Dade Behring Diagnostic, Marburg, Germany). Thus, the values of the two assays are considered to be reasonably comparable. Based on the seven-point capillary glucose profile, the *M*-value was calculated [15]. This parameter is a quantitative measure of the deviation of several blood glucose values in a specified time-period from an arbitrarily selected point (e.g. 5.0 mmol/l). The deviation index (δ) of each individual glucose value (γ) is first calculated as $\delta = (10 \times \log{[\gamma/5.0]})^3$. The *M*-value is the average of all the individually calculated deviation indices ($\sum \delta / n$).

Statistical analysis The Kolmogorov–Smirnov test was used to identify Gaussian distribution. Statistical differences between groups for continuous variables were analysed with the Student's *t* test for Gaussian parameters, the Mann–Whitney *U* test for non-Gaussian data or with Fisher's exact probability test for categorical variables. The cumulative free incidence rate of each diabetic complication was compared using the Kaplan–Meier method (95% CIs) with log-rank test. Multiple logistic regression analysis was performed to evaluate the relationship between patients versus patients without retinopathy, nephropathy or neuropathy (categorical variable, yes or no) and other variables. Independent variables included in the analysis were age, mean postprandial C-peptide levels and mean HbA_{1c} levels. Data are presented as mean±SD unless otherwise specified. A two-sided $p<0.05$ was considered statistically significant.

Results

Baseline characteristics The baseline characteristics of fulminant and type 1A diabetic subjects are shown in Table 1. HbA_{1c} and fasting serum C-peptide levels at onset were significantly lower in fulminant type 1 diabetic patients than in the type 1A patients.

Characteristics during follow-up of fulminant and type 1A diabetic patients During the 5 years after onset, ten out of 41 patients (24.4%) in the fulminant type 1 diabetic group and two out of 76 (2.6%) in the type 1A group developed microangiopathy. In longitudinal studies using the Kaplan–Meier method, the cumulative incidence of each microangiopathy was significantly higher in patients with fulminant type 1 diabetes than in patients with type 1A diabetes (Table 2). Mean UAE was significantly higher in

Table 1 Baseline characteristics of the fulminant and type 1A diabetic patients

	Fulminant	Type 1A	p value
N	41	76	
Sex (male/female)	21/20	33/43	NS[a]
Age (years)	38 (14–77)	33 (17–63)	NS[b]
GADAb, ICA or IA-2Ab positive	0 (0)	76 (100)	<0.0001[a]
Fasting serum C-peptide (nmol/l)	0.05±0.02	0.16±0.09	0.034[c]
HbA$_{1c}$ at onset (%)	6.4±0.5	11.4±1.4	<0.0001[c]

Data are n (%), mean±SD or median (range)
[a] Fisher's exact probability test
[b] Mann–Whitney U test
[c] Student's t test

patients with fulminant type 1 diabetes than in type 1A diabetic patients. Mean HbA$_{1c}$ levels were similar in both groups during the follow-up period. However, the mean M-value, mean insulin dosages and the frequency of severe hypoglycaemic episodes were significantly higher in patients with fulminant type 1 diabetes than in patients with type 1A diabetes. Blood pressure and body weight did not differ between the two groups. Significantly lower levels of mean postprandial C-peptide were observed in fulminant type 1 diabetic subjects. We also compared the clinical characteristics (including cumulative incidence of each complication) of subjects in whom C-peptide data were obtained and of subjects in whom these data were not obtained; no significant differences were observed in any

Table 2 Cumulative incidence of diabetic microangiopathy and other clinical parameters during follow-up of the fulminant and type 1A diabetic patients

	Fulminant	Type 1A	p value
Retinopathy	4 (9.8)	0 (0)	0.014[d]
Nephropathy	5 (12.2)	2 (2.6)	0.015[d]
Neuropathy	5 (12.2)	1 (1.3)	0.010[d]
UAE (mg/g creatinine)[a]	8.8 (5.9–11.8)	4.4 (1.7–7.1)	<0.0001[e]
Systolic blood pressure (mmHg)[a]	117±10	117±11	NS[f]
Diastolic blood pressure (mmHg)[a]	72±6	70±7	NS[f]
HbA$_{1c}$ (%)[a]	7.4±1.2	7.7±1.8	NS[f]
M–value[a,b]	29.2±13.5	23.0±15.3	0.047[f]
Insulin dose (U/kg)[a]	0.76±0.22	0.60±0.21	0.0001[f]
Postprandial serum C–peptide (nmol/l)[a,c]	0.08±0.04	0.24±0.15	0.0007[f]
Severe hypoglycaemia (n per year per person)	0.3±1.0	0.0±0.1	0.018[f]

Data are n (%), mean±SD or median (interquartile range)
[a] Mean or median of 5 years of measurements in patients
[b] $n=28$ in fulminant and $n=42$ in Type 1A, respectively
[c] $n=22$ in fulminant and $n=38$ in Type 1A, respectively
[d] Kaplan–Meier method with log–rank test
[e] Mann–Whitney U test
[f] Student's t test

variables between these two groups, either in the fulminant type 1 or in the typical type 1A diabetic subjects. Postprandial C-peptide levels in the fulminant type 1 diabetic group remained low during the 5 years after onset.

