A follow-up study of fulminant type 1 diabetes mellitus

Jie Wang
Nanjing Medical University affiliated Nanjing Hospital: Nanjing First Hospital
Bing-li Liu
Nanjing Medical University affiliated Nanjing Hospital: Nanjing First Hospital
Zheng Li
Zhejiang Hospital
Hui-qin Li
Nanjing Medical University affiliated Nanjing Hospital: Nanjing First Hospital
Gu-ping Yin
Nanjing Medical University affiliated Nanjing Hospital: Nanjing First Hospital
Lei Ye
Singapore Heart Centre: National Heart Centre Singapore
Xiaofei Su (suxiaofeifei@126.com)
Nanjing First Hospital of nanjing medical university
Jian-hua Ma
Nanjing Medical University affiliated Nanjing Hospital: Nanjing First Hospital

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Abstract

Objectives

To explore the possible mechanisms of glycol-metabolism and islet function in patients with fulminant type 1 diabetes (FT1DM).

Methods

A follow-up study was conducted on 13 patients with FT1DM from September 2000 to March 2018. Patient general clinical data were collected and analyzed. The gene sequences of Human leukocyte antigen (HLA)-DRB1, HLA-DQA1 and HLA-DQB1 were analyzed by polymerase chain reaction (PCR).

Results

Compared with baseline, the waist-hip ratio was significantly increased at follow-up ($P<0.05$). Compared with baseline, HbA1c significantly increased; C-P0 and C-P120 significantly decreased, and the differences were statistically significant ($P<0.05$). Compared with baseline, White blood cell count (WBC), aspartate aminotransferase (AST), serum potassium (K), creatinine (Cr), glutamyl transpeptidase (GGT), creatine kinase (CK), alkalinity phospholipase (AKP) decreased significantly ($P<0.05$), while cholesterol (TC) and high-density lipoprotein (HDL) increased significantly ($P<0.05$). Viral antibody was detected in 13 cases of FT1DM: Coxsackie viral antibody was positive in 2 cases and herpes simplex viral antibody was positive in 3 cases. Gene detection: The higher frequency of HLA-DRB1 allele was DRB1*0301 (88.9%), DRB1*07 (44.4%), and the higher frequency of HLA-DQA1 allele was DQA1*0104 (55.6%), DQA1*0103 (44.4%), and the higher frequencies of HLA-DQB1 allele were DQB1*0201 (50.0%), DQB1*0502 (33.3%), and DQB1*0301 (25.0%).

Conclusions

Although the β-cell function of FT1DM was progressively irreversibly destroyed with the progression of the disease, metabolic disorders and stress responses were relieved at the later stage. Viral infections (herpes simplex virus, Coxsackie virus), HLA-DQ, DR genes, GAD-Ab and other related antibodies may be involved in the occurrence of FT1DM.

Introduction

According to the etiological classification criteria of diabetes established by WHO in 1999, type 1 diabetes mellitus (T1DM) can be divided into two types: autoimmunity (type 1A) and idiopathy (type 1B) [1]. Fulminant type 1 diabetes mellitus (FT1DM) is a special subtype of T1DM. FT1DM is extremely rare, prevalence of FT1DM in Japan was revealed as 1.0-8.9% of T1DM and 0.1–0.2% of all types of diabetes [1, 2]. It was first proposed by Imagawa [1] in 2000. It has the characteristics of acute onset, dangerous condition, ketoacidosis (DK) or ketoacidosis (DKA), high blood glucose, low glycated hemoglobin (HbA1c), and severe islet failure [1]. It is temporarily classified as type 1B diabetes. In the recent years,

FT1DM has attracted worldwide attention with the increasing number of cases. There are more reports of FT1DM, especially in East Asia [2–6]. These reports mainly described the clinical characteristics and etiological analysis of FT1DM. However, there are few follow-up studies on FT1DM. At present, the pathogenesis of FT1DM has not been fully understood. Most studies suggested that viral infection and human leukocyte antigen (HLA) gene might be related to its pathogenesis [7]. However, there were few reports about the viral infection in FT1DM patients and the correlation of HLA-DRB1, DQA1 and DQB1 genes in Chinese population.

We studied 13 FT1DM in-patients from September 2000 to March 2015to investigate the changes of glucose metabolism and islet function in patients with fulminant type 1 diabetes mellitus (FT1DM) over time and possible underlying mechanisms.

