INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Incidence and Development of Diabetic Microangiopathy of Fulminant Type 1 Diabetes —Comparison with Non-fulminant Type 1 Diabetes—

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Abstract

Objective The data from the Fulminant Type 1 Diabetes Committee suggested that patients with fulminant type 1 diabetes are a subgroup at high risk for diabetic microangiopathy in the first 5 years after diagnosis associated with the lack of endogenous insulin secretion from the onset of diabetes. The aim of this study was to assess the development of microangiopathy in patients with fulminant type 1 diabetes followed in our diabetes center.

Methods Sixteen patients with fulminant type 1 diabetes and 60 age-matched patients with non-fulminant type 1 diabetes were recruited as subjects. The existence or lack of diabetic retinopathy and nephropathy, average HbA_{1C} level, serum C-peptide level, average blood pressure, insulin level, whether or not they were taking antihypertensive agents, and smoking history were investigated retrospectively based on medical records.

Results The 5-year incidence of microangiopathy was lower in fulminant than in non-fulminant type 1 diabetes patients; retinopathy cases occurred in 0% vs. 8.3% of patients, and nephropathy occurred in 0% vs. 1.7% of patients. The 10-year incidence of retinopathy was 0% vs. 24.1%, and that of nephropathy was 11.1% vs. 3.4%. The cumulative incidence of microangiopathy did not differ between the fulminant and non-fulminant type 1 diabetes patients. Mean HbA_{1C} levels and systolic blood pressure were significantly lower in fulminant type 1 diabetes patients.

Conclusion No difference between the patients visiting the center with fulminant type 1 diabetes and those with non-fulminant type 1 diabetes was observed in the development of microangiopathy complications.

Key words: fulminant type 1 diabetes, retinopathy, nephropathy

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Introduction

Fulminant type 1 diabetes, for which the period between the advent of symptoms and the onset is very short, is a form of diabetes that occurs as a result of the rapid and complete breakdown of pancreatic β cells (1, 2). Because endogenous insulin secretion is depleted starting from early onset, uneven blood glucose levels and serious low glucose levels are often observed in fulminant type 1 diabetes patients, and it is predicted to have clinical conditions resembling those of brittle diabetes (3), which is reported to have a high risk of the onset of microangiopathy. The Fulminant Type 1 Diabetes Research and Study Committee reported that fulminant type 1 diabetes patients are among those of the high-risk group, where microangiopathy complications tend to occur and develop (4).

We have reported that the mortality and incidence of end-stage renal disease in patients with type 1 diabetes in our diabetes center were significantly lower than those in general hospitals (5). This time, we investigated whether the patients with fulminant type 1 diabetes visiting our center for treatment tended to develop microangiopathy complications and compared these results with those from cases of non-fulminant type 1 diabetes, as reported by a nationwide survey.

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Table 1. Cumulative Incidence of Diabetic Microangiopathy and Other Clinical Parameters during Follow-up for 5 Years

	Fulminant	Non-fulminant	p value
N	16	60	
Sex (male/female)	11/5	28/32	NS[a]
Onset age (years)	40.0 ± 11.1	41.8 ± 12.6	NS[b]
BMI at onset (kg/m^2)	19.9 ±3.0	19.7 ±3.0	NS[b]
Fasting serum C-peptide (ng/mL)	0.24 ± 0.11	0.71 ± 0.38	<0.01[c]
HbA_{1c} at onset	6.27 ± 0.79	11.8 ± 2.69	<0.0001[c]
Retinopathy (%)	0 (0)	5 (8.3)	NS[d]
Nephrophy (%)	0 (0)	1 (1.7)	NS[d]
ACR (mg/g・Cr)	6.7 ± 3.1	9.3 ± 13.2	NS[b]
Systolic blood pressure (mmHg)	121 ± 10	122 ± 14	NS[c]
Diastolic blood pressure (mmHg)	77 ± 5	74 ± 8	NS[c]
Mean HbA_{1c} (%)	6.9 ± 0.6	8.5 ± 1.8	<0.0001[c]
Insulin dose at onset (U/kg)[e]	0.57 ± 0.12	0.40 ± 0.19	<0.0001[c]
Insulin dose at 5th year (U/kg)	0.80 ±0.25	0.67 ±0.23	NS[c]
Smoking (yes/no)	7/9	26/34	NS[a]

mean ± SD

[a]Fisher's exact probablity test
[b]Mann-Witney U test
[c]Student's *t* test
[d]Kaplan-Meier method with log-rank test
[e]n=14 in fulminant, and n=59 in non-fulminant

