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ORIGINAL ARTICLE

Clinical characteristics of fulminant type 1 diabetes associated with pregnancy in China

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Abstract To report 12 cases of pregnancy-associated fulminant type 1 diabetes mellitus (PF) found in China from 2003 to 2010. The clinical and biochemical characteristics of these cases with PF were compared with a group of cases of child-bearing age with fulminant type 1 diabetes that was not associated with pregnancy (NPF). The clinical and biochemical characteristics of 12 PF cases were analyzed retrospectively and then compared with those characteristics of 20 NPF cases in China. The difference between Chinese and Japanese PF cases was investigated. The mean values of the characteristics from PF and NPF cases in China, including postprandial serum C-peptide concentration, plasma glucose concentration, and serum chloride were different. Compared to the 22 PF cases in Japan, the mean age of these 12 PF cases was much younger. The mean fasting and postprandial serum C-peptide concentration level were lower, and the mean HbA1c levels was higher in 12 PF cases in China. Eight of 12 PF cases in China developed the disease during pregnancy. Other four PF case developed the disease within 2 weeks after delivery. 12 PF cases in China showed more severe beta-cell destruction, the prognosis of their fetuses was extremely poor.

Keywords Fulminant · Type 1 diabetes · Pregnancy · China

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Introduction

According to the classification of diabetes by the American Diabetes Association (ADA) and the World Health Organization (WHO), type 1 diabetes is divided into two subtype: autoimmune type 1 (immune-mediated; type 1A) diabetes and idiopathic (type 1B) diabetes. Fulminant type 1 diabetes mellitus (fT1DM) has been identified as a new subtype of idiopathic diabetes which was firstly introduced by Imagawa et al. in 2000 [1]. The clinical characteristics of this subtype of type 1 diabetes are: (1) remarkably abrupt onset of disease; (2) very short (<1 week) duration of diabetic symptoms; (3) acidosis at diagnosis; (4) negative status of islet-related autoantibodies; (5) virtually no C-peptide secretion (<10 μg/day in urine); and (6) elevated serum pancreatic enzyme levels [2].

One of the characteristics of fulminant type 1 diabetes is that it develops with diabetic ketoacidosis (DKA) during pregnancy without preceding diabetes. It is well-known that the immunological milieu is significantly changed during pregnancy. However, the issue of whether the clinical and biochemical characteristics are different between the patients associated with and without pregnancy remains to be determined. DKA can be a catastrophic event during pregnancies. Shimizu et al. [3] reported that the onset of fulminant type 1 diabetes occurred during pregnancy or after delivery in the Ehime Study. Despite intensive therapy, maternal mortality

persists, with fetal loss rate reported to be as high as 9–35%. Imagawa et al. [2] confirmed that almost all cases who develop type 1 diabetes during pregnancy appeared to have fulminant type 1 diabetes and accounted for 21% of females aged 13–49 year in a nationwide survey. Autoimmune type 1 diabetes developing during pregnancy is rare in both reports. So it is necessary from a clinical point of view to analyze the clinical characteristics of pregnancy-associated fulminant type 1 diabetes (PF).

Our current understanding of pregnancy-associated fulminant type 1 diabetes is mainly based on studies carried out in Japanese population [2–4]. Owing to the potential genetic contribution to the disease onset, it is of great significance to further characterize PF in the Chinese population. Since the recognition of fulminant type 1 diabetes, a few cases and small group epidemiologic studies have been reported in China [5–9]. Rare PF cases had been reported. In this article, we investigated 12 cases of PF found in China since 2003 and compared them with 20 female cases of child-bearing age with fulminant type 1 diabetes not associated with pregnancy (NPF) [10].

Subjects and methods

Selection criteria

Inclusion criteria [11] for fulminant type 1 diabetes in our group were: (1) ketosis or ketoacidosis within a week after the onset of hyperglycemic symptoms; (2) plasma glucose level $\geq$16 mmol/l and HbA1c $\leq$8.5% at the first visit; and (3) fasting serum C-peptide level <0.3 ng/ml (0.1 nmol/l), or serum C-peptide level <0.5 ng/ml (0.17 nmol/l) after glucagon injection or meal load. PF was defined as those who developed fulminant type 1 diabetes during pregnancy as well as those who developed the disease within 2 weeks after delivery [4].