Characteristics of fulminant type 1 diabetic patients according to microangiopathic status Fulminant type 1 diabetic patients with microangiopathy had significantly higher mean HbA$_{1c}$ and mean M-value levels than those without microangiopathy (Table 3). Fisher's exact probability test showed that patients with retinopathy tended to have nephropathy ($p=0.06$) and neuropathy ($p=0.06$), but these findings were not statistically significant. Multiple logistic regression analysis showed that mean HbA$_{1c}$ and mean postprandial C-peptide levels were independent risk factors for retinopathy ($\beta=0.29$, $p=0.04$; $\beta=-0.27$, $p<0.05$, respectively) and for neuropathy ($\beta=0.39$, $p=0.01$; $\beta=-0.25$, $p<0.05$, respectively), but not for nephropathy. Characteristics, including grading of retinopathy and nephropathy, of the patients with fulminant type 1 diabetes and microangiopathy are shown in Table 4. There were no differences in sex, age, blood pressure, insulin dosages, postprandial C-peptide levels or frequency of severe hypoglycaemic episodes between those with and without micoangiopathy.

Discussion

In the present study, we found a high cumulative incidence of diabetic microangiopathies in patients with fulminant

Table 3 Characteristics of the fulminant type 1 diabetic patients with or without microangiopathy

	With	Without	p value
N	10	31	
Sex (male/female)	6/4	15/16	NS[d]
Age (years)	46 (24–58)	37 (14–77)	NS[e]
Systolic blood pressure (mmHg)[a]	119±7	117±12	NS[f]
Diastolic blood pressure (mmHg)[a]	72±4	72±7	NS[f]
HbA$_{1c}$ (%)[a]	8.2±0.7	7.1±0.5	0.036[f]
M-value[a,b]	36.5±13.5	25.2±12.0	0.031[f]
Insulin dose (U/kg)[a]	0.8±0.2	0.8±0.3	NS[f]
Postprandial serum C-peptide (nmol/l)[a,c]	0.07±0.02	0.08±0.03	NS[f]
Severe hypoglycaemia (n per year per person)	0.3±0.7	0.3±0.7	NS[f]

Unless otherwise stated, data are mean±SD or median (range)
[a] Mean of 5 years of measurements in patients
[b] $n=18$ and [c] $n=12$ in patients without microangiopathy
[d] Fisher's exact probability test
[e] Mann–Whitney U test
[f] Student's t test

Table 4 Characteristics of the fulminant type 1 diabetic patients with microangiopathy at 5th year

Characteristic	Case									
	1	2	3	4	5	6	7	8	9	10
Age/sex (years/ male or female)	57/M	58/M	24/F	45/F	32/F	47/M	29/F	36/M	54/M	47/M
Retinopathy (levels)	SDR (31/31)	SDR (21/10)	SDR (21/21)	SDR (21/21)	NDR	NDR	NDR	NDR	NDR	NDR
UAE (mg/g Cr)	113	39.7	28	9.2	136	39.5	83.3	5.7	14.5	3.9
Neuropathy (+ or −)	+	−	+	−	−	−	−	+	+	+
HbA$_{1c}$ (%)[a]	10.1±0.9	6.9±0.5	8.3±1.2	9.6±0.7	6.3±0.7	7.2±0.2	7.5±0.2	8.0±0.6	11.2±1.7	7.4±0.4
M-value[a]	22.2±17.3	43.2±17.3	59.6±18.0	ND	39.7±6.7	36.7±9.1	47.7±6.7	32.7±27.8	40.3±11.0	10.6±4.8
Postprandial serum C-peptide (nmol/l)[a]	0.05±0.02	0.04±0.04	0.03±0.03	0.08±0.00	0.08±0.00	0.05±0.06	0.06±0.01	0.08±0.02	0.08±0.03	0.05±0.06

