Clinical analysis of fulminant type 1 diabetes in China and comparison with a nationwide survey in Japan

Analyse clinique du diabète de type 1 fulminant en Chine et comparaison avec une enquête nationale japonaise

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Abstract

Objectives. – To report 26 cases of fulminant type 1 diabetes found in Guangdong Medical College Futian Hospital and Central South University Second Xiangya Hospital in China and to study the difference between Chinese and Japanese patients.

Methods. – The clinical and biochemical characteristics of 26 patients who had been diagnosed with fulminant type 1 diabetes mellitus in China were analyzed retrospectively and then compared with those characteristics of 161 patients from a nationwide survey in Japan at the time of diagnosis and follow-up 6 months.

Results. – The mean values of the characteristics from these two data sets, including fasting and postprandial serum C-peptide concentration, serum sodium and potassium level, were significantly different (P = 0.003, P = 0.005, P = 0.035, P = 0.030, P < 0.001, respectively).

Conclusions. – The clinical and biochemical characteristics of Chinese patients did not largely differ from those of Japanese patients. Further studies are needed for some unique characteristics found in our group.

Résumé

Objectifs. – Rapporter 26 cas de diabète de type 1 fulminant observés à l’hôpital Futian de l’École de médecine Guangdong et à l’hôpital Xiangya II de l’université Sud-Centrale et étudier la différence entre les patients chinois et japonais.

Méthodes. – Analyse rétrospective des caractéristiques cliniques et biologiques de 26 patients chinois ayant un diabète de type 1 fulminant et comparaison avec les caractéristiques correspondantes de 161 patients japonais étudiés au moment du diagnostic et à six mois de suivi dans une enquête nationale.

Résultats. – La comparaison des valeurs moyennes des caractéristiques de ces deux séries de patients montrait des différences significatives : C-peptide à jeun et postprandiale (p = 0.003) ; natrémie (p = 0.005) ; kaliémie (p = 0.030) ; présence d’anticorps anti-GAD (p = 0.001).

Conclusions. – Les caractéristiques cliniques et biologiques des patients chinois ne diffèrent pas substantiellement de ceux des patients japonais. D’autres études seront nécessaires en ce qui concerne certaines caractéristiques particulières de nos patients.

1. Introduction

According to the recently proposed 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:

- remarkably abrupt onset of disease;
- very short (< 1 week) duration of diabetic symptoms;
- acidosis at diagnosis;
- negative status of islet-related autoantibodies;
• virtually no C-peptide secretion (< 10 μg/day in urine);
• elevated serum pancreatic enzyme levels [2].

Since the recognition of fulminant type 1 diabetes, a few cases and small group epidemiologic studies have been reported in China [3–6]. In this paper, we investigated 26 cases of fulminant type 1 diabetes found in the two hospitals since 2003. The results were compared with a nationwide survey in Japan which has 161 cases of fulminant type 1 diabetes.

2. Subjects and methods

2.1. Selection criteria

Inclusion criteria [7] for fulminant type 1 diabetes in our group were:

• ketosis or ketoacidosis within a week after the onset of hyperglycemic symptoms;
• plasma glucose level greater or equal to 16 mmol/L and HbA1c less or equal to 8.5% at the first visit;
• fasting serum C-peptide level less than 0.3 ng/mL (0.1 nmol/L), or peak serum C-peptide level less than 0.5 ng/mL (0.17 nmol/L) after glucagon injection or meal load.

2.2. Methods

Clinical characteristics and laboratory data (age, sex, 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 patients were recorded and analyzed. In addition, dosages of daily insulin injection and the following laboratory data were determined at the onset and the following 6 months: plasma glucose concentration; HbA1c levels; urinary ketone bodies; arterial pH; serum concentrations of sodium, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, and triglyceride; fasting serum C-peptide level; and serum concentrations of amylase. Ketosis was determined by ketonuria: urinary ketone bodies greater or equal to 2+. GADAb, islet cell antibody (ICA), islet cell antibody (ICA), and ZenT8Ab were determined at the onset of diabetes.