Cases

First, using retrospective review of case records, we identified 19 cases diagnosed with fulminant type 1 diabetes in our hospital and 43 cases diagnosed with fulminant type 1 diabetes that were published literature in China during 2003–2010 [10]. Second, we identified 32 female cases of child-bearing age (13–49 year) from these 62 cases of fulminant type 1 diabetes. Among them, 12 cases were diagnosed with PF and 20 cases were diagnosed with NPF using the criteria described above. Then we collected the clinical characteristics and laboratory data of these cases. The clinical characteristics and laboratory data of these 12 cases with PF were compared with those of 20 NPF cases and Japanese PF cases.

Methods

Clinical characteristics and laboratory data (age, BMI, date of onset of hyperglycemic symptoms, date of insulin therapy started, family history of diabetes, symptoms accompanying onset of diabetes, and diabetic complications) of all cases were recorded and analyzed. Obstetrical state at the onset of 12 PF cases was recorded. In addition, the following laboratory data were determined at the onset: plasma glucose concentration; HbA_{1c} levels; urinary ketone bodies; arterial pH; serum concentrations of sodium, potassium, chloride, fasting serum C-peptide level; and serum concentrations of amylase. Ketosis was determined by ketonuria: urinary ketone bodies $\geq$2+. Glutamic acid decarboxylase antibody (GADAb) was were measured by radioimmunoassay at the onset of diabetes. HbA1c levels were measured by high-performance liquid chromatography. Fasting plasma C-peptide and postprandial C-peptide levels were determined using the chemical-luminescence method after the resolution of diabetic ketoacidosis. IgM antibodies against mumps and coxsackie viruses were detected using quantitative in vitro enzyme-linked immunosorbent assays. Coxsackie viruses A (23 serotypes), B (6 serotypes), and Echoviruses (31 serotypes) were covered. All laboratories have participated in quality control procedures using commercially available kits. All patients were evaluated with ultrasonograms. Individual patients with elevated concentrations of serum amylase were further evaluated with abdominal computed tomography scans.

Statistics

Statistical analyses were done by using SPSS 17.0 statistical software. All continuous variables with a normal distribution are expressed as mean $\pm$ SD (Standard deviation), unless otherwise specified.

Results

Clinical and obstetrical characteristics of PF and NPF cases in China

All cases in the PF and NPF groups in China had the same characteristics of fulminant type 1 diabetes, as shown in Table 1. In comparison with the NPF cases, PF cases in our group had lower concentration of plasma glucose (36.2 $\pm$ 7.1 vs. 55.3 $\pm$ 21.2 mmol/l), and lower HbA1c levels (6.4 $\pm$ 0.5% vs. 6.5 $\pm$ 0.7%). They showed more severe beta-cell destruction, evidenced by lower concentration of fasting serum C-peptide (36.0 $\pm$ 36.2 vs. 69.7 $\pm$ 50.3 pmol/l) and postprandial serum C-peptide

