Distinct Diagnostic Criteria of Fulminant Type 1 Diabetes Based on Serum C-Peptide Response and HbA1c Levels at Onset

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OBJECTIVE — Diagnostic criteria in fulminant type 1 diabetes, a novel subtype of type 1 diabetes, remain unclear.

RESEARCH DESIGN AND METHODS — We analyzed basal and longitudinal changes of serum C-peptide levels during a 75-g oral glucose tolerance test (OGTT) in 125 consecutively recruited patients with type 1 diabetes including fulminant type 1 diabetes (n = 25) and acute-onset type 1 diabetes (n = 100). Discriminating criteria of fulminant type 1 diabetes were examined using receiver-operating characteristic curve analysis and multiple logistic regression analysis.

RESULTS — The integrated values of serum C-peptide response during OGTT (ΣC-peptide) in fulminant type 1 diabetes at onset, 1 year, and 2 years after onset were markedly lower than those in acute-onset type 1 diabetes. None of the patients with fulminant type 1 diabetes had improvement of C-peptide response to OGTT. Fasting C-peptide values at onset in fulminant type 1 diabetes were significantly lower than those in acute-onset type 1 diabetes. We established diagnostic criteria of serum C-peptide and HbA1c levels at onset that discriminate fulminant type 1 diabetes from acute-onset type 1 diabetes with high sensitivity and specificity: a criterion in which the levels of both the fasting C-peptide is ≤0.033 nmol/l and HbA1c is ≤8.0% or a criterion in which the levels of both the ΣC-peptide is ≤0.540 nmol/l and HbA1c is ≤8.0%.

CONCLUSIONS — Fulminant type 1 diabetes has extremely low β-cell function at onset that rarely recovers after onset. Sensitive and specific diagnostic criteria were established for detection of fulminant type 1 diabetes based on serum C-peptide and HbA1c levels at onset.

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In 1988, a study suggested that there might be a novel subtype of type 1 diabetes that was called the “fulminant form of type 1 diabetes” (1,2). In 2000, this subtype, which had the same characteristics as the subtype discussed in the 1988 study, was described and named “fulminant type 1 diabetes” (3–6). The characteristic features at onset of this subtype of type 1 diabetes (1–6) include: 1) abrupt onset of diabetes with fulminant symptoms including marked hyperglycemia, severe diabetic ketoacidotic coma, and normal or near-normal HbA1c levels; 2) absence of autoantibodies against islet cells including islet cell antibodies (ICA), GAD autoantibodies (GADAb), insulinoma-associated protein 2/islet cell antigen 512 autoantibodies (IA-2Ab), and insulin autoantibodies (IAA); and 3) involvement of exocrine pancreas as well as pancreatic islets with elevated serum levels of pancreatic enzymes. The key issue for the diagnosis in this new subtype of type 1 diabetes is absence of autoantibodies against islet cells. However, the measurement of pancreatic autoantibodies including GADAb, ICA, IA-2Ab, and IAA is in the process of being standardized (7), and these autoantibodies can be measured in a limited number of laboratories. Data on longitudinal changes of serum C-peptide levels as well as the basal values in newly diagnosed patients with type 1 diabetes, including fulminant type 1 diabetes and classical type 1 diabetes, were obtained prospectively. We tried to establish sensitive and specific criteria for clinical diagnosis of fulminant type 1 diabetes at onset based on serum C-peptide concentration.

RESEARCH DESIGN AND METHODS — A total of 126 newly diagnosed type 1 diabetic patients (onset age 34 ± 15 years [mean ± SD]; age range 2–71; 70 men, 56 women) were consecutively recruited in the “Toranomon Prospective Study on Type 1 Diabetes” from
1980 to 2001 (5,8–13). All patients met the American Diabetes Association criteria for type 1 diabetes (14). The duration from onset of diabetes symptoms to hospitalization was within 90 days in all case subjects. The exclusion criteria were the presence of mitochondrial DNA mutation (A/G) at 3,243 bp and/or hepatocyte nuclear factor-1α gene mutation. One patient was excluded because of the presence of mitochondrial DNA mutation (A/G) at 3,243 bp. According to the tentative criteria in previous studies (3,5), 25 patients who were negative for autoantibodies against pancreatic antigens (including ICA, GADAb, IA-2Ab, and IAA) and had normal or near-normal HbA1c levels (=8.3%) at onset of diabetes were diagnosed as having fulminant type 1 diabetes. The remaining 100 patients were subdivided as acute-onset type 1 diabetes. Residual β-cell function of the total 125 patients, including 25 patients with fulminant type 1 diabetes and 100 patients with acute-onset type 1 diabetes, was analyzed in this study.