Subjects And Methods

Subjects

The protocol and informed consent document were approved by the Institutional Ethics Committee at Nanjing First Hospital. All patients subsequently gave written informed consent. 1. Inclusion criteria: Diagnosis of FT1DM was based on the diagnostic criteria proposed by Imagawa et al. [8] : 1) ketosis or ketoacidosis within a week of hyperglycemia; 2) initial blood glucose > 16 mmol/L (> 288 mg/dl) and glycosylated hemoglobin < 8.7%; The abdominal plasma C-peptide was < 0.1 nmol/L (< 0.3 ug/L) at onset and < 0.17 nmmol/L (< 0.5 ug/L) after stimulation (after meal or glucagon injection). 2. Exclusion criteria: Complicated with severe acute myocardial infarction, acute pancreatitis, primary liver disease and kidney disease; other mental illness that the researchers considered unsuitable for participation. 3. Thirteen FT1DM patients with ketoacidosis as the first symptom were enrolled into Department of Endocrinology, Nanjing First Hospital from September 2000 to March 2015. All FT1DM patients were followed up from March 2015 to March 2018.

Methods

Data collection: All the participated subjects were filled out by the residents of Endocrinology Department in a uniform form of questionnaire, which was checked by the quality supervisor and entered uniformly. The survey included: general information: name, sex, age,: height, weight, body mass index (BMI), waist circumference, hip circumference, waist-hip ratio, insulin dosage; admission diagnosis; history of DM, and discharge diagnosis. Hematological or metabolite parameters: All patients were tested for blood routine, biochemical indexes, HbA1c, fasting C-peptide (C-P), postprandial 120-point C-peptide (C-P120), GAD-Ab, ICA-Ab, INS-Ab, virus antibody, etc. C-P was detected by chemiluminescence (Roche-E170, Roche® Diagnostics GmbH, Mannheim, Germany), and HbA1c was measured by high performance liquid chromatography (HPLC) assay (Bio-Rad Laboratories, Inc. CA, USA). Liver and kidney function, myocardial enzymes, blood lipids and electrolytes were measured by Kodak 750 automatic biochemical analyzer (Kodak Company, USA). Viral antibody was detected by ELISA (Atu biological reagent, China).

For further diagnosis of molecular genetics, 2ml of peripheral blood samples for the patients were collected. The genotypes of HLA-DRB1, DQA1 and DQB1 were amplified and analyzed by polymerase chain reaction (PCR) amplification with sequence-specific primers (PCR-SSP) as previous reported 54 pairs primers[9, 10].The primers were synthesized by Shanghai Genomics institution (Shanghai, China). PCR Products were identified by DNA Agarose Gel Electrophoresis.

Analyses were performed using the SPSS 22.0 (SPSS, Science, Chicago, USA) statistical package. All variables were tested for normal distribution of the data. The normal distribution data were analyzed by the t-test and presented as means ± SD. The data of non-normal distribution were tested by Mann-Whitney test and expressed as median (IQR). Chi-square test was used to compare the rates between two groups. All comparisons were 2-sided at the 5% significance level. P value < 0.05 was considered to be statistically significant.

Results

1. The follow-up results of 13 FT1DM

The average age of onset was (46.54 + 7.14) years. The average course of disease was 7.38 ± 4.89 years in general data. Compared with the baseline (at the time when patient was diagnosed as F1TM), the waist-hip ratio significantly increased during follow-up period ($P < 0.05$). There was no significant difference among the pre-meal insulin dose, basal insulin dose and daily total insulin dose (u/d/Kg) ($P > 0.05$). (Table 1)

Table 1
Patient demographic data

Groups	FT1DM baseline (n = 13)	FT1DM follow-up (n = 13)	t/z	p
Age (years)	46.54 ± 7.14	53.92 ± 9.10		
Duration	4.31 ± 3.04 (days)	7.38 ± 4.89 (years)		
Body Mass Index (kg/m^2)	23.13 ± 3.92	23.2 ± 3.42	-0.045	0.965
Wasit to hip ratio (%)	0.93 ± 0.03	0.97 ± 0.04	-2.428	0.023*
The basal dosages of Insulin (u/Kg/day)	0.27 ± 0.1	0.28 ± 0.11	-0.167	0.868
The pre-meal dosages of insulin (u/Kg/day)	0.33 ± 0.13	0.39 ± 0.16	-1.058	0.301
The daily dosages of Insulin (u/Kg/day)	0.6 ± 0.18	0.67 ± 0.2	-0.923	0.365
Glycosylated hemoglobin(%)	7.18 ± 1.01	8.19 ± 1.2	-2.311	0.030*
Insulin antibodies (%)	2.9(2.43,6.39)	4.17(2.85,14.75)	-1.051	0.293
Fasting C-peptide (ug/L)	0.1(0.04,0.12)	0.01(0.01,0.02)	-3.381	0.001*
2-hr postprandial C-peptide (ug/L)	0.11(0.04,0.23)	0.01(0.01,0.06)	-3.07	0.002*