Methods

Subjects were 16 patients with fulminant type 1 diabetes (FT1DM) who had been clinically followed up for more than five years, selected from among those who developed diabetes after 18 years of age between 1989 and 2002 and had been visiting the center since the onset, and 60 patients with non-fulminant type 1 diabetes (NFT1DM), whose ages were matched with the subjects with fulminant type 1 diabetes. The existence or lack of diabetic retinopathy and nephropathy, average HbA_{1C} level, serum C-peptide level (CPR), average blood pressure, insulin level, whether or not they were taking antihypertensive agents, and smoking history for the five years after onset were investigated backwardly based on medical records. From among the above cases, the investigation of 9 patients with FT1DM and 29 patients with NFT1DM who had been clinically followed up for ten years after the onset was continued following these first ten years.

The selection criteria for fulminant and non-fulminant type 1 diabetes

The selection criteria for fulminant type 1 diabetes were: 1) ketosis or ketoacidosis for approximately one week after the onset of diabetes, 2) blood glucose level of more than 288 mg/dL and HbA_{1C} level of less than 8.5% at the initial visit, and 3) urine CPR <10 μg/day at the time of onset, serum CPR <0.3 ng/mL while fasting, or serum CPR <0.5 ng/mL after glucagon loading (or two hours after a meal) (6). The diagnostic criteria for non-fulminant type 1 diabetes were: 1) a symptomatic period before the diagnosis of three months or less in length, 2) the patient developed ketosis or DKA and start of insulin treatment at around the time of the diagnosis, and insulin treatment was necessary at six months after the onset, 3) in the cases where pancreatic islet-related autoantibodies were negative, insulin secretion was markedly less (urine CPR<20 μg/day, serum CPR<0.5 ng/mL while fasting, or serum CPR<1.0 ng/mL after loading), and 4) in the cases where pancreatic islet-related autoantibodies were positive and the above 1) and 2) were satisfied.

Diagnosis of retinopathy and nephropathy

Eye complications were recognized as retinopathy when they were diagnosed as more than simple retinopathy during a regular examination by an ophthalmologist. Kidney complications were recognized as nephropathy when albumin levels were more than 30 mg/g・Cr on more than two occasions when tested by regular early morning urine albumin tests.

Statistical analysis

For the comparison between the two groups, the Student's t test was used for the equally distributed continuous variables, the Mann-Whitney test for unequally distributed continuous variables, and Fisher's exact probability test for category variables. The log rank test of the Kaplan-Meier method was used to compare the onset of microagiopathy. $p<0.05$ was regarded as statistically significant.

Results

The clinical conditions five years after the onset of diabetes

Table 1 shows the clinical backgrounds of the two groups in the 5th year after the onset of diabetes. As clearly shown by the diabetes definitions of the two groups, there are sig-

Table 2. Cumulative Incidence of Diabetic Microangiopathy and Other Clinical Parameters during Follow-up for 10 Years

	Fulminant	Non-fulminant	p value
N	9	29	
Sex (male/female)	5/4	14/15	NS[a]
Onset age (years)	40.7 ± 9.2	40.7 ± 11.9	NS[b]
BMI at onset (kg/m^2)	19.3 ±1.5	19.5±2.6	NS[b]
Fasting serum C-peptide (ng/mL)	0.25 ± 0.15	0.64 ± 0.27	<0.0001[c]
HbA_{1c} at onset	6.4 ± 1.0	12.1 ± 3.0	<0.0001[c]
Retinopathy (%)	0 (0)	7(24.1)	NS[d]
Nephrophy (%)	1 (11.1)	1 (3.4)	NS[d]
Systolic blood pressure (mmHg)	118 ± 7	125 ± 10	<0.05[b]
Diastolic blood pressure (mmHg)	75 ± 4	76 ± 6	NS[c]
Mean HbA_{1c} (%)	7.1 ± 0.7	8.5 ± 1.6	<0.0001[c]
Insulin dose at onset (U/kg)	0.63 ± 0.22	0.43 ± 0.21	<0.05[c]
Insulin dose at 10th year (U/kg)	0.77 ±0.27	0.78 ±0.20	NS[c]
Smoke (yes/no)	4/5	13/16	NS[a]