2.3. Treatment and follow-up

According to Imagawa et al. [7], all patients were treated as usual diabetic ketoacidosis as soon as possible. The goal is to cure ketoacidosis without any complication. After recovering from diabetic ketoacidosis, insulin injection therapy including continuous subcutaneous insulin injection (CSII) and multiple daily insulin injection (MDI) was recommended to all the patients. All patients were followed up for 6 months or more.

2.4. Statistics

Statistical analyses were done by using SPSS 11.0 statistical software. Statistical results were shown as mean ± standard deviation (SD), unless otherwise specified. Group comparisons were done by using two independent t tests, whereas frequency comparisons were done by using Fisher’s exact test. All tests were two-sided, and a \( P < 0.05 \) was required for statistical significance.

3. Results

In the two hospitals, 477 patients were diagnosed with type 1 diabetes mellitus since 2003. Of these 477 patients, 26 (5.45%) were diagnosed with fulminant type 1 diabetes and the remaining 451 patients (94.55%) were classified as having autoimmune type 1 diabetes. The morbidity of fulminant type 1 diabetes in the two hospitals was 5.45%, which was higher than that given by the Second Xiangya Hospital in China (1.5%) [8,9], yet lower than that given by the nationwide survey in Japan (19.4%) [2].

As shown in Table 1, the mean age at the onset of fulminant type 1 diabetes (22.2 ± 12.1 years) of these 26 patients in our group was much younger than that of Japanese patients (39.1 ± 15.7 years, \( P = 0.001 \)). Twelve of these 26 patients were male in our group, while 51.6% Japanese patients were male. No significant differences were found between these two groups in the mean BMI at the onset of fulminant type 1 diabetes and the mean duration of hyperglycemic symptoms before diagnosis. The mean plasma glucose concentration was 45.4 ± 17.8 mmol/L in our group and 44.4 ± 20 mmol/L in Japanese nationwide survey (\( P = 0.914 \)). In addition, the mean HbA1c levels was 6.7 ± 0.8% in our group and 6.4 ± 0.9% in the Japanese nationwide survey (\( P = 0.412 \)). These two values were very close.

Thirst, polydipsia, and polyuria, as common symptoms accompanying the onset of overt diabetes, were observed in 21 cases (80.8%) in our group. Disturbance of consciousness was observed in 17 cases (65.4%), flu-like symptoms and fever were observed in 13 cases (50%), and abdominal pain was observed in five cases (19.2%). None of them was significantly different from the Japanese nationwide survey, as listed in Table 1.

Compared to the Japanese nationwide survey, fulminant type 1 diabetes in our group showed more severe beta-cell destruction. The mean fasting serum C-peptide concentration level was 0.04 ± 0.02 nmol/L (0.10 ± 0.07 nmol/L in Japanese patients, \( P = 0.003 \)). The mean postprandial serum C-peptide concentration level was 0.07 ± 0.03 nmol/L after recovering from diabetic ketoacidosis (0.10 ± 0.10 nmol/L in Japanese patients, \( P = 0.005 \)).

3.1. All patients in our group had ketoacidosis at the onset

The urinary ketone bodies were 2+ ~ 3+. The mean levels of arterial pH, base excess, serum bicarbonate, carbon dioxide combining power, sodium, chloride, and potassium were 7.163 ± 0.066, −21.1 ± 3.8 mmol/L, 7.8 ± 2.8 mmol/L, 7.1 ± 2.1 mmol/L, 124.03 ± 5.94 mmol/L, 90.8 ± 6.4 mmol/L, and 6.29 ± 0.64 mmol/L, respectively. Among these, serum sodium and potassium levels were significantly

3.3. Follow-up

14 patients. or urine amylase levels were out of the normal range in eridemia, which may lead to acute pancreatitis. The serum was 1.40 family history of diabetes. The mean serum triglyceride level had either history of diabetes and autoimmune diseases or been reported by our previous study[10]; none of these patients diabetes, and the clinical characteristics of these patients had been diagnosed with pregnancy-associated fulminant type 1 diabetes mellitus (fT1DM) in China compared with those in Japan. Table 1

Clinical and biochemical characteristics of patients with Fulminant type 1 diabetes mellitus (fT1DM) in China compared with those in Japan.