Note:*= p<0.05

2. Laboratory measurements

Compared with the baseline, HbA1c significantly increased at follow-up (P < 0.05), while C-P0 and C-P120 significantly decreased (P < 0.05). The titer of INS-Ab did not significantly increased (P > 0.05) (Table 1). TC and HDL significantly increased (P < 0.05), while white blood cell count (WBC), aspartate aminotransferase (AST), serum potassium (K), creatinine (Cr), glutamyl transpeptidase (GGT), creatine kinase (CK), and alkalinity phospholipase (AKP) all significantly decreased (P < 0.05). Cholesterol (TC) and high-density lipoprotein (HDL) increased significantly (P < 0.05). Other biochemical parameters were not statistically different (P > 0.05). (Table 2)

Table 2
Comparison of biochemical characteristics

Groups	F1DM baseline (n = 13)	F1DM follow-up (n = 13)	t/z	p
White blood cells (*10^9/l)	14.45 ± 9.11	6.01 ± 3	3.172	0.004*
Haemoglobin (g/L)	130.54 ± 17	130.54 ± 9.14	0	1.000
Alanine aminotransferase (U/l)	30(25.5,143.5)	21(15,31)	-1.899	0.058
Aspartate aminotransferase (U/l)	47(22.5,138.5)	21(16.5,24)	-2.696	0.007*
Cholesterol (mmol/l)	3.95 ± 0.91	4.85 ± 0.82	-2.639	0.014*
Triglyceride (mmol/l)	1.18 ± 0.41	1.19 ± 0.74	-0.029	0.977
HDL-cholesterol (mmol/l)	0.92 ± 0.41	1.66 ± 0.77	-3.05	0.006*
Glutamyl transpeptidase (U/L)	61.38 ± 46.81	23.92 ± 20.43	2.645	0.014*
Creatine kinase (U/L)	285.31 ± 234.17	145.69 ± 65.77	2.07	0.049*
Alkaline phosphatase (U/L)	122.54 ± 41.7	84.62 ± 26.32	2.773	0.011*
Potassium (mmol/l)	4.98 ± 0.84	4.04 ± 0.29	3.821	0.001*
Sodium (mmol/l)	134.9 ± 12.41	140.53 ± 4.03	-1.555	0.133
Chloride (mmol/l)	99.24 ± 8.38	103.42 ± 5.37	-1.516	0.143
Creatinine (mmol/l)	127.38 ± 56.98	85.51 ± 32.46	2.302	0.03*
Blood urea nitrogen (mmol/l)	10.29 ± 5.72	7.34 ± 2.92	1.656	0.111
Uric Acid (umol/L)	353.53 ± 199.43	325.11 ± 161.51	0.332	0.744
Urinary albumin (mg/L)	15.6(8.64,50.66)	12.96(7.45,27.52)	-0.493	0.622

Note:*= $p<0.05$

The viral antibody assay showed that the total positive rate was 38.46% (5/13), including 1 case of coxsackievirus antibody positive, 1 case of weak positive, and 3 cases of herpes simplex virus antibody positive at the onset of the disease.

The initial positive rate of GAD-Ab in the FT1DM patients was 20%, and the positive rate during follow-up decreased to 7.7%. FT1DM patients did not detect the ICA-Ab titer at the onset of the disease, and the positive rate of ICA-Ab was 11.1% during follow-up. The positive rate of INA-Ab in the initial stage of FT1DM was 30.8%, and the positive rate of INA-Ab during follow-up increased to 38.5%.

