Endocrine Journal 2006, **53** (5), 577–584

REVIEW

Fulminant Type 1 Diabetes Mellitus

AKIHISA IMAGAWA AND TOSHIAKI HANAFUSA

First Department of Internal Medicine, Osaka Medical College, Takatsuki 569-8686, Japan

Key words: Idiopathic, Diagnosis, HLA, Enterovirus, CSII

(*Endocrine Journal* **53**: 577–584, 2006)

FULMINANT type 1 diabetes is a novel clinical entity within diabetes mellitus described in 2000 [1, 2]. In the first paper, 11 patients with fulminant type 1 diabetes were reported, and the clinical and histological characteristics are listed in Table 1. Because islet-related autoantibodies, such as islet cell antibodies (ICA), anti-glutamic acid decarboxyalse antibody (GADAb), insulin autoantibody (IAA) or anti-insulinoma-associated antigen 2 antibody (IA-2Ab) were not detected even at the time of disease onset, this subtype is classified into not autoimmune (type 1A) but idiopathic (type 1B) diabetes according to the classification of diabetes mellitus by the American Diabetes Association or the World Health Organization.

Fulminant type 1 diabetes is defined as a subtype of diabetes mellitus that results from remarkably acute and almost entire destruction of pancreatic beta cells. The area of pancreatic beta cells decreased to 1/255 of normal subjects and even to 1/37 of type 1A diabetes [3]. Pancreatic alpha cells are also damaged in fulminant type 1 diabetes, while exocrine pancreas keeps its structure. Rapid loss of pancreatic beta cells is confirmed by low level of glycosylated hemoglobin despite the presence of high serum glucose concentration at the disease onset. Sekine *et al.* reported a patient whose fasting blood glucose and serum C-peptide levels were monitored for a couple of weeks around the onset of fulminant type 1 diabetes. Blood glucose level was within normal limit a day before the onset and suddenly increased at the onset with the simultaneous fall of serum C-peptide level [4]. In addition, hypoglycemia is sometimes observed just before the onset of fulminant type 1 diabetes [1]. This is probably because the destruction of beta cells is so rapid that insulin in the destroyed beta cells may flow into the blood stream within a short period of time. A similar phenomenon is also observed when streptozotocin (STZ) is injected to make rodent model of type 1 diabetes.

Table 1. Characteristics of fulminant type 1 diabetes in the first report

1. Account for 20% of acute onset type 1 diabetes in Japan
2. Abrupt onset with ketosis or ketoacidosis
3. High plasma glucose level accompanied with almost normal HbA_{1c} level
4. Elevation in pancreatic enzyme levels
5. Islet-associated autoantibodies were not detected
6. Urinary CPR was less than 10 μg/day
7. No Insulitis but lymphcytic infiltration in the exocrine pancreas was observed

Correspondence to: Akihisa IMAGAWA, M.D., Ph.D., FACP
First Department of Internal Medicine, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki 569-8686, Japan

Epidemiology

Reports of fulminant type 1 diabetes have been concentrated in Japan until now. Prevalence of fulminant type 1 diabetes among ketosis-onset type 1 diabetes was 19.0% in the first report [1] and 19.4% in a nationwide survey performed under the auspices of the Japan Diabetes Society [5]. In Ehime study, a regional hospital-based study for diabetes, Murao *et al.* reported the prevalence of fulminant type 1 diabetes was in 8.9% in all type 1 diabetic patients and 0.2% in consecutive 4980 newly-diagnosed all diabetic patients [6]. The Japanese Ministry of Health, Labour

and Welfare has reported that there are more than 7 million diabetic patients, thus we can speculate that at least ten thousand patients with fulminant type 1 diabetes are in Japan. Patients with fulminant type 1 diabetes were reported from all over Japan, and no significant seasonal and regional preference was observed [5]. In addition, the number of newly-diagnosed patients has not increased over past 10 years, indicating that fulminant type 1 diabetes is not an emerging disease [5].

On the other hand, few patients have been reported outside of Japan. A Korean and a Filipino patient were confirmed to be fulminant type 1 diabetes by Jung *et al.* [7] and Taniyama *et al*. [8], respectively. Another Chinese patient was also suspected to be fulminant type 1 diabetes [9]. In Caucasians, Pozzilli *et al.* reported no such patient in 82 cases newly-diagnosed in Italy [10]. Weets *et al.* reported that antibody-negative patients with type 1 diabetes were on average older and had less symptoms, a slower disease onset, higher body mass index, and random C-peptide levels, but lower insulin needs, glycemia, and prevalence of ketonuria, HLA-DQ, and 5' insulin gene susceptibility genotypes in 1584 recent-onset Belgian Caucasian patients [11]. These findings suggest that there are few patients, if any, with fulminant diabetes in Caucasians. Maldonado *et al.* also reported that no fulminant diabetic patients in consecutive 41 ketosis-prone diabetic patients in Houston [12]. Their patients were African-American, Hispanic-American, Caucasian-American and a few Asian-American. Balasubramanian *et al.* reported no patient susceptible to fulminant type 1 diabetes in north Indian children [13]. However, a susceptible Caucasian case of fulminant type 1 diabetes was reported from the Netherlands [14]. Besides fulminant type 1 diabetes, cases of ketosis-prone diabetes without loss of pancreatic beta cells were reported both in Japanese [15] and African American [12].