<table>
<thead>
<tr>
<th></th>
<th>China (n = 26)</th>
<th>Japan (n = 161)</th>
<th>P value</th>
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<tr>
<td><strong>Clinical characteristics</strong></td>
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<tr>
<td>Age (years)</td>
<td>29.2 ± 12.1</td>
<td>39.1 ± 15.7</td>
<td>0.001</td>
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<tr>
<td>Male (%)</td>
<td>43.2 (12/26)</td>
<td>51.6 (83/161)</td>
<td>0.431</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 6.0</td>
<td>20.7 ± 3.9</td>
<td>0.487</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>0</td>
<td>0.6 (1/161)</td>
<td></td>
</tr>
<tr>
<td>Anti-GAD Abs (%)</td>
<td>30.7 (8/26)</td>
<td>4.8 (7/145)</td>
<td>0.001</td>
</tr>
<tr>
<td>Association with pregnancy (%)</td>
<td>0</td>
<td>21 (13/62)</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>3.3 ± 1.0</td>
<td>4.4 ± 3.1</td>
<td>0.053</td>
</tr>
<tr>
<td>Thirst (%)</td>
<td>80.8</td>
<td>93.7</td>
<td>0.310</td>
</tr>
<tr>
<td>Flu-like symptoms (%)</td>
<td>50.0</td>
<td>71.7</td>
<td>0.220</td>
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<tr>
<td>Fever</td>
<td>50.0</td>
<td>60</td>
<td>0.456</td>
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<tr>
<td>Abdominal pain (%)</td>
<td>19.2</td>
<td>50.2</td>
<td>0.219</td>
</tr>
<tr>
<td>Disturbance of consciousness (%)</td>
<td>65.4</td>
<td>45.2</td>
<td>0.255</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
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<tr>
<td>Plasma glucose level (mmol/L)</td>
<td>45.2 ± 17.6</td>
<td>44.4 ± 20</td>
<td>0.914</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.7 ± 0.8</td>
<td>6.4 ± 0.9</td>
<td>0.412</td>
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<tr>
<td>Fasting serum C-peptide (nmol/L)</td>
<td>0.04 ± 0.02</td>
<td>0.10 ± 0.07</td>
<td>0.003</td>
</tr>
<tr>
<td>Postprandial serum C-peptide (nmol/L)</td>
<td>0.07 ± 0.03</td>
<td>0.10 ± 0.10</td>
<td>0.005</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.163 ± 0.066</td>
<td>7.125 ± 0.125</td>
<td>0.216</td>
</tr>
<tr>
<td>Serum amylase level (mmol/L)</td>
<td>185.16 ± 174.00</td>
<td>57.8 (74/128)</td>
<td>0.208</td>
</tr>
<tr>
<td>Serum sodium level (mmol/L)</td>
<td>124.03 ± 5.94</td>
<td>131 ± 9</td>
<td>0.035</td>
</tr>
<tr>
<td>Serum potassium level (mmol/L)</td>
<td>6.29 ± 0.64</td>
<td>5.5 ± 1.2</td>
<td>0.030</td>
</tr>
<tr>
<td>Serum total cholesterol level (mmol/L)</td>
<td>4.372 ± 0.779</td>
<td>5.1 ± 1.6</td>
<td>0.071</td>
</tr>
<tr>
<td>Serum triglycerides level (mmol/L)</td>
<td>1.740 ± 1.842</td>
<td>2.0 ± 1.8</td>
<td>0.774</td>
</tr>
</tbody>
</table>

Different from the Japanese national survey (P=0.035, P=0.030).

All cases in our group were negative for ICAb, IAAb, and ZnT8Ab, except that eight cases (30.7%) were suspected for positive GADAb. This ratio was much higher than that given by the Japanese national survey (4.8%, P<0.001).