At onset of overt diabetes, all patients were hospitalized. Their clinical characteristics were recorded, and plasma glucose, HbA1c, arterial pH, serum elastase 1, serum amylase, and serum lipase were measured within 2 days after initial diagnosis. HbA1c levels were measured by a high-performance liquid chromatography method calibrated with Japan Diabetes Society Calibrator Lot 2 (15). This method for HbA1c assay was standardized by the Japan Diabetes Society/Japanese Society of Clinical Chemistry and established a firm and reproducible link to the method of the International Federation of Clinical Chemistry (15). In all patients with type 1 diabetes, blood samples for the assay for pancreatic autoantibodies were obtained at least twice within 10 and 30 days after the diagnosis of diabetes. All serum samples for autoantibody and C-peptide assays were kept at −80°C until assay.

Diabetes-related autoantibodies (including ICA, GADAb, IA-2Ab, and IAA) and had their improvement of residual β-cell function in different subgroups of type 1 diabetes were compared using Fisher’s exact test. Receiver-operating characteristic (ROC) curves were analyzed to define the optimal cutoff values of clinical and laboratory findings at onset for discrimination of fulminant type 1 diabetes from acute-onset type 1 diabetes (22). Each discriminating criterion of clinical or laboratory finding at onset was devised based on the corresponding cutoff value. The areas under ROC curves (AUCs), which indicate the accuracy of the tests, were calculated and compared (23). A multiple logistic regression analysis was performed to identify independent factors for prediction of fulminant type 1 diabetes. The following variables of clinical and laboratory findings at onset were included in the multiple regression analysis: age at onset, sex, BMI, duration of hyperglycemic symptoms before diagnosis, plasma glucose levels, arterial pH, serum amylase levels, serum lipase levels, serum elastase 1 levels, ΣC-peptide values, and fasting C-peptide levels. Continuous variables were dichotomized based on whether they met or did not meet the discriminating criteria, which were devised by the optimal cutoff values as mentioned above, and then these variables were included in multiple regression analysis. A multiple regression model for predicting diagnosis of fulminant type 1 diabetes was devised and evaluated on our study population. The model was constructed by stepwise selection with $P = 0.05$ used as the criterion for both entry into and retention in the model. We used JMP software (version 5) and MedCalc software (version 7) for statistical analyses. All data except for AUCs were expressed as mean ± SD. The protocol of the Toranomon Prospective Study on Type 1 Diabetes was approved by the Ethical Committee of Toranomon Hospital.

**RESULTS**

**Clinical features at onset of diabetes in patients with fulminant type 1 diabetes**

Twenty-five patients with fulminant type 1 diabetes had significantly shorter duration of hyperglycemic symptoms before diagnosis (mean 4 ± 3 days, range 1–10, $P < 0.0001$) versus acute-onset type 1 diabetes (mean 48 ± 32 days, range 1–90, $n = 100$). Plasma glucose levels at onset of...
diabetes in patients with fulminant type 1 diabetes (47.4 ± 20.4 mmol/l [16.9 – 102.0]) were significantly higher than those in patients with acute-onset type 1 diabetes (26.7 ± 12.8 mmol/l [11.3 – 71.1]) (P < 0.0001). In contrast, the levels of HbA1c at onset of diabetes in patients with fulminant type 1 diabetes (6.5 ± 1.1% [4.3 – 8.3]) were significantly lower than those in patients with acute-onset type 1 diabetes (11.3 ± 2.7% [5.1 – 19.1]) (P < 0.0001). The degree of acidosis in patients with fulminant type 1 diabetes (arterial blood pH 7.11 ± 0.14 [6.91 – 7.34]) was more severe than that in patients with acute-onset type 1 diabetes (7.28 ± 0.09 [7.02 – 7.39]) (P < 0.0001). Ninety-six percent (24/25) of patients with fulminant type 1 diabetes remained unchanged during a 2-year period after onset (Fig. 1). The mean values in patients with acute-onset type 1 diabetes (0.243 ± 0.087 nmol/l at onset (n = 25), 0.083 ± 0.157 nmol/l at 1 year after onset (n = 15), and 0.025 ± 0.078 nmol/l at 2 years after onset (n = 12). The mean values in patients with acute-onset type 1 diabetes (C) were 2.443 ± 1.530 nmol/l at onset (n = 100), 2.611 ± 1.970 nmol/l at 1 year after onset (n = 51), and 1.791 ± 1.548 nmol/l at 2 years after onset (n = 48).