Fulminant type 1 diabetes is equally observed in males and females. In a nationwide survey, 83 male and 78 female patients with fulminant type 1 diabetes were reported in Japan [5]. Age at onset ranged from 1 to 80 years old and their mean (±SD) age was 42.8 (±14.8) years in men and 35.1 (±15.8) years in women, respectively. To note, only 14 (3 male and 11 female) patients (8.7%) were under 20 years old and the other patients (91.3%) were all adolescent or adult. Child patients were also reported [16], but these findings were quite different from those of type 1A diabetes in which female and prepubital cases were predominant [5].

Fulminant type 1 diabetes is not predominant in females but pregnancy is sometimes associated with this disease [5, 17–19]. Almost all patients who suffered from type 1 diabetes in pregnancy and just after delivery showed similar characteristics with fulminant type [5]. Shimizu *et al.* reported clinical characteristics of 22 patients of fulminant diabetic patients associated with pregnancy. In those 22 patients, 18 patients developed diabetes during pregnancy and 4 patients developed diabetes immediately after delivery. The onset of 13 patients was in the trimester and fetal demise occurred in 12 out of 18 patients who developed fulminant diabetes during pregnancy. Five of 6 fetal alive cases were rescued by Cesarean-section [19]. The patients with fulminant diabetes associated with pregnancy showed more severe clinical form, lower arterial pH and glycosylated hemoglobin levels, than the patients not associated with pregnancy at the onset of overt diabetes.

Mechanism of beta cell destruction

Genetic factor — HLA

It has been reported that HLA strongly confers susceptibility and resistance to the development of type 1 diabetes [20]. HLA DR4-DQ4 (usually encoded by *DRB1*0405-DQB1*0401*) and DR9-DQ3 (encoded by *DRB1*0901-DQB1*0303)* has been reported to confer susceptibility to and DR2-DQ1 (encoded by *DRB1*1501/*1502-DQB1*0602/*0601)* resistance to type 1 diabetes in Japanese, while HLA DR4-DQ1 (encoded by *DRB1*0401-DQB1*0302*) and DR3-DQ2 (encoded by *DRB1*0301-DQB1*0201)* but not DR4-DQ4 confer susceptibility to and DR2-DQ1 (encoded by *DRB1*1501-DQB1*0602)* also confers to resistance to type 1 diabetes in Caucasians [20, 21].

As a part of the nationwide survey, HLA-A, -DR and -DQ serotypes were investigated in 91 fulminant and 81 autoimmune (type 1A) diabetic patients together with 190 normal controls [22]. The distribution of HLA-A, class I HLA, was not different among the 3 groups. As to class II HLA, DR4-DQ4 was observed in 41.8% and significantly more frequent, and both DR2-DQ1 and DR8-DQ1 were less frequent in fulmi-

nant diabetes. In type 1A diabetes, DR2-DQ1 was extremely rare while DR9-DQ3 was significantly more frequent. In the combination analysis, the homozygote of DR4-DQ4 in fulminant type 1 diabetes and DR9-DQ3 in typical type 1A diabetes indicated high odds ratios (13.3 and 13.3, respectively). These results suggest that class II HLA also contributes to the development of fulminant type 1 diabetes, but susceptibility and resistance of the HLA subtype to type 1 diabetes are distinct between fulminant and typical autoimmune type 1 diabetes. HLA-DR4-DQ4 haplotype is common in Japanese but rare in Caucasian population. It might contribute to the different incidence of fulminant type 1 diabetes between Japanese and Caucasian. The role of class II HLA has been emphasized in the context of antigen-presenting process in typical autoimmune type 1 diabetes [20], but it remains to be elucidated how a certain class II HLA can contribute towards the molecular mechanisms of beta cell destruction in fulminant type 1 diabetes. One possibility is that HLA molecule is associated with immune reaction of fulminant diabetes like type 1A diabetes, but another is that it may interact with some kind of virus shown in mice [23]. Small pilot studies suggest DR4-DQ4, which is susceptible to fulminant diabetes, is encoded *DRB1*0405-DQB1*0401* [24, 25]. HLA gene or the gene showing linkage disequilibrium to HLA gene contributes to the development of fulminant type 1 diabetes.

