

High Frequency of HLA B62 in Fulminant Type 1 Diabetes with the Drug-Induced Hypersensitivity Syndrome

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Context: Fulminant type 1 diabetes (FT1D) is a subtype of type 1 diabetes characterized by an extremely abrupt onset. FT1D cases associated with the drug-induced hypersensitivity syndrome (DIHS) have recently been reported.

Objective: The clinical characteristics of FT1D associated with DIHS were investigated in this study.

Methods: Case reports of FT1D associated with DIHS in Japanese subjects were collected and analyzed by means of a questionnaire to the authors. A nationwide questionnaire survey was administered to dermatology specialists, concerning the frequency of FT1D associated with DIHS.

Results: In 15 case reports, the mean age at onset of FT1D was 53.4 yr and the mean time for its development from the onset of DIHS was 39.9 d. A higher frequency of human leukocyte antigen (HLA) B62, but not of HLA DR was found in FT1D with DIHS than that for cases without DIHS ($P < 0.001$). The reactivation of herpes virus 6 and cytomegalovirus was detected in 11 and four cases, respectively. Among 746 patients with DIHS in the nationwide survey, four developed FT1D during a 3-yr period. The frequency of FT1D in DIHS (0.54%) was much higher than that in the general Japanese population (0.010%).

Conclusions: The clinical characteristics of FT1D with DIHS were similar to those without DIHS except for the high frequency of HLA B62, which may be involved in the pathogenesis of FT1D with DIHS. Because the frequency was much higher than that in the general Japanese population, FT1D should be kept in mind when DIHS develops. (*J Clin Endocrinol Metab* 97: E2277–E2281, 2012)

Fulminant type 1 diabetes (FT1D) is a subtype of type 1 diabetes (T1D) characterized by an extremely rapid onset, absence of islet-related autoantibodies, and

the nearly complete destruction of pancreatic β -cells (1, 2). FT1D is not rare in the Asian population. Approximately 20% of cases of ketosis-onset T1D in Japan

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Abbreviations: CMV, Cytomegalovirus; DIHS, drug-induced hypersensitivity syndrome; EBV, Epstein-Barr virus; FT1D, fulminant type 1 diabetes; HbA1c, glycated hemoglobin; HHV, human herpes virus; HLA, human leukocyte antigen.

results from FT1D and 7% in Korea. Although genetic and environmental factors, such as human leukocyte antigen (HLA) and viral infections, are associated with FT1D, its pathogenesis is unclear (3).

The drug-induced hypersensitivity syndrome (DIHS) is characterized by severe multi-organ hypersensitivity, with clinical signs that include a rash, fever, lymphadenopathy, leukocytosis, and acute hepatitis (4). The hypersensitivity reaction is triggered by exposure to a limited number of drugs. DIHS has been characterized by the reactivation of human herpes virus (HHV)-6 at 2–4 wk after the onset of DIHS (4). DIHS has been suggested to be a complex pathological condition involving both immunological reactions to a drug and virus reactivation.

Some cases of FT1D have been reported to be associated with DIHS (5, 6), suggesting that the pathogenesis of FT1D could be shared with that of DIHS. However, the clinical features in the FT1D with DIHS remain unknown. To address this question, we analyzed the clinical characteristics of FT1D with DIHS by collecting case reports for Japanese subjects. We also administered a nationwide questionnaire survey to dermatology specialists concerning the frequency of FT1D with DIHS.

Materials and Methods

A literature search in the published articles or the proceedings of the meetings for cases of the abrupt onset of T1D associated with DIHS in the Japanese population was conducted. Of 16 case reports dealing with FT1D with DIHS, 15 were affirmed to be valid cases. Inclusion criteria for FT1D were 1) ketosis or ketoacidosis within 1 wk after the onset of hyperglycemic symptoms; 2) urinary C-peptide excretion below 10 $\mu\text{g/d}$, fasting serum C-peptide below 0.3 ng/ml (0.10 nmol/liter), or serum C-peptide below 0.5 ng/ml (0.17 nmol/liter) after glucagon injection or meal load soon after disease onset; and 3) plasma glucose level above 16.0 mmol/liter (>288 mg/dl) and glycated hemoglobin (HbA1c) below 8.9% at the first visit (2). Basically, FT1D was diagnosed by the attending physician or was based on literature data or answers to the questionnaire. DIHS was diagnosed by dermatology specialists based on the diagnostic criteria for DIHS, the presence of cutaneous eruptions, and systemic symptoms such as liver dysfunction, fever, or hematological abnormalities (leukocytosis, eosinophilia, and/or the appearance of atypical lymphocytes) subsequent to the recent initiation of a specific drug treatment (7). A 4-fold or greater increase in anti-HHV-6 IgG antibody titer was defined as significant (8).