[a]Fisher's exact probablity test
[b]Mann-Witney U test
[c]Student's *t* test
[d]Kaplan-Meier method with log-rank test

mean ± SD

nificant differences between the two groups in endogenous insulin secretion abilities and HbA_{1C} levels at the onset of diabetes.

The clinical conditions five years after the onset of diabetes are also shown in Table 1. Although there were no patients who developed retinopathy or nephropathy in the FT1DM group, there were five patients who developed retinopathy and one who developed nephropathy in the NFT1DM group (60 subjects). However, no significant difference between the two groups in the development of microangiopathy was observed. During these five years, the average HbA_{1C} level was significantly lower and the insulin usage at the time of the onset of diabetes was significantly higher in the FT1DM group. There was no significant difference between the two groups in average blood pressure (Table 1). All cases of retinopathy diagnosed within five years of the onset of diabetes spontaneously disappeared, and nephropathy was considered to be affected by nephrosclerosis.

The clinical conditions ten years after the onset of diabetes

The conditions ten years after the onset of diabetes are shown in Table 2. In the FT1DM group (9 subjects), there was no case of retinopathy, but there was one case of nephropathy. In the NFT1DM group (29 subjects) there were seven cases of retinopathy and one case of nephropathy. However, there was no significant difference between the two groups in the development of microangiopathy. The average systolic blood pressure and average HbA_{1C} level were significantly lower in the FT1DM group. However, there were no differences between the two groups in average diastolic blood pressure or insulin usage 10 years after the onset of diabetes.

Characteristics of the fulminant and non-fulminant type 1 diabetes patients with or without microangiopathy

Next, the FT1DM and NFT1DM groups were combined and then divided into two groups according to the presence or absence of microangiopathy, and the clinical data for these two groups were compared. In the microangiopathy group, there were more females, their ages at the onset of diabetes were significantly higher (47.2±10.5 vs. 40.0±12.0 years old), and their insulin usage five years after the onset of diabetes was significantly higher (0.60±0.24 vs. 0.54± 0.25 U/kg). There were no differences in serum CPR while fasting, average HbA_{1C} level, blood pressure, whether or not the patients smoked, or whether or not they were taking antihypertensive agents (Table 3).

Characteristics of the fulminant type 1 diabetes patients

The clinical data for the 16 subjects of the FT1DM group are shown in Table 4. The disease duration shows the number of years during which clinical follow-ups were conducted. Two cases of retinopathy were observed during the full observation period, both of which were diagnosed ten years after the onset of diabetes. Two cases of nephropathy were observed, which were diagnosed 9.8 and 10.4 years after the onset of diabetes.

Conclusion

No difference in the development of microangiopathy complications was observed between the patients visiting the center with fulminant type 1 diabetes and those with non-fulminant type 1 diabetes. The Diabetes Control and Complications Trial Research Group (DCCT) USA clarified that

Table 3. Characteristics of the Fulminant and Non-fulminant Type 1 Diabetes Patients with or without Microangiopathy