Table 1 Clinical and obstetrical characteristics of PF and NPF patients in China

	PF	NPF	Fulminant
No.	12	20	62
Clinical characteristics			
Onset age (years)	25.0 ± 3.3	29.7 ± 11.4	29.9 ± 12.5
Duration of symptoms (days)	3.5 ± 1.9	3.4 ± 2.5	3.9 ± 2.1
BMI (kg/m^2)	20.8 ± 2.8	20.2 ± 1.2	21.6 ± 3.8
Accompanying symptoms			
Disturbance of consciousness (%)	16.7	40	31.0
Flu-like symptoms (%)	41.6	44.4	43.0
Gastrointestinal symptoms (%)	58.3	53.3	63.3
Laboratory data			
Plasma glucose level (mmol/l)	36.2 ± 7.1	55.3 ± 21.2	45.3 ± 18.1
HbA1c (%)	6.4 ± 0.5	6.5 ± 0.7	6.5 ± 0.7
Fasting serum C-peptide (pmol/l)	36.0 ± 36.2	69.7 ± 50.3	46.5 ± 45.0
Postprandial serum C-peptide (pmol/l)	35.1 ± 47.4	103.8 ± 58.4	68.6 ± 56.4
Arterial pH	7.12 ± 0.2	7.06 ± 0.2	7.09 ± 0.1
Serum amylase level (mmol/l)	423.8 ± 407.9	336.6 ± 319.0	390.2 ± 390.3
Serum sodium level (mmol/l)	133.9 ± 8.2	122.0 ± 8.5	129.1 ± 10.1
Serum potassium level (mmol/l)	5.6 ± 1.43	5.9 ± 1.5	6.0 ± 1.7
Serum chloride level (mmol/l)	107.1 ± 7.0	81.0 ± 6.2	94.6 ± 10.5
Urinary ketosis	2.7 ± 0.9	3.3 ± 0.7	3.0 ± 0.8
Autoantibodies			
GADAb (−/+)	11/1	19/1	
Insulin injection dosages (U kg^{-1} d^{-1})	0.74 ± 0.2	0.74 ± 0.3	0.72 ± 0.2

Data are the number or mean (range)

BMI body mass index, *HbA1c* hemoglobulin A1c

after recovering from diabetic ketoacidosis (35.1 ± 47.4 vs. 103.8 ± 58.4 pmol/l). In addition, they also had higher serum chloride level and serum sodium level. The mean age, mean BMI at the onset of fulminant type 1 diabetes and the mean duration of hyperglycemic symptoms before diagnosis were similar to those in NPF cases.

Thirst, polydipsia, and polyuria, as common symptoms accompanying the onset of overt diabetes, were observed in all PF cases. Disturbance of consciousness was observed in two cases (16.7%), Flu-like symptoms such as fever, headache, sore throat, cough, rhinorrhea, and joint pain were observed in five cases (41.6%), and complained of gastrointestinal symptoms, such as nausea, vomiting, abdominal pain and diarrhea were observed in seven cases (58.3%). These frequencies were similar to NPF cases, as listed in Table 1.

All cases in our group had ketoacidosis at the onset: The urinary ketone bodies were 2+–4+. The mean levels of arterial pH, potassium, amylase, and insulin injection dosages in PF cases were similar to those in NPF cases. Eleven of 12 PF cases were negative for GADAb, and one case was positive for GADAb. Nineteen of 20 NPF cases also were negative for GADAb. These frequencies were similar to NPF cases.

Other clinical characteristics in PF cases in China: no case died; none of these cases had history of diabetes and autoimmune diseases; one case had family history of diabetes. There had no hypertriglyceridemia which may lead to acute pancreatitis. Ultrasonograms or computed tomography scans of pancreas were normal in all cases, while serum or urine amylase levels were out of the normal range in three cases. No anti-virus antibody had been found in any PF case. In NPF cases: one case died in severe acidosis, one case developed acute pancreatitis which was confirmed by ultrasonograms and computed tomography scans of pancreas.

Clinical and obstetrical characteristics of PF in China compared with those in Japan

As shown in Table 2, the mean age at the onset of these 12 PF cases in our group was much younger than that of Japanese cases. The mean BMI and the mean duration of hyperglycemic symptoms before diagnosis in 12 PF cases in China were similar to those in Japan. Compared to the 22 PF cases in Japan, 12 PF cases in our group showed more severe beta-cell destruction. The mean fasting and postprandial serum C-peptide concentration level after recovering from diabetic ketoacidosis were lower than those 22 PF cases in Japan. The mean plasma glucose concentration was 36.2 mmol/l in our group and 39.8 mmol/l in Japan. In addition, the mean HbA1c levels were 6.4% in our group and 5.8% in Japanese PF cases.