Environmental factor — viral infection

The involvement of viral infection in the pathogenesis of fulminant type 1 diabetes has been suggested because of the markedly acute onset [1]. A nationwide survey revealed that flu-like symptoms were observed in 71.2% of fulminant type 1 diabetic patients [5], also suggesting that viral infection is critical in the development of fulminant type 1 diabetes. Indeed, cases of fulminant type 1 diabetes were reported in which the onset of diabetes was accompanied with the reactivation of human herpes virus-6 [3] and the infection of herpes simplex virus [26] or coxsackie B_3 virus [27].

IgA antibody titers to enterovirus were significantly higher in fulminant type 1 diabetes than those in typical type 1A diabetes and controls [28]. This system to detect enterovirus antibodies reacts with several different serotypes of enterovirus such as coxsackie A, coxsackie B, and echo viruses. Titers of IgA antibodies would be increased if different serotypes of enteroviruses repeatedly infected a single patient. Thus, these results suggest that fulminant type 1 diabetic patients are more susceptible to enterovirus infections than autoimmune diabetic patients and controls.

Shimada and Maruyama reported that encephalomyocarditis (EMC)-virus-induced diabetes model resembled fulminant type 1 diabetes in humans [29]. Intraperitoneal injection of male DBA/2 mice with EMC virus diabetic strain can induce very rapid onset of diabetes. Not only the very rapid onset pattern but also the involvement of exocrine tissue damage, as indicated by histological findings and the high serum amylase level in the EMC-virus-induced diabetes model resembles fulminant type 1 diabetes.

However, the nationwide survey revealed no pandemic of fulminant type 1 diabetes has ever occurred. No antibody of 24 serotype specific neutralizing antibodies, including cytomegalovirus, Epstein-Barr virus, rotavirus, human herpes virus (HHV)-6, HHV-7, coxsackie A_{2-10} viruses, coxsackie B_{1-6} viruses, was elevated in paired sera of 24 recent-onset fulminant type 1 diabetic patients (unpublished observation).

These findings suggest that factors within host will play more important role in the development of fulminant diabetes than virus itself, which was also shown in EMC-virus-induced diabetes model [30].

Approach from pancreas histology

The presence or absence of insulitis in the pancreas of fulminant type 1 diabetes is still controversial. In the first report of fulminant type 1 diabetes, no insulitis and mononuclear cell infiltration to exocrine pancreas were observed in the biopsy specimens of 3 patients within 5 months after the onset of overt diabetes [1]. Yamazaki and Hayashi also reported no insulitis in the biopsied specimens taken 33rd day after the onset of fulminant diabetes [31]. On the other hand, Tanaka *et al.* reported an autopsy case of fulminant type 1 diabetes with the infiltration of lymphocytes into both endocrine and exocrine pancreas soon after the onset of overt diabetes [32].

Hyperexpression of MHC class I antigens in islet, another histological evidence of abnormal cellular autoimmunity, was observed in type 1A diabetes [33], but not in fulminant type 1 diabetes [1]. Fas was expressed in islet cells and Fas ligand was expressed in infiltrating mononuclear cells in islet in type 1A dia-

betes, but not in fulminant type 1 diabetes [3]. Both pancreatic beta and alpha cells were decreased in fulminant type 1 diabetes, but only beta cells were decreased in autoimmune type 1 diabetes [3]. All these findings suggest that the mechanism of beta cell destruction in fulminant type 1 diabetes is different from that in autoimmune type 1 diabetes. In the latter one, pancreatic beta cells were damaged by beta cell specific cytotoxic T lymphocytes (CTL) through Fas and Fas ligand system [34]. In fulminant type 1 diabetes, the precise mechanism has yet to be revealed, but both alpha and beta cell were involved in the destruction of beta cells. We can speculate that some kind of bystander mechanism such as cytokines or nitric oxide might play a role in the development of fulminant type 1 diabetes.

Autoantibody and autoreactive T cells

Islet autoantibodies seldom appear in fulminant type 1 diabetes. In the initially reported 11 patients with fulminant type 1 diabetes, all those antibodies were negative in all patients [1]. The situation is similar in a nationwide survey, in which GADAb was positive only in 4.7% with low titer, and neither IA-2Ab, IAA, nor ICA were positive in fulminant diabetic patients at all [5]. In addition, thyroid autoantibodies or thyroid and other autoimmune diseases are less frequent in fulminant diabetes than in autoimmune type 1 diabetes [5].

