



## Case Report:

# Fulminant type 1 diabetes in China: a case report and review of the literature

Yun-fei FENG<sup>1</sup>, Mei-fen YAO<sup>2</sup>, Qi LI<sup>1</sup>, Yan SUN<sup>1</sup>, Cheng-jiang LI<sup>1</sup>, Jian-guo SHEN<sup>†‡1</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China)

<sup>2</sup>Department of Emergency, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China)

<sup>†</sup>E-mail: jgshen@medmail.com.cn

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**Abstract:** Fulminant type 1 diabetes is a recently discovered subtype of idiopathic type 1 diabetes, defined as diabetes with an extremely rapid process of  $\beta$ -cell destruction and progression to hyperglycemia and ketoacidosis. In this report, we present a case of fulminant type 1 diabetes in a 45-year-old Chinese woman, along with a review of the literature. The patient presented with sudden onset of polydipsia and polyuria after flu-like symptoms. Findings on admission included a high blood glucose level and ketoacidosis, but normal HbA1c level. The C-peptide stimulation test showed severe impairment of insulin secretion. Autoantibodies to glutamic acid decarboxylase (GAD) were negative. These results are compatible with the diagnosis of fulminant type 1 diabetes. Human leukocyte antigen-DR7 (HLA-DR7) was available in this case. It is concluded that this rapidly progressing type of diabetes exists, and we propose that HLA-DR7 might be predisposed to fulminant type 1 diabetes in Chinese patients.

**Key words:** Fulminant type 1 diabetes, Diabetic ketoacidosis, Flu-like symptoms

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## 1 Introduction

Fulminant type 1 diabetes is a recently discovered subtype of type 1 diabetes. It was first introduced by Imagawa *et al.* (2000), and defined as diabetes in which the process of  $\beta$ -cell destruction and the progression of hyperglycemia and ketoacidosis are extremely rapid. Fulminant type 1 diabetes is characterized by a rapid onset of diabetic ketoacidosis within a short period, normal or near-normal HbA1c level at onset, and complete  $\beta$ -cell destruction. Although evidence has suggested that viral infection and genetics are associated with the development of fulminant type 1 diabetes, the pathogenesis of this type of diabetes remains unknown. According to the data from a nationwide survey in Japan (Imagawa *et al.*, 2003), fulminant diabetes accounted for 15%–20% of

Japanese type 1 diabetes with ketosis or ketoacidosis at onset. In Korea, the prevalence of fulminant type 1 diabetes was 7.1% among all patients newly diagnosed with type 1 diabetes, and 30.4% among patients with adult-onset diabetes (Cho *et al.*, 2007). Only a few related cases have been reported in China, but without genotypic analysis (Zhou *et al.*, 2007; Zhang and Wen, 2008). Here we report one case of fulminant type 1 diabetes with human leukocyte antigen-DR7 (HLA-DR7) from the First Affiliated Hospital, School of Medicine, Zhejiang University, China, along with a review of the literature.

## 2 Case report

A 45-year-old Han Chinese woman presented to a local hospital with fever and chills over 8 d and the highest temperature up to 40 °C. She had been diagnosed as having an infectious fever and was given

<sup>†</sup> Corresponding author

levofloxacin. However, 2 d later she developed obvious polydipsia and polyuria with normal temperature, and her plasma glucose was 50.6 mmol/L. Thus she was transferred to our hospital immediately.