3. The genotypes of HLA-DRB1, DQA1 and DQB1

The higher frequencies of HLA-DQB1 alleles were DQB1*0201 (50.0%), DQB1*0502 (33.3%) and DQB1*0301 (25.0%). The higher frequencies of HLA-DQA1 alleles were DQA1*0104 (55.6%) and DQA1*0103 (44.4%). The higher frequencies of HLA-DRB1 alleles were DRB1*0301 (88.9%) and DRB1*07 (44.4%). The genotypes with two susceptible alleles were DQA1*03-DQB1*0303 (16.7%), DQA1*0302-DQB1*0303 (8.3%), DQA1*0103-DQB1*0601 (8.3%) and DRB1*0901-DQB1*0303 (8.3%). (Tables 3 and 4)

Table 3
The allele frequencies of FT1DM

	Gene	FT1DM(%)
HLA-DQB1	DQB1*0201	50.0
	DQB1*0301	25.0
	DQB1*0502	33.3
HLA-DQA1	DQA1*0103	44.4
	DQA1*0104	55.6
HLA-DRB1	DRB1*0301	88.9
	DRB1*07	44.4

Note:*= p<0.05

Table 4
The genotype frequencies of FT1DM

Gene	n	FT1DM(%)
DQA1*03-DQB1*0303	2	16.7
DQA1*0302-DQB1*0303	1	8.3
DQA1*0103-DQB1*0601	1	8.3

Note:*= p<0.05

Discussions

FT1DM is a rare and often misdiagnosed T1DM. There are few follow-up studies about FT1DM, especially those with a history of more than 5 years.

In this study, 13 patients with FT1DM were followed up for an average of 7.38 years. Patient WBC, AST, K, Cr, GGT, CK and AKP follow-up were significantly lower than those at onset of FT1DM, while TC and HDL were significantly higher than those in FT1DM follow-up, and tended to normalize, indicating that acute metabolic disorders recovered over time.

The results showed that the blood glucose of FT1DM patients was poorer, the function of islets was worse, and HbA1c was significantly higher compared than those at the onset stage of the disease. FT1DM had the characteristics of higher blood glucose and lower HbA1c at the onset stage of the disease. With the prolongation of the course of disease, the increased HbA1c indicated that the control of blood glucose was still unsatisfactory even after insulin treatment in the later stage of the disease. C-P and C-P 120 were significantly lower than those at the onset of FT1DM, indicating that islet beta cells did not completely damaged and they progressively reduced function after acute phase. It is different from our previous knowledge that the islet function of FT1DM patients was almost lost at onset of the disease [1, 4, 6]. This may be related to the short follow-up time and limited case reported.

A short-term follow-up of FT1DM patients by Imagawa [11] et al., showed that there was no difference in HbA1c between FT1DM patients and T1DM patients in 3, 6, and 12 months of follow-up. However, a 5-year follow-up study of FT1DM patients by Murase et al. [12] indicated that C-P120 maintained a low level for 5 years and C-P120 was lower in FT1DM patients than in T1DM patients. Furthermore, Tang et al., reported five FT1DM patients with follow-ups of 52 months [13]. The study showed that the HbA1c level of the F1DM patients increased and the islet function of all patients was worse than at the onset of the disease even after intensive treatment. This is similar to the current study.

Lan Liu et al. showed that HbA1c was elevated after 6 months of follow-up of FT1DM patients and C-P0 and C-P120 were not significantly different from onset of the disease [5]. 5 FT1DM patients were followed up by Lu Zeyuan et al. for 3–26 months indicated that C-P0 and C-P 120 were extremely poor, and there was no difference with the onset of FT1DM[14]. 6 patients were followed up with FT1DM for 9–72 months by Fan Yujuan et al. [15].They found that C-P0 and C-P120 were close to the level at admission, suggesting that pancreatic beta cells were completely and irreversibly destroyed. Huang Huibin et al., reported 2 patients and followed up the function of their pancreatic beta cell at 1 and 7 months respectively [16]. The results showed no improvement in the function of their pancreatic beta cell and the second case showed the function of islet B cells decreased significantly in the later stage. But our study showed followed-up C-P0 and C-P120 were significantly decreased compared with baseline.

At present, the pathogenesis of FT1DM is not completely clear. The pathogenesis of FT1DM may be mediated by many factors, including viral infection, pregnancy, drugs, autoimmune and genetic factors [17]. A study in Japan reported that the onset of the disease was related to genetic background and viral infection in 2012 [18].