On the other hand, cellular immunoreactivity to beta cell antigens may be upregulated in fulminant type 1 diabetes after the onset of overt diabetes. GAD-reactive Th1 cells and insulin $B_{9–23}$-reactive Th1 cells in peripheral blood mononuclear cells were identified in 9 of 13 and 3 of 12 fulminant type 1 diabetic patients by using ELISPOT assay [35]. Shimada *et al.* reported a fulminant diabetic patient with a high serum level of CXCL10, a chemokine inducing migration of activated T-cells to local lesions, and GAD-reactive $CD4^+$ cells in the periphery [36]. These findings indicate that autoreactive T cells might contribute, at least in part, to the development of fulminant type 1 diabetes.

Disorder of exocrine pancreas

Around the onset of fulminant type 1 diabetes, disorder of exocrine pancreas was often observed. Elevation of serum pancreatic amylase, lipase, elastase-1 or phospholipase level is a common disorder, and swelling of pancreas in computed tomography or ultrasonography is sometimes observed [1]. Some patients suffered from those disorders, which resemble pancreatitis, before the onset of overt diabetes [37], but symptoms of exocrine dysfunction such as diarrhea or fatty stool are not long-standing, and increased serum pancreatic enzyme levels and swelling of pancreas disappear only by the treatment for diabetic ketoacidosis. Histological analysis revealed mononuclear infiltration to exocrine pancreas, but no necrosis, hemorrhage, edema or fatty degeneration, which is usually observed in acute pancreatitis, both in autopsy and biopsy cases [1, 31, 32]. Taniguchi *et al.* reported the patients with antibodies to exocrine pancreas, though the number is small [38]. Further examination would be necessary to clarify the contribution of abnormalities in exocrine pancreas in the pathogenesis of fulminant type 1 diabetes.

Tentative hypotheses for the destruction of beta cells

Our tentative hypothesis of beta cell destruction in fulminant type 1 diabetes is shown in Fig. 1. The results of HLA analysis and antibody to enterovirus suggest that there are several risk factors susceptible to the development of fulminant type 1 diabetes. Viral infection triggers the destruction of beta cells in the

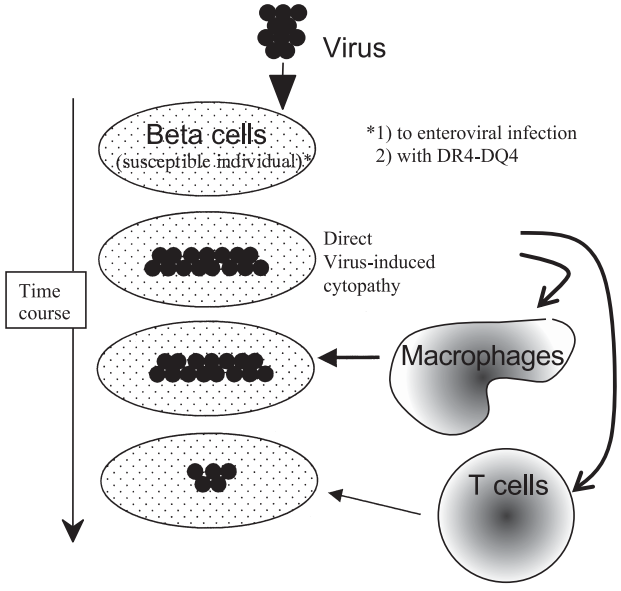

Fig. 1. Tentative hypothesis of beta cell destruction in fulminant type 1 diabetes

susceptible individuals. The first pathway to beta cell death would be via viral infection to and its self-duplication in the beta cells. Viral infection also activates innate immune response to delete virus and infected cells mainly through macrophages-derived agents, for example, cytokines and nitric oxide. This would be the second pathway and would play an important role in the destruction of beta cells in fulminant diabetes. It is noteworthy that the damage of both beta and alpha cells suggest a less specific mechanism to beta cells in fulminant diabetes than that in typical autoimmune diabetes. Finally, adaptive immune system is activated and the remaining viruses and its host, beta cells, are destructed through T cells, which is the third pathway, though the detailed mechanism remains unclarified.

Diagnosis

According to the epidemiological study, the Committee of the Japan Diabetes Society of the Research of Fulminant Type 1 Diabetes Mellitus set out both screening criteria for not overlooking the disease and diagnostic criteria for definitely diagnosing the disease (Table 2 and 3) [39].