Physical data on admission showed a height of 160 cm and a weight of 55 kg, with a body mass index of 21.5 kg/m<sup>2</sup>. Laboratory data showed that urinary and blood ketone were strongly positive, arterial pH was 7.31 (normal range 7.35–7.45), serum level of bicarbonate was 25.8 mmol/L (normal range 35–45 mmol/L), and standard base excess (SBE) was –12.4 mmol/L (normal range –3.0–3.0 mmol/L). Her plasma glucose was 14.21 mmol/L, whereas HbA1c was 5.7% (normal range 3.8%–5.8%). Complete blood count was as follows: white blood cell count (WBC), 17.0×10<sup>9</sup> L<sup>-1</sup>; nitrogen (N), 81.5%; haematocrit (Hct), 29.2%; haemoglobin (Hb) level, 102 g/L. Serum level of amylase was 256 U/L (normal range 17–220 U/L). Blood chemistry showed potassium 3.3 mmol/L (normal range 3.5–5.5 mmol/L), and all of aspartate aminotransferase (AST), alanine transaminase (ALT), albumin, sodium, urea nitrogen, total cholesterol, and triglyceride were normal. Abdominal ultrasound showed no remarkable findings in the pancreas on admission. Chest X-ray, electrocardiogram, urine examinations, and serum troponin I (TNI), creatine kinase (CK), MB isoenzyme of creatine kinase (CK-MB), and lactate dehydrogenase (LDH) measurements were negative. According to above data, we considered the patient to have type 1 diabetes and diabetic ketoacidosis. The patient was treated by intravenous infusion of saline and insulin and eventually switched to intensive insulin therapy four times a day. After initial treatment, her condition was stabilized gradually. Further examination showed that the autoantibodies to GAD were negative. C-peptide stimulation tests on admission and 18 d later showed that the serum C-peptide was <0.5 ng/ml at different time points after oral administration of 83.5 g glucose. The results showed severe impairment of insulin secretion. Two weeks later, serological tests of virus antibody titers showed that immunoglobulin G (IgG) antibody titers for cytomegalovirus and Epstein-Barr virus (EBV) were 8.2 and 1.7, respectively, while all of immunoglobulin M (IgM) antibody titers for cytomegalovirus, EBV, coxsackie virus, and enterovirus RNA test were negative. Genotypic analysis revealed that the

patient was heterozygous for HLA-DR7-DQ2 and HLA-DR9-DQ9.

The case demonstrated a rapid progression of hyperglycemia and ketoacidosis, C-peptide at all points <0.5 ng/ml, and hyperglycemia on admission with normal HbA1c. According to criteria set by fulminant type 1 diabetes research of Hanafusa and Imagawa (2007), the patient was diagnosed with fulminant type 1 diabetes.

We have no competing interests to declare.

### 3 Discussion

Fulminant type 1 diabetes is a subtype of type 1 diabetes, and the pathogenesis of this disease involves both genetic background and viral infection (Imagawa and Hanafusa, 2006; Kawasaki and Eguchi, 2006; Nagata *et al.*, 2007; Goto *et al.*, 2008; Sano *et al.*, 2008; Akatsuka *et al.*, 2009). Accumulated evidence has shown that class II HLA is associated with this disease (Imagawa *et al.*, 2005; Kawabata *et al.*, 2009). In Japanese people, it is reported that the percentage of HLA-DR4-DQ4 in fulminant type 1 diabetes is 41.8%, higher than that in classic type 1 diabetes (22.8%). The Japanese study suggests that the *CTLA4* gene increases the risk of fulminant type 1 diabetes (Kawasaki *et al.*, 2008). Recently, another study strongly suggested the presence of a circuit of enterovirus infection, CXC chemokine ligand 10 (CXCL10), and CXC receptor 3 (CXCR3) for the destruction of  $\beta$ -cells in fulminant type 1 diabetes (Tanaka *et al.*, 2009). However, HLA-DR7 is rare in the Japanese population, and patients with fulminant type 1 diabetes and HLA-DR7 have not been reported thus far (Imagawa *et al.*, 2005). A case was reported in France (Moreau *et al.*, 2008). In this case, HLA-DR7 was available too. No genotypic analysis in Chinese fulminant type 1 diabetes has been reported to date. Here we propose that HLA-DR7 might be predisposed to fulminant type 1 diabetes in Chinese patients, but further study is required.

In this case, the patient presented a sudden onset of hyperglycemic and flu-like symptoms, with laboratory features typical of fulminant type 1 diabetes. Fulminant type 1 diabetes should be considered in Chinese diabetics, because without prompt and correct diagnosis and treatment, it may be fatal.

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