CHAPTER 3

FULMINANT TYPE 1 DIABETES MELLITUS: A New Class of Type 1 Diabetes

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Abstract: Fulminant Type 1 diabetes is a novel subtype of Type 1 diabetes. In this disease, extremely rapid and almost complete β-cell destruction occurs, resulting in nearly no residual insulin secretion even just after the onset. The number of patients presumably amounts to 5,000~7,000 in Japan. The involvement of both, genetic background and viral infection, has been suggested in the pathogenesis of this disease. Diagnostic criteria were established by a committee of the Japan Diabetes Society in 2004. Intensive insulin therapy is a standard therapy. We should pay special attention to early development of microvascular complications in fulminant Type 1 diabetes.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is characterized by an insulin deficiency due to nearly complete destruction of pancreatic β cells and classified into Type 1A (immune mediated) and Type 1B (idiopathic). We previously reported a novel subtype of Type 1B diabetes called "fulminant Type 1 diabetes."[1] Diagnostic criteria are listed in Table 1.[2] In this chapter, we introduce epidemiology, genetic background, pathogenesis, and treatments including new findings in fulminant T1DM.

EPIDEMIOLOGY

Prevalence of fulminant T1DM in Japan was revealed as 19.4% of acute-onset (ketosis-onset) T1DM and 0.61% of all types of diabetes receiving insulin therapies.[3]

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Table 1. 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 ≥ 16.0 mmol/L (288 mg/dL) and $HbA1_C$ level < 8.5% (JDS unit) at first visit.
3. Urinary C-peptide level <10 μg/day or fasting serum C-peptide level < 0.10 nmol/l (0.3 ng/mL) and peak serum C-peptide level < 0.17 nmol/l (0.5 ng/mL) after glucagon (1 mg) or a meal load soon after disease onset.

Related findings

A. Islet-related autoantibodies such as glutamic acid decarboxylase antibodies (GADAb) are 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. Elevation of serum pancreatic enzyme levels (amylase, lipase or elastase-1) is observed in 98% of the patients.

D. Flu-like symptoms such as fever, upper respiratory symptoms, or gastrointestinal symptoms are observed in 70% of the patients.

E. The disease can occur during pregnancy or just after delivery.

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Approximately 5000 to 7000 fulminant Type 1 diabetic patients exist in Japan. Many cases have been reported from outside of Japan, mainly from East-Asia. In Korea, the prevalence of fulminant T1DM was 7.1% in newly diagnosed Type 1 diabetic patients including children. Several cases were also reported from Europe. Fulminant T1DM would exist worldwide regardless of racial and regional difference.

In a Japanese nationwide survey, fulminant T1DM is equally observed in male and female.[3] Mean age at onset was 35 years in female and 43 years in male respectively. 91.3% of patients were adult and pregnancy is sometimes associated with the disease. There is no regional, seasonal and chronological variation at least in Japan.

GENETIC BACKGROUND

It has been reported that class II human leukocyte antigen genes (*HLA-DR-DQ*), cytotoxic T-lymphocyte antigen-4 (*CTLA-4*) genes and class I HLA genes (*HLA-B*) confer susceptibility and resistance to the development of fulminant T1DM.[4-6] *DRB1*04:05-DQB1*04:01* and *DRB1*09:01-DQB1*03:03* confer susceptibility but *DRB1*15:01-DQB1*06:02/DRB1*15:02-DQB1*06:01* confers resistance.[4] CTLA-4 molecule suppresses T-cell activation and CT60AA genotype, a variant of the *CTLA-4* gene, confers susceptibility.[5] Class I HLA is involved in the recognition of viral antigens by T cells and *B*4002* is associated with fulminant T1DM.[6]

PATHOGENESIS

The involvement of viral infection has been suggested as the pathogenesis of fulminant T1DM. Flu-like symptoms were observed in 71.2% of the patients.[3] Widespread viral antibody elevation was observed around the onset in sera obtained from 55 patients with fulminant T1DM.[7] Enterovirus RNA was directly detected in the pancreas at autopsy in a patient with this form of diabetes.[8] Viral infection would trigger host immune response. Macrophages and T cells infiltrate to the islets bringing almost complete β-cell destruction in addition to partial alpha cell damage. They infiltrate even to exocrine lesions, indicating that there exists the destructive mechanism relatively nonspecific to β cells. The pathogenesis of β-cell death is not clear yet, but involvement of both, antiviral innate immunity and subsequent immunity have been suggested. Toll-like receptor 3 (TLR3) recognizes virus-derived double-stranded RNA and induces antiviral innate immune responses. We revealed the high expression of TLR3 in macrophages and T cells in the pancreas of patients with fulminant T1DM.[8] Cytoplasmic retinoic acid-inducible protein I-like receptors and melanoma differentiation-associated gene-5, which are also innate immune response stimulating receptors, were found in the islets of pancreas.[9] In addition, autoimmunity to β-cell antigens may be up-regulated subsequently to viral infection. GAD-reactive Th1 cells and insulin B_{9-23}-reactive Th1 cells in peripheral blood mononuclear cells were identified in the patients.[10] CXC chemokine ligand 10, which activates T cells and macrophages, was detected in β cells and the receptor for CXCL10 (CXCR3) was detected in T cells and macrophages.[11] Recently, autoantibodies against amylase alpha-2A and heat shock protein 10 were detected both in autoimmune pancreatitis and fulminant T1DM.[12,13]

TREATMENTS

The acute phase of ketoacidosis should be treated by intravenous regular insulin and saline infusion at the onset of fulminant T1DM. Once ketoacidosis is mended, multiple insulin injection or continuous subcutaneous insulin infusion therapy should be applied. Intensive insulin therapy is useful to stabilize blood glucose levels in the patients whose endogenous residual insulin secretion is very scarce.[14] Continuous Glucose Monitoring System (CGMS) would be useful for better blood glucose control. Special attention to be paid to avert early development of microvascular complications in this diabetes.[15] It has recently been reported that glucagon-like peptide 1 (GLP-1) receptor agonist ameliorates β-cell destruction and prevents the onset of diabetes in encephalomyocarditis virus-induced diabetic model mouse.[16] GLP-1 receptor agonist might be a new therapeutic candidate for fulminant T1DM.

CONCLUSION

Fulminant T1DM is a novel subtype of T1DM and has recently been recognized worldwide. Epidemiological and pathogenetic data have been accumulating, but further investigation is necessary to clarify the pathogenesis, clinical characteristics, predictive markers, and preventive means of this diabetes.

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