The screening criteria are important because it is sometimes difficult to diagnose fulminant diabetes without delay at the disease onset. A patient with fulminant type 1 diabetes was reported who fell into cardiac arrest on arrival at hospital after incorrect initial diagnosis at another clinic [40]. One of the reasons for the delay of diagnosis is markedly acute progression of insulin deficiency in fulminant type 1 diabetes. To diagnose fulminant diabetes without delay, it is essential for all physicians to know that fulminant diabetes is an emergent disease. Second, ketotic symptoms such as general fatigue, nausea and vomiting, are more common than hyperglycemic symptoms such as thirst, polyuria and body weight loss at the onset of fulminant type 1 diabetes. Therefore, physicians should be careful not to miss the patient's signs. Third, urinalysis should be done to avoid misdiagnosis as a routine examination in emergency room. If urinary sugar and ketone bodies were detected with or without hyperglycemic symptoms, diabetic ketosis, including fulminant type 1 diabetes, is strongly suspected. Once diabetes is suspected, blood glucose should be measured by using a glucose monitor immediately. Do not wait until next day. In 90% cases of fulminant type 1 diabetes, blood glucose level is more than 400 mg/dl [39]. Flu-like symptoms, abdominal symptoms and drowsiness were characteristic to fulminant diabetes at onset was shown in a nationwide survey [5].

Table 2. Findings strongly suggesting the diagnosis of fulminant type 1 diabetes mellitus

1. Ketosis or ketoacidosis within a week after the onset of hyperglycemic symptoms.
2. Plasma glucose level ≥288 mg/dl (16.0 mmol/l) at first visit.

Table 3. Criteria for definite diagnosis of fulminant type 1 diabetes mellitus

Fulminant type 1 diabetes mellitus is confirmed when all the following 3 findings are present.

1. Ketosis or ketoacidosis within a week after the onset of hyperglycemic symptoms (presence of increased urinary and/or serum ketone bodies at first visit).
2. Plasma glucose level ≥288 mg/dl (16.0 mmol/l) and HbA_{1c} level <8.5% at first visit.
3. Urinary C-peptide level <10 μg/day or fasting plasma C-peptide level <0.3 ng/ml and <0.5 ng/ml after glucagon (or meal) load at onset.

<Related findings>

A) Islet-related autoantibodies such as GAD antibodies were negative in general.
B) Duration of the disease is within a week in general but in some patients it is between 1 and 2 weeks.
C) Ninety-eight percent of the patients have increased serum pancreatic enzyme levels (amylase, lipase or elastase-1).
D) Seventy percent of patients have preceding symptoms such as fever, upper respiratory infections, or gastrointestinal symptoms.
E) The disease could occur during pregnancy or just after delivery.

Hepatic dysfunction of elevated transaminase level was common at the onset of fulminant type 1 diabetes [1, 5]. Takaike *et al.* reported that the increase of liver-kidney contrast in ultrasonography suggested fat deposition to the liver in those patients but the deposition was transient [41].

Cardiac disorder is rarely observed around the onset of fulminant type 1 diabetes such as T-wave inversion, atrial fibrillation or cardiac arrest due to unknown origin [40, 42]. Acute renal failure with elevated creatinine kinase level or rhabdomyolysis was reported in a severe case of fulminant type 1 diabetes [43]. Hypersensitivity syndrome was also reported in some cases [4, 44, 45].

Therapy and prognosis

Fulminant type 1 diabetes usually accompanied diabetic ketoaciosis as a result of acute insulin deficiency at the time of disease onset. Those patients should be treated as usual diabetic ketoacidosis as soon as possible. The goal is the cure of ketoacidosis without any complication.

After recovering from diabetic ketoacidosis, multiple insulin injection therapy is recommended. Due to the lack of endogenous insulin secretion even at the onset of diabetes, strict control of blood glucose is usually difficult. Some cases show brittleness in the blood glucose level, and other cases fall into ketosis soon after the cessation of insulin injection. Both physicians and patients should understand the risk resulting from virtually no endogenous insulin secretion.

Continuous subcutaneous insulin injection (CSII) is another means to treat patients with fulminant diabetes, especially when fasting blood glucose is poorly controlled. We have reported three patients whose glucose control was improved and hemoglobin A_{1c} was decreased to below 7% by using CSII therapy [46].

Ultra long-acting insulin analog has been available since 2003 also in Japan. Our preliminary reports showed that the control of blood glucose by using ultra long-acting insulin analog would be better than that by using NPH insulin but not CSII [47].

Mean glycosylated hemoglobin levels were not significantly different between fulminant and autoimmune type 1 diabetic patients, but insulin injection doses were significantly higher in fulminant diabetic patients than in autoimmune diabetic patients 3, 6, and 12 months after the onset of overt diabetes [5]. No case of fulminant type 1 diabetes with "honeymoon phase" was reported in the nationwide survey [5]. Insulin secreting capacity did not recover in fulminant type 1 diabetic patients by 7-year follow-up study, though the number of patients was small [48]. The precise prognosis including diabetic complication has not been reported.