[a] Mean±SD of 5 years of measurements in each patient

Cr, creatinine; NDR, no evidence of retinopathy; ND, not determined

type 1 diabetes during the first 5 years after diagnosis. For example, the cumulative incidence of retinopathy in fulminant type 1 diabetic patients was 9.8%, significantly higher than the 0% in type 1A patients. The high incidence is notable compared with the result of the nationwide population-based Diabetes Incidence Study in Sweden (DISS) [11]. DISS resembled our study because all patients were adolescents and adults who were followed from disease onset and had mean HbA$_{1c}$ of 7.5% at follow-up. In the type 1 diabetic cohort of the DISS, cumulative incidence of retinopathy was approximately 5% during the 5 years after onset. The Diabetes Control and Complications Trial (DCCT) [16] also showed a less frequent rate of retinopathy in the intensively treated group of the primary prevention cohort than that in our fulminant diabetic group during the first 5 years. Considering these results, patients with fulminant type 1 diabetes have a higher risk of developing diabetic microangiopathy than type 1 diabetic patients overall.

The rapid appearance of diabetic microangiopathy is accompanied by unstable blood glucose control in fulminant type 1 diabetic patients. During the follow-up period, the mean M-value, mean insulin dosages and the frequency of severe hypoglycaemic episodes in the fulminant type 1 diabetic group were significantly higher than those in the type 1A diabetic group, while mean HbA$_{1c}$ values were similar in both groups. Of course, HbA$_{1c}$, which reflects mean blood glucose concentration for the preceding 1–2 months, is the most important determinant of the progression of diabetic microangiopathy, as shown in the DCCT, where a 2% reduction of HbA$_{1c}$ reduced the mean risk of developing diabetic retinopathy by 76% [17]. In our 5-year study, too, the mean HbA$_{1c}$ level was significantly higher in fulminant type 1 diabetic patients with micro-

angiopathy than in those without. In addition, elevated HbA$_{1c}$ was an independent risk factor for retinopathy and neuropathy in patients with fulminant type 1 diabetes. However, our results suggest that the degree of fluctuation in blood glucose concentration indicated by an increased M-value is also associated with the complications.

Unstable blood glucose control in type 1 fulminant diabetic patients is associated with the extremely low insulin-producing capacity of such patients in the present study. The mean postprandial C-peptide levels were significantly lower in fulminant diabetic patients than those in type 1A diabetic patients. They were almost undetectable even at the onset of diabetes and throughout the study in fulminant diabetic patients. An inverse correlation has also been reported between residual beta cell function and the degree of glycaemic instability [18]. In the DCCT, the 138 of 412 patients in the intensive treatment group who responded to mixed meal stimulation for C-peptide at baseline had a lower risk of hypoglycaemic events than those who did not respond [19]. In addition, those responders showed a lower risk of diabetic retinopathy and nephropathy than non-responders. A negative relationship between preserved beta cell function and progression of diabetes complications has also been shown in other studies [20–22]. Logistic regression analysis showed that decreased C-peptide secretion was a risk for retinopathy and neuropathy in this study. All these findings suggest that depleted and irreversible loss of insulin production is associated with unstable blood glucose control and thereby a high incidence of diabetic microvascular complications in fulminant type 1 diabetic patients.

Our present study also shows that postprandial C-peptide levels did not recover, at least not over a 5-year period from disease onset in fulminant type 1 diabetes. C-peptide is

considered to be a good marker of insulin secretion and has no biological activity of its own. However, over the last decade, several reports have suggested that C-peptide may exert a number of physiological effects, which are probably mediated by stimulation of Na$^+$,K$^+$-ATPase and endothelial nitric oxide synthetase activities in several tissues [23]. In the early stage of type 1 diabetes, C-peptide replacement results in diminished UAE rate and ameliorates nerve dysfunction [24]. Based on these findings, lack of C-peptide itself might be one of the causal factors in the development of microangiopathy in fulminant type 1 diabetic patients.

While the aetiology of fulminant type 1 diabetes is not clear, substantial regeneration of pancreatic beta cells was found to be impossible in this subtype, as well as in conventional type 1A diabetes [19]. Early progression of diabetic complications and long-standing unstable blood glucose control might necessitate a more aggressive intervention, such as islet-transplantation from living donors [25], in fulminant type 1 diabetes.

In conclusion, the present study suggests that fulminant type 1 diabetes represents a high-risk subgroup for diabetic microangiopathy. The condition is associated with extremely low beta cell function from the onset of diabetes, although our sample size is small and our follow-up period is short. The establishment of a therapeutic approach for fulminant type 1 diabetes is an important task for the future.

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