To estimate the frequency of FT1D with DIHS, a nationwide questionnaire survey was administered by mail. The questionnaire was sent to all the hospitals having dermatology specialists and that were providing a clinical training program for dermatology specialists certified by the Japanese Dermatological Association. Dermatology specialists were requested to provide the number of cases of DIHS seen in the hospital and those that developed FT1D from 2007–2009. The questionnaires were sent to 641 hospitals, and 441 replies were obtained. Because we

received only one reply from a representative dermatology specialist in each hospital, no overlapping cases would be expected. Basically, DIHS was diagnosed by dermatology specialists, and FT1D was diagnosed by the physicians. The significance of the difference in the frequency of human leukocyte antigen (HLA) class I or II alleles between patients with FT1D with DIHS, and either those without DIHS or nondiabetic control subjects was determined by Fisher's exact probability test. A binomial test was used for assessing the significance of the difference in the frequency of FT1D between patients with DIHS and the general Japanese population.

Results

We found 15 reported cases (eight males, seven females) of FT1D associated with DIHS in Japan between 1985 and 2010. Their characteristics are summarized in Table 1. There were no differences in morbidity related to sex, in agreement with a previous nationwide survey of FT1D in Japan (2). The mean age at onset of FT1D with DIHS was 53.4 yr (males 50.6, females 55.9), which was older than that without DIHS reported in the nationwide survey (40.0 yr), even when FT1D cases with pregnancy (29.1 yr) were excluded (2). The mean levels of HbA1c and blood glucose at onset was 6.6% (National Glycohemoglobin Standardization Program value), and 617 mg/ml, respectively, similar to the values for FT1D in the nationwide survey. The duration from the onset of DIHS to the development of FT1D was 39.9 d on average.

No islet-related autoantibodies were detected in any of the cases analyzed. Of seven cases in which HLA class I were analyzed, the frequency of B62 was significantly higher than that for either FT1D without DIHS ($P < 0.001$) or nondiabetic controls ($P < 0.001$) (Table 1) (9). The frequency of A24 tended to be higher, but not significantly so. Of 10 cases in which HLA class II were analyzed, no difference was found in HLA class II compared with FT1D without DIHS.

The causative drugs were mexiletine and carbamazepine for three cases, diaminodiphenyl sulfone and allopurinol for two cases, and zonisamide, phenytoin, salazosulapyridine, and minocycline, for one case each. In case 15, a causative drug was not identified, despite the typical symptoms of DIHS. The frequency of the use of an anticonvulsant, such as carbamazepine and phenytoin, appears to be lower (five of 15, 33.3%) than that observed in the previous study for DIHS in Japan (60 of 94; 63.9%) (10).

Of 13 cases in which anti-HHV-6 antibody was examined, reactivation of HHV-6 was detected in 11 cases, but not in two cases (cases 5 and 11). Cytomegalovirus (CMV) reactivation was detected in four cases, in which concom-

TABLE 1. Clinical characteristics of FT1D associated with DIHS

Case	Age (yr)	Sex	Causative drug	Onset of FT1D after DIHS (d)	Virus reactivation		HbA1c (at the time of onset of FT1D) ^a	GADAb (autoantibody)	HLA class I B	HLA class II DR	Underlying disease
					HHV-6	Other viruses					
1	70	F	Mexiletine	16	+	–	5.8	–	B62/B62	DRB1*04:03/*08:03	Arrhythmia
2	46	M	Mexiletine	43	+	ND	6.7	–	B62(5)/B48	DR2/DR4	Type 2 diabetes
3	61	F	Mexiletine	20	+	ND	7.0	–	B52/B62	DR2/DR4	Rheumatic fever, valve replacement
4	77	F	Carbamazepine	22	+	–	6.3	–	ND	DRB1*15:01/*08:03	Post-therapeutic neuralgia
5	63	M	Carbamazepine	14	–	–	6.1	–	ND	ND	Alcoholism
6	19	F	Carbamazepine	35	+	–	7.5	–	B62/B62	DR9	Schizophrenia
7	31	F	DDS	21	+	ND	ND	ND	ND	ND	Livedo reticularis
8	60	F	DDS	24	ND	CMV coxsackie B3	6.2	ICA –	ND	DR4/DRW12(5)	Erythema nodosum
9	40	M	Allopurinol	45	ND	–	ND	ICA –	BW35/BW35	DR4/DRw8	Hyperuricemia
10	69	M	Allopurinol	23	+	CMV	ND	–	ND	ND	Atrial fibrillation, hyperuricemia
11	56	M	Phenytoin	199	–	CMV	7.2	–	ND	ND	Subarachnoid hemorrhage
12	61	M	Zonisamide	14	+	CMV	6.9	–	ND	ND	Cerebral hemorrhage, convulsion
13	19	M	Salazosulphapyridine	89	+	–	6.6	–	ND	DRB1*04:05/*16:02	Drug addiction
14	57	F	Minocycline or Cefdynyle	13	+	–	5.8	–	B44(12)/B61(40)	DRB1*04:05/*13:02	Hepatitis C
15	72	F	Unknown	20	+	–	6.7	–	B13/B62	DRB1*12:02/*14:06	Atrial fibrillation

For virus reactivation, a 4-fold or greater increase in IgG antibody titer was interpreted as significant (+). For autoantibodies, (–) represents negative for GADAb or ICA. DDS, Diaminodiphenyl sulfone; F, female; M, male; ND, not determined or not available; ICA, islet cell antibodies; GADAb, glutamic acid decarboxylase antibodies.