Conclusions

Fulminant type 1 diabetes mellitus is a disease in which disregard or oversight results directly in death of the patient. Saving the life of patients with this rapidly progressing diabetes depends on the physician's knowledge of this disease. Epidemiological data have increased in these years, but the pathogenesis of beta cell death is largely unknown. Further study is necessary to clarify the pathophysiology of fulminant type 1 diabetes.

Acknowledgement

We are indebted to Drs. Naoto Itoh, Jun-ichiro Miyagawa, David M Harlan, Hiroshi Ikegami and Yuji Matsuzawa for discussion, and also to doctors of the Osaka IDDM study group (shown in ref.1) and the Committee of the Japan Diabetes Society of the Research of Fulminant Type 1 Diabetes Mellitus (shown in ref. 5) for collaboration. This study was supported by a grant-in-aid for scientific research from the Japan Society for the Promotion of Science, and a grant-in-aid from the Japan Medical Association.

References

1. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y for the Osaka IDDM study group (2000) A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. *N Engl J Med* 342: 301–307.
2. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y (2000) A proposal of three distinct subtypes of type 1 diabetes mellitus based on clinical and pathological evidence. *Ann Med* 32: 539–543.
3. Sayama K, Imagawa A, Okita K, Uno S, Moriwaki M, Kozawa J, Iwahashi H, Yamagata K, Tamura S, Matsuzawa Y, Hanafusa T, Miyagawa J, Shimomura I (2005) Pancreatic beta and alpha cells are both decreased in patients with fulminant type 1 diabetes: a morphometrical assessment. *Diabetologia* 48: 1560–1564.
4. Sekine N, Motokura T, Oki T, Umeda Y, Sasaki N, Hayashi M, Sato H, Fujita T, Kaneko T, Asano Y, Kikuchi K (2001) Rapid loss of insulin secretion in a patient with fulminant type 1 diabetes mellitus and carbamazepine hypersensitivity syndrome. *JAMA* 285: 1153–1154.

5. Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Toyoda T, Maruyama T, Makino H (2003) Fulminant type 1 diabetes: a nationwide survey in Japan. *Diabetes Care* 26: 2345–2352.
6. Murao S, Makino H, Kaino Y, Konoue E, Ohashi J, Kida K, Fujii Y, Shimizu I, Kawasaki E, Fujiyama M, Kondo S, Tanaka K, Tarumi Y, Seto I, Kato K, Ohno K, Kusunoki Y, Ebisui O, Takada Y, Tanabe K, Takemoto K, Onuma H, Nishimiya T, Osawa H (2004) Differences in the contribution of HLA-DR and -DQ haplotypes to susceptibility to adult-onset and childhood-onset type 1 diabetes in Japanese patients. *Diabetes* 53: 2684–2690.
7. Jung TS, Chung SI, Kim MA, Kim SJ, Park MH, Kim DR, Kang MY, Hahm JR (2004) A Korean patient with fulminant autoantibody-negative type 1 diabetes. *Diabetes Care* 27: 3023–3024.
8. Taniyama M, Katsumata R, Aoki K, Suzuki S (2004) A Filipino patient with fulminant type 1 diabetes. *Diabetes Care* 27: 842–843.
9. Foulis AK, Francis ND, Farquharson MA, Boylston A (1988) Massive synchronous B-cell necrosis causing type 1 (insulin-dependent) diabetes — a unique histopathological case report. *Diabetologia* 31: 46–50.
10. Pozzilli P, Visalli N, Leslie D, IMDIAB Group (2000) No evidence of rapid onset (Japanese) Type I diabetes in Caucasian patients. *Diabetologia* 43: 1332.
11. Weets I, Siraux V, Daubresse J-C, De Leeuw IH, Fery F, Keymeulen B, Krzentowski G, Letiexhe M, Mathieu C, Nobels F, Rottiers R, Scheen A, Van Gaal L, Schuit FC, Van der Auwera B, Rui M, De Pauw P, Kaufman L, Gorus FK (2002) Relation between disease phenotype and HLA-DQ genotype in diabetic patients diagnosed in early adulthood. *J Clin Endocrinol Metab* 87: 2597–2605.
12. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A (2003) Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and β-cell functional classification, prospective analysis, and clinical outcomes. *J Clin Endocrinol Metab* 88: 5090–5098.
13. Balasubramanian K, Dabadghao P, Bhatia V, Colman PG, Gellert SA, Bharadwaj U, Agrawal S, Shah N, Bhatia E (2003) High frequency of type 1B (idiopathic) diabetes in north Indian children with recent-onset diabetes. *Diabetes Care* 26: 2697–2697.
14. Vreugdenhil GR, Schloot NC, Hoorens A, Rongen C, Pipeleers DG, Melchers WJ, Roep BO, Galama JM (2000) Acute onset of type I diabetes mellitus after severe echovirus 9 infection: putative pathogenic pathways. *Clin Infect Dis* 31: 1025–1031.
15. Yamada K, Nonaka K (1996) Diabetic ketoacidosis in young obese Japanese men. *Diabetes Care* 19: 671.
16. Urakami T, Nakagawa M, Morimoto S, Kubota S, Owada M, Harada K (2002) A subtype of markedly abrupt onset with absolute insulin deficiency in idiopathic type 1 diabetes in Japanese children. *Diabetes Care* 25: 2353–2354.
17. Otsubo M, Shiozawa T, Kimura K, Konishi I (2002) Nonimmune "fulminant" type 1 diabetes presenting with diabetic ketoacidosis during pregnancy. *Obstet Gynecol* 99: 877–879.
18. Shimizu I, Makino H, Osawa H, Kounoue E, Imagawa A, Hanafusa T, Kawasaki E, Fujii Y (2003) Association of fulminant type 1 diabetes with pregnancy. *Diabetes Res Clin Pract* 62: 33–38.
19. Shimizu I, Makino H, Hanafusa T, Imagawa A, Uchigata Y, Kawasaki E, Kanatsuka A, Kobayashi T, Shimada A, Maruyama T (2005) Immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy: a nationwide survey. *J Jpn Diab Soc* 48 (suppl 1): A15–19 (In Japanese).
20. Eisenbarth GS, Polonsky KS, Buse JB (2003) Type 1 diabetes mellitus. In: Reed Larsen P, *et al.* (eds) Williams Textbook of Endocrinology 10th ed., Saunders, Philadelphia, pp. 1485–1504.
21. Ikegami H, Ogihara T (1996) Genetics of insulin-dependent diabetes mellitus. *Endocr J* 43: 605–613.
22. Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Maruyama T, Makino H (2005) Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus. *Diabetologia* 48: 294–300.
23. Wykes MN, Shellam GR, McCluskey J, Kast WM, Dallas PB, Price P (1993) Murine cytomegalovirus interacts with major histocompatibility complex class I molecules to establish cellular infection. *J Virol* 67: 4182–4189.
24. Tanaka S, Kobayashi T, Nakanishi K, Koyama R, Okubo M, Murase T, Odawara M, Inoko H (2002) Association of HLA-DQ genotype in autoantibody-negative and rapid-onset type 1 diabetes. *Diabetes Care* 25: 2302–2307.
25. Nakamura T, Nagasaka S, Kusaka I, Yatagai T, Yang J, Ishibashi S (2003) HLA-DR-DQ haplotype in rapid-onset type 1 diabetes in Japanese. *Diabetes Care* 26: 1640–1641.
26. Nagaoka T, Terada M, Miyakoshi H (2001) Insulin-dependent diabetes mellitus following acute pancreatitis caused by herpes simplex virus; a case report. *J Jpn Diab Soc* 44: 335–340 (In Japanese).
27. Nishida W, Hasebe S, Kawamura R, Hashiramoto M, Onuma H, Osawa H, Makino H (2005) A case of fulminant type 1 diabetes associated with high titer of coxsackie B3 virus antibody. *J Jpn Diab Soc* 48 (suppl 1): A23–27 (In Japanese).
28. Imagawa A, Hanafusa T, Makino H, Miyagawa JI, Juto P (2005) High titres of IgA antibodies to enterovirus in