In our study, we found that the HSV and Coxsackievirus antibodies were detected in 5 (out of 13 patients) during follow-up of FT1DM. Imagawa et al. reported that the positive rate of enterovirus antibodies was 6/19 (31.58%) at onset of FT1DM [19].Zheng et al. reported that the positive rate of coxsackievirus and mumps virus antibodies in acute stage was 6/20 (30%) [2] and HanafusaT et al. reported that the viral antibodies (Coxsackievirus, Cytomegalovirus, Human Herpes Virus 6) were found in 16.36% patients with acute FT1DM [6]. Thus, it is speculated that the pathogenesis of FT1DM is not caused by the virus itself, but the secondary immune response caused by virus infection.

Studies suggested that enteroviruses and chemokines not only destroyed the islet beta, but also further accelerated the autoimmune response mediated by remaining islet beta cells until all function of islet beta cells was destroyed [20, 21]. Our study shows that there is a high positive rate of viral antibody titer detected in the non-acute stage of FT1DM, which may support the above pathogenesis mechnism.

To explore the role of genetic background in FT1DM, we performed PCT and found the higher frequencies of HLA-DQB1 alleles at DQB1*0201 (50.0%), DQB1*0502 (33.3%) and DQB1*0301 (25.0%), higher frequencies of HLA-DQA1 alleles at DQA1*0104 (55.6%) and DQA1*0103 (44.4%), and higher frequencies of HLA-DRB1 alleles at DRB1*0301 (88.9%) and DRB1*07 (44.4%). These were not identified by the studies reported by Tsutsum or Tanaka et al. [22, 23]. They found higher frequencies of HLA-DQB1 alleles were DQB1*0401 (32.1%), DQB1*0303 (26.3%), DRB1*0405 (32.6%), DRB1*0901 (25.6%), DQA1*0303 (68%) and DQA1*0302 (36%). Xu et al., also reported the higher frequencies of DQB1*0303 (28%) and DRB1*0901 (28%) [24]. The study of 19 FT1DM patients showed the higher frequencices of DQA1-DQB1 genotype were DQA1*03-DQB1*0303 (18.4%) and DQA1*0102-DQB1*0601 (15.8%) by Zheng Chao et al. [2]. Our study has some same genotypes with the Japanese study, which showed that DRBl*0405-DQBl*0401 (32%) and DRB1*0901-DQB1*0303 (25%) were higher genotype frequencies in 255 cases and 414 cases of Japanese FT1DM patients, respectively [6, 22]. DQA1*0303-DQB1*0401 (68%), DQA1*0302-DQB1*0303 (36%), DQA1*0102-DQB1*0604 (14%) and DQA1*0103-DQB1*0601 (9%) were found with higher genotype frequencies in 22 FT1DM patients by Tanaka et al. [23]. However, the frequency of distribution is mostly inconsistent. This may be due to the different races and sample size. The results showed that the mechanism of HLA-II gene in FT1DM was different among different populations.

Imagawa et al. showed that GAD-Ab and INS-Ab were detected in FT1DM patients with low titer and short duration [11], while the ICA-Ab did not appear in FT1DM [4]. In the current study, it was found that GAD-Ab in the FT1DM patients was initially 20% and decreased to 7.7% during follow-up, while INA-Ab increased from 30.8% initially in the early stage of FT1DM to 38.5% during follow-up, and ICA-Ab was detected in 11.1% FT1DM patients during follow-up. These findings are quite surprising contrast with Imagawa's study, which showed only 4.8% (7/138) patients had GAD-Ab detected in a national survey in 2003 [12]. However, they are consistent with Zheng or Liu's studies that detected GAD-Ab in 35% and 30%, respectively, of FT1DM patients [2, 5].

The increased INA-Ab was probably due to the use of insulin. These results showed that the persistence of multiple antibodies in FT1DM from the initial stage of onset to several years later might be one of the reasons for the progressive decline and irreversible function of beta cells. In this study, multiple antibodies detected may support the autoimmune involvement in the occurrence of FT1DM [2].

In summary, with the progress of the disease, the function of FT1DM islet beta cells showed a trend of progressively irreversible destruction; various metabolic disorders and stress reactions of FT1DM were alleviated at the later stage of onset. Viral infection (herpes simplex virus, coxsackievirus), virus antibody production, HLA-DQ, DR gene, GAD-Ab and other related antibodies may be involved in the occurrence of FT1DM.

Declarations

Compliance with Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest: All authors declare that they have no conflict of interest.

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Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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