Eight of 12 PF cases developed the disease during pregnancy (6th, 24th, 25th, 27th, 29th, 32nd, 33rd, and 38th week of gestation; average of eight cases, 26.9 week). The onset of four PF cases that developed after delivery was within 2 weeks after delivery (2nd, 2nd, 5th, and 7th d; average of 4 cases, 4 d). Fetal demise occurred in 7 of 8 PF

Table 2 Clinical and biochemical characteristics of PF in China compared with those in Japan

	China($n = 12$)	Japan($n = 22$)
Clinical characteristics		
Onset age (years)	25.0(21–32)	30.2(23–38)
Duration of symptoms (days)	3.5(1–6)	3.3(1–9)
BMI (kg/m^2)	20.8(17.3–26.2)	21.4(16.9–29.5)
Duration of pregnancy (week)	26.9(6–38)	26.3(7–38)
Family history of diabetes (−/+)	11/1	17/4
Prognosis of fetus (alive/dead)	4/8	6/12
Accompanying symptoms		
Flu-like symptoms (%)	42	70
Gastrointestinal symptoms (%)	58	45
Laboratory data		
Plasma glucose level (mmol/l)	36.2(22.5–48.7)	39.8(16.8–72.4)
HbA_{1c} (%)	6.4(5.7–7.1)	5.8(4.8–8.2)
Fasting serum C-peptide (pmol/l)	36.0(10–100)	63.3(10–133)
Postprandial serum C-peptide (pmol/l)	35.1(10–100)	53.3(10–133)
Arterial pH	7.12(6.93–7.40)	7.06(6.87–7.28)
Serum amylase level[a] (mmol/l)	4.2(0.41–21.5)	5.1(0.6–37.2)
Autoantibodies		
GADAb (−/+)	11/1	20/1

Data are the number or mean (range)

BMI body mass index, *HbA_{1c}* hemoglobulin A_{1c}

[a] Values are expressed as multiples of the upper limit of the normal range

cases who developed diabetes during pregnancy (87.5%), one case developed PF 2 days after delivered a dead fetal. The gestational week at onset and fetal demise occurred in Chinese cases were similar to Japanese PF cases, as shown in Table 2.

Flu-like symptoms and gastrointestinal symptoms occurred in PF cases in China were similar to the Japanese PF cases, as listed in Table 2. The mean levels of arterial pH and serum amylase in 12 PF cases in China were similar to those in Japan. Eleven of 12 PF cases in China were negative for GADAb, while twenty of 21 PF cases in Japan were negative for GADAb. These frequencies were similar to NPF cases.

Discussion

Shimizu et al. [4] compared the clinical characteristics of 22 PF cases with 48 NPF cases in Japan. They reported that the PF group showed a more severe acidosis than the NPF group, and the prognosis of PF group fetuses was extremely poor. In our study, the mean HbA1c levels and amylase was similar in PF cases and NPF cases. The mean plasma glucose concentration in PF cases was lower than those in NPF cases. In addition, the mean serum chloride level in the PF cases was higher than those in the NPF cases. The reason remains unclear. In normal pregnancy, insulin secretion increases throughout gestation whereas peripheral insulin sensitivity decreases. Fasting levels of plasma glucose was reduced by approximately 10 per cent during pregnancy in Chinese group [12]. This may be one of the factors that affect the plasma glucose concentration in PF cases.

In our group, besides those typical symptoms, the mean plasma glucose concentrations, arterial pH, serum amylase, BMI, duration of diabetes, GADAb were close to those in Japanese PF study. It demonstrated that our data did not largely differ from the Japanese data. However, the mean levels of HbA1c, fasting and postprandial serum C-peptide concentration were differ than those in Japan, which showed more severe beta-cell destruction and metabolic disorders in Chinese PF cases.

The pathogenesis of fulminant type 1 diabetes remains unclear [13]. Some evidences suggest that both genetic factors, such as human leukocyte antigen (HLA) [10], and environmental factors, such as viral infection, contribute to the development of this disease. Based on the findings made to date, both viral infection and the subsequent immune reaction in genetically susceptible individuals cause β-cell destruction and lead to fulminant type 1 diabetes. Flu-like symptoms were observed in five PF cases in our group indicating that viral infection was critical in the development of disease. Yet no anti-virus antibody had been reported in any PF case. Islet-related autoantibodies seldom appeared in PF. Our study showed that 8.33% of PF cases were positive for GADAb but we had no evidence showing that other autoimmune diseases were related to Chinese PF cases. Further research in depth is needed to understand the pathophysiology of PF.

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