fulminant type-1 diabetes. *Diabetologia* 48: 290–293.
29. Shimada A, Maruyama T (2004) Encephalomyocarditis-virus-induced diabetes model resembles "fulminant" type 1 diabetes in humans. *Diabetologia* 47: 1854–1855.
30. Jun HS, Yoon JW (2001) The role of viruses in type I diabetes: two distinct cellular and molecular pathogenic mechanisms of virus-induced diabetes in animals. *Diabetologia* 44: 271–285.
31. Yamazaki M, Hayashi T (2002) Rapid-onset type 1 diabetes mellitus without pancreatic exocrine dysfunction. *Ann Intern Med* 137: 145–146.
32. Tanaka S, Kobayashi T, Momotsu T (2000) A novel subtype of type 1 diabetes mellitus. *N Engl J Med* 342: 1835–1838 (Correspondence).
33. Itoh N, Hanafusa T, Miyazaki A, Miyagawa J, Yamagata K, Yamamoto K, Waguri M, Imagawa A, Tamura S, Inada M, Tarui S, Kono N, Matsuzawa Y (1993) Mononuclear cell infiltration and its relation to the expression of major histocompatibility complex antigens and adhesion molecules in pancreas biopsy specimens from newly diagnosed insulin-dependent diabetes mellitus patients. *J Clin Invest* 92: 2313–2322.
34. Moriwaki M, Itoh N, Miyagawa J, Yamamoto K, Imagawa A, Yamagata K, Iwahashi H, Nakajima H, Namba M, Nagata S, Hanafusa T, Matsuzawa Y (1999) Fas and Fas ligand expression in inflamed islets in pancreas sections of patients with recent-onset Type I diabetes mellitus. *Diabetologia* 42: 1332–1340.
35. Kotani R, Nagata M, Imagawa A, Moriyama H, Yasuda H, Miyagawa J, Hanafusa T, Yokono K (2004) T lymphocyte response against pancreatic beta cell antigens in fulminant Type 1 diabetes. *Diabetologia* 47: 1285–1291.
36. Shimada A, Morimoto J, Kodama K, Oikawa Y, Irie J, Nakagawa Y, Narumi S, Saruta T (2002) T-cell-mediated autoimmunity may be involved in fulminant type 1 diabetes. *Diabetes Care* 25: 635–636.
37. Fukui K, Imagawa A, Iwahashi H, Kashine S, Moriwaki M, Nanmo T, Misugi S, Sekiguchi K, Yamagata K, Miyagawa JI, Matsuzawa Y (2002) A case of diabetes mellitus after acute pancreatitis with histological findings compatible to non-autoimmune fulminant type 1 diabetes. *J Jpn Diab Soc* 45: 759–765 (In Japanese).
38. Taniguchi T, Okazaki K, Okamoto M, Seko S, Nagashima K, Yamada Y, Iwakura T, Seino Y (2005) Autoantibodies against the exocrine pancreas in fulminant type 1 diabetes. *Pancreas* 30: 191–192.
39. Hanafusa T, Imagawa A, Iwahashi H, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Maruyama T, Makino H (2005) Report of Japan Diabetes Society Committee on Fulminant Type 1 Diabetes Mellitus Research: Epidemiological and clinical analysis and proposal of diagnostic criteria. *J Jpn Diab Soc* 48 (suppl 1): A1–13 (In Japanese).
40. Uto Y, Uto K, Teno S, Isono K, Omori Y (2002) A case of fulminant type 1 diabetes mellitus detected after cardiac arrest due to diabetic ketoacidosis. *J Japan Diab Soc* 45: 689–693 (In Japanese).
41. Takaike H, Uchigata Y, Iwasaki N, Iwamoto Y (2004) Transient elevation of liver transaminase after starting insulin therapy for diabetic ketosis or ketoacidosis in newly diagnosed type 1 diabetes mellitus. *Diabetes Res Clin Pract* 64: 27–32.
42. Kobayashi T, Isomine S, Goto M, Sato M, Kanazawa T, Sakaida K, Iwaoka H (2005) A case of fulminant type 1 diabetes with ECG changes in the first trimester of pregnancy. *J Jpn Soc Intensive Care Med* 12: 25–30 (In Japanese).
43. Iwaoka T (2003) A case of fulminant type 1 diabetes with transiently positive anti-GAD antibodies. *Endocr J* 50: 225–231.
44. Ohta K, Takamoto T, Izumi H, Yoshida T, Ishihara Y, Hirata Y (2001) A case of fulminant type 1 diabetes mellitus during steroid therapy for hypersensitivity syndrome. *J Jpn Diab Soc* 44: 907–912 (In Japanese).
45. Yamamoto S, Fujimoto H, Hirakawa N, Morimoto I (2003) A case of fulminant type 1 diabetes mellitus accompanied by hypersensitivity syndrome *J Jpn Diab Soc* 46: 949–954 (In Japanese).
46. Miura A, Imagawa A, Iwahashi H, Itoh H, Sayama K, Uno S, Okita K, Yamagata K, Namba M, Hanafusa T, Miyagawa J, Matsuzawa Y (2003) Efficacy of continuous subcutaneous insulin infusion (CSII) therapy for fulminant type 1 diabetes. *J Jpn Diab Soc* 46 (Suppl. 1): S-221 (Abstract) (In Japanese).
47. Sano H, Imagawa A, Iwahashi H, Terasaki J, Yamagata K, Miyagawa J, Shimomura I, Hanafusa T (2005) Efficacy of intensive insulin therapy using ultra long acting insulin analog in fulminant type 1 diabetes: a comparison to continuous subcutaneous insulin infusion (CSII) therapy. *J Jpn Diab Soc* 48 (Suppl.2): S249 (Abstract) (In Japanese).
48. Yamaguchi H, Seino H, Misaki A, Sakata Y, Kitagawa M, Yamazaki T, Kikuchi H, Abe R (2003) Prospective study of the capacity of insulin secretion of fulminant type 1 diabetic patients from the onset of diabetes. *J Jpn Diab Soc* 46: 211–215 (In Japanese).