^a HbA1c indicated by NGSP value.

itant HHV-6 reactivation was detected in cases 10 and 12, and coxsackie virus B3 reactivation in case 8 (5).

In a nationwide questionnaire survey concerning the frequency of FT1D with DIHS, we found 746 cases of DIHS between 2007 and 2009. Of 746 cases of DIHS diagnosed during these 3 yr, four cases developed FT1D (0.54%). In addition, four cases developed T1D other than FT1D.

Discussion

We analyzed 15 reported cases of FT1D associated with DIHS in Japan. No islet-related autoantibodies were detected in FT1D without DIHS, where most cases were reported to have negative antibodies (2). In Japanese subjects, HLA DR4 and DR9 are susceptible to FT1D as well as autoimmune T1D (3), whereas HLA DR2 confers strong protection against autoimmune T1D but weak protection against FT1D. In this study, the genetic contribution of HLA class II appeared to be similar in FT1D with and without DIHS. Although HLA B5801 and A3101 were reported to be associated with DIHS with allopurinol (11) and carbamazepine (12), respectively, in Japanese, they were not found in the present study. There were no differences in the frequency of HLA B61 compared with nondiabetic controls, although HLA B61 was reported to be associated with FT1D in the nationwide survey in Japan (9). On the other hand, the frequency of HLA B62 was significantly increased in FT1D with DIHS. These findings suggest that some drugs that induce DIHS

may bind to specific class I alleles, resulting in the direct activation of CD8 T cells. In a large number of activated T cells, a subset of T cells with simple T-cell receptor motifs may target an islet molecule as reported for the class I (13) or class II (14) major histocompatibility complex.

HHV-6 reactivation was observed in most of the cases. The mean duration from the onset of DIHS to the development of FT1D was 39.9 d and, in most cases, between 2 wk and 2 months. Because HHV-6 is commonly reactivated 2–4 wk after the onset of DIHS (4), FT1D appeared to develop just after HHV-6 reactivation. In fact, two cases of FT1D with DIHS were reported to be associated with HHV-6 reactivation (6, 15).

The reactivation of CMV and coxsackie virus B3 were also detected, in addition to HHV-6. It was reported that HHV-6 reactivation sometimes results in the sequential reactivation of CMV or Epstein-Barr virus (EBV) (4, 16). In fact, CMV activation was detected in two cases (cases 10 and 12) concomitant with HHV-6 activation. On the other hand, in the cases of FT1D without DIHS, antibody titers for viruses, such as coxsackie virus, rotavirus, EBV, and CMV, were elevated in nine of 55 FT1D patients (3). Furthermore, influenza B, herpes simplex, mumps, EBV, coxsackie, and hepatitis A virus were reported to be associated with FT1D. Despite the preceding DIHS, it appears that the viral infections may be involved in the pathogenesis of FT1D.

Whereas HHV-6 reactivation in DIHS is considered to require immunosuppression, skin inflammation may in-

duce immunosuppressive conditions (16). It was recently reported that plasmacytoid dendritic cells from the systemic circulation accumulate in skin, resulting in a reduced circulation. This could reduce antiviral responses, facilitating viral reactivation in areas other than the skin (4). Enteroviral infections and subsequent innate immunity, such as the expression of toll-like receptor-3 or laboratory of genetics and physiology 2 (LGP2), were observed in islets from autopsied patients with FT1D without DIHS (3, 17). Like viral infections of FT1D without DIHS, the accelerated innate immune response by viral reactivation may result in the rapid destruction of pancreatic β -cells in FT1D with DIHS.

In the questionnaire sent to the hospitals concerning the frequency of FT1D with DIHS, four of 746 cases (0.54%) developed FT1D between 2007 and 2009. However, caution is advised in the interpretation of the data. In the 15 reported cases, four cases were reported between 2007 and 2009. Of the four cases, two cases (cases 6 and 15) were overlapped with the cases from the questionnaire survey, and two cases (cases 5 and 10) were not included in the cases from the questionnaire survey. We also received only 441 replies of 641 hospitals in the nationwide survey. Therefore, the possibility that the frequency of FT1D with DIHS could be higher cannot be excluded.

In the Ehime study, a survey of T1D in Japan, nine cases of FT1D were observed in 4980 cases of diabetes (18). The frequency of FT1D in DIHS (0.54%) is much higher than that in the general Japanese population (0.010%) estimated from the Ehime study finding and diabetes morbidity in Japan ($P < 0.001$); therefore, FT1D should be kept in mind when DIHS develops.

On the other hand, four cases developed T1D other than FT1D. In addition to FT1D, autoimmune T1D associated with DIHS has been reported (19), and a case of autoimmune T1D with DIHS was found in the present study. It would be interesting to examine the difference between the DIHS cases that developed FT1D and autoimmune T1D.

In conclusion, the clinical features of 15 cases of FT1D with DIHS in Japanese subjects were investigated. HLA B62 was associated with FT1D with DIHS, suggesting that it may be involved in this pathogenesis. Further analyses of additional cases would be useful in clarifying the pathogenesis of FT1D associated with DIHS.

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