3.2. Other clinical characteristics in our group

A patient with fulminant type 1 diabetes died; six patients were diagnosed with pregnancy-associated fulminant type 1 diabetes, and the clinical characteristics of these patients had been reported by our previous study[10]; none of these patients had either history of diabetes and autoimmune diseases or family history of diabetes. The mean serum triglyceride level was 1.40 ± 1.01 mmol/L; hence, there were no hypertriglyceridemia, which may lead to acute pancreatitis. The serum or urine amylase levels were out of the normal range in 14 patients.

3.3. Follow-up

The mean HbA1c levels was (8.6 ± 1.8)% at 6 months after the onset in our group. The HbA1c levels were 7.3% and 7.4% in seven patients treated by CSII, and 7.5 ~ 11.8% in others who were not treated by CSII. The fasting and postprandial serum C-peptide concentration levels in our group were 0.02 ~ 0.06 (0.04 ± 0.02) nmol/L and 0.03 ~ 0.09 (0.06 ± 0.03) nmol/L at 6 months after the onset, which were not significantly different than those corresponding levels at the onset (P=0.093, P=0.363). Additionally, the mean dosages of insulin injection was 0.62 ± 0.16U·kg⁻¹·d⁻¹ at 6 months after the onset, which was not significantly different than the level at the onset (P=0.929) either.

Compared to the Japanese national survey, fulminant type 1 diabetes in our group showed much higher HbA1c levels (P=0.007) and lower insulin injection dosages (P=0.013) at 6 months after the onset. However, they were close to each other at the onset, as shown in Fig. 1 and Table 1.

4. Discussion

In our group, besides those typical symptoms, the mean plasma glucose concentrations, HbA1c levels, arterial pH, base excess, serum bicarbonate, carbon dioxide combining power, sodium, chloride, and potassium levels were close to those in Japanese national survey (P>0.05). It demonstrated that our data did not largely differ from the Japanese data. However, the mean levels of serum sodium, serum potassium, fasting and postprandial serum C-peptide concentration were significantly different than those in Japanese nationwide survey, which indicated that fulminant type 1 diabetes has more severe beta-cell destruction and metabolic disorders in Chinese patients.

The pathogenesis of fulminant type 1 diabetes was not clear. Viral infection would play an important role to the destruction of beta-cells in susceptible individuals. Flu-like symptoms were observed in 13 cases in our group indicating that viral infection was critical in the development of fulminant type 1 diabetes. Yet we had not found any anti-virus antibody. Titers of antibodies of human herps virus-6, herpes simplex virus, coxsackie A, coxsackie B virus, echo virus, Epstein-Barr virus, and
mumps virus were identified in some cases reported [4,11]. However, the Japanese nationwide survey found that no antibody of 24 serotype specific neutralizing antibodies was raised in 24 patients of fulminant type 1 diabetic patients. Above findings suggested that factors within host will play more important role in the development of fulminant diabetes than virus itself dose [2].

Islet-related autoantibodies seldom appeared in fulminant type 1 diabetes. Whether or not the pathogenesis of fulminant type 1 diabetes was associated with autoimmunity was still unknown. Some findings indicated that auto-reactive T cells might contribute, at least in part, to the development of fulminant type 1 diabetes [7]. Our study showed that 30.7% of fulminant diabetes patients were positive for GADAb but we had no evidence showing that other autoimmune diseases were related to Chinese patients.

The mean HbA1c levels of patients using CSII therapy was lower than that of using MDI in our group. This demonstrated that using CSII therapy will benefit to the treatment of fulminant type 1 diabetes especially when fasting blood glucose is poorly controlled [12].

Obesity (BMI = 34 kg/m²), moderate fatty liver, acanthosis nigricans-like changes in neck and armpit skin [5] which indicated insulin resistance were found in one patient in our group. This patient was treated by insulin injection therapy 0.71U·kg⁻¹·d⁻¹, plus metformin 1500 mg/day and rosiglitazone 4 mg/day. Different genes or gene mutation may be involved in the pathogenesis of fulminant type 1 diabetes [13,14]. Further research in depth is needed to understand the pathophysiology of fT1DM.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References