	With	Without	p value
N	18	58	
Sex (male/female)	5/13	34/24	< 0.05[a]
Onset age (years)	47.2 ± 10.5	40 ± 12	< 0.01[b]
BMI at onset (kg/m^2)	19.6 ±2.4	19.8 ±3.1	NS[b]
Fasting serum C-peptide (ng/mL)	0.65 ± 0.34	0.59 ± 0.40	NS[c]
Mean HbA_{1c} (%)	8.5 ± 1.9	8.0 ± 1.6	NS[c]
Systolic blood pressure (mmHg)	122 ± 14	122 ± 13	NS[c]
Diastolic blood pressure (mmHg)	75 ± 7	75 ± 8	NS[c]
Insulin dose at onset (U/kg)	0.40 ± 0.18	0.44 ± 0.19	NS[c]
Insulin dose at 5th year (U/kg)	0.60 ± 0.24	0.54 ± 0.25	<0.05[c]
Smoke (yes/no)	8/10	25/33	NS[a]
Anti-HT drug (yes/no)	2/16	5/53	NS[a]

[a]Fisher's exact probablity test
[b]Mann-Witney U test
[c]Student's *t* test

mean ± SD

Table 4. Characteristics of the Fulminant Type 1 Diabetes Patients

onset age (yrs.)	sex	duration (yrs.)	retino-pathy	duration at diagnosis of retinopathy	nephro-pathy	duration at diagnosis of nephropathy	mean HbA_{1c}(%) ±SD
47	F	16.9	-		-		7.1 ±0.5
33	M	14.2	+	(12.6)	-		5.9 ±0.6
49	F	13.0	+	(10.1)	-		7.4 ±0.7
47	M	11.7	-		+	(9.8)	7.4 ±0.4
49	M	11.1	-		-		6.9 ±0.4
42	F	10.6	-		+	(10.4)	7.7 ±0.4
38	F	6.0	-		-		6.1 ±0.4
35	M	9.4	-		-		8.4 ±0.3
22	M	7.9	-		-		7.3 ±0.6
49	M	6.4	-		-		6.3 ±0.4
38	M	6.1	-		-		5.8 ±0.2
64	M	6.3	-		-		7.9 ±0.4
25	M	6.2	-		-		7.3 ±0.5
27	M	5.0	-		-		7.2 ±0.3
30	M	5.5	-		-		8.0 ±0.4
37	F	5.4	-		-		6.3 ±0.9

intensive blood glucose control can prevent the development of microangiopathy complications in type 1 diabetes (7). It goes without saying that blood pressure control (8, 9), that is important in the prevention of diabetic retinopathy and nephropathy, has been proven to be one of the two biggest factors so far in the prevention of microangiopathy complications. In this research, the average HbA_{1C} level and average systolic blood pressure of the FT1DM group are rather low. As a result, the development of microangiopathy complications was considered to have been prevented in the center's FT1DM patients, which is different from the results of the nationwide survey of FT1DM patients (4).

It has been clarified that decreases in endogenous insulin secretion cause unstable blood glucose control and high HbA_{1C} levels (10, 11), and they are also considered a possible cause of microangiopathy complications in FT1DM. We compared the mean M-value, which is a quantitative measure of the deviation of several blood glucose values in a specific time-period from an arbitrarily selected point (12), between the patients with FT1DM and NFTIDM, and also patients with or without microangiopathy (data not shown). There was no significant difference between these two groups, and our result did not support that unstable blood glucose was observed in patients with FT1DM. Moreover, blood glucose control in the FT1DM patients visiting the center was in relatively good condition, the reason for which is unknown. This is considered to be one of the reasons that since 2000, when the concept of fulminant type 1 diabetes was reported (1), diabetes specialists, who have more often diagnosed patients with type 1 diabetes, have been treating patients with FT1DM. And, the Diabetes Center of Tokyo Women's Medical University has established a system for life-long diabetes care using a multidisciplinary approach, including many diabetes specialists (5).

According to the research conducted by the Center on type 1 diabetes that occurred before 1984, the cumulative incidence rates of preproliferative diabetic retinopathy and overt proteinuria over 10 years of diabetes were 4% and 1%, those over a period of 20 years were 33% and 13%, and those over a period of 28 years were more than 50% and 20%, respectively, and there were many cases where microangiopathy complications occurred ten years or more

after the onset of diabetes (13). In order to clarify whether microangiopathy complications really tend to develop in fulminant type 1 diabetes patients, it is important to carefully and continuously follow-up on their clinical conditions, even more than 10 years after the onset of diabetes.

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