**Figure 1**—Longitudinal changes of residual β-cell function in type 1 diabetes. The mean integrated values of serum C-peptide levels obtained during OGGT (2C-peptide) in patients with fulminant type 1 diabetes (○) were 0.087 ± 0.190 nmol/l at onset (n = 25), 0.083 ± 0.157 nmol/l at 1 year after onset (n = 15), and 0.025 ± 0.078 nmol/l at 2 years after onset (n = 12). The mean values in patients with acute-onset type 1 diabetes (C) were 2.443 ± 1.530 nmol/l at onset (n = 100), 2.611 ± 1.970 nmol/l at 1 year after onset (n = 51), and 1.791 ± 1.548 nmol/l at 2 years after onset (n = 48).

Longitudinal changes of residual β-cell function and diagnostic criteria in patients with fulminant type 1 diabetes

**Residual β-cell function.** The values of 2C-peptide in patients with fulminant type 1 diabetes were markedly lower than those in patients with acute-onset type 1 diabetes at onset (P < 0.0001), 1 year after onset (P < 0.0001), and 2 years after onset (P < 0.0001) (Fig. 1). The 2C-peptide values in patients with fulminant type 1 diabetes remained unchanged during a 2-year period after onset (Fig. 1). None of the patients with fulminant type 1 diabetes had improvement of their 2C-peptide values during a 2-year period after onset. In contrast, in patients with acute-onset type 1 diabetes, the 2C-peptide values at 2 years after onset were significantly lower than those at onset (P < 0.0001) and 1 year after onset (P < 0.0001), although there was no significant change between the 2C-peptide values at onset and 1 year after onset. Furthermore, 39% (20/51) of patients with acute-onset type 1 diabetes had improvement of their 2C-peptide values at 1 year after onset (P = 0.0030 vs. fulminant type 1 diabetes). Fasting serum C-peptide values at onset (mean 0.009 ± 0.021 nmol/l, n = 25) as well as 2C-peptide values in fulminant type 1 diabetes were significantly lower than those in acute-onset type 1 diabetes (0.243 ± 0.139 nmol/l, n = 100, P < 0.0001).

**ROC curve analysis.** The AUCs for 2C-peptide values (0.974 ± 0.013 [mean ± SE]) and fasting C-peptide levels (0.973 ± 0.013) were significantly greater than AUCs for serum amylase levels (0.877 ± 0.046, P = 0.034 and P = 0.038, respectively), arterial pH (0.841 ± 0.037, P < 0.001 and P = 0.001, respectively), plasma glucose levels (0.827 ± 0.053, both P = 0.006), serum lipase levels (0.797 ± 0.056, P = 0.002 and P = 0.001, respectively), BMI (0.715 ± 0.062, both P < 0.001), and onset age (0.555 ± 0.066, both P < 0.001) (Fig. 2A – D). The AUCs for HbA1c levels (0.969 ± 0.014) and duration of hyperglycemic symptoms (0.944 ± 0.020) were significantly greater than AUCs for arterial pH (P = 0.001 and P = 0.004, respectively), plasma glucose levels (P = 0.009 and P = 0.021, respectively), serum lipase levels (P = 0.003 and P = 0.011, respectively), BMI (both P < 0.001), and onset age (both P < 0.001). The AUC for serum elastase 1 levels (0.918 ± 0.039) was significantly greater than AUCs for serum lipase levels (P = 0.041), BMI (P = 0.006), and onset age (P < 0.001). There was no significant difference among AUCs for 2C-peptide values, fasting C-peptide levels, HbA1c levels, duration of hyperglycemic symptoms, and serum elastase 1 levels.

Table 1 indicated discriminating criteria devised from the optimum cutoff values based on ROC curve analysis of clinical and laboratory findings at onset of diabetes and sensitivities, specificities, positive predictive values, and negative predictive values for these criteria. Sensitivities and specificities of the discriminating criteria of 2C-peptide values and fasting C-peptide levels were >90%. Positive predictive values of the discriminating criteria of 2C-peptide values and fasting C-peptide levels were both 80%, whereas those of the discriminating criteria of the other variables were <70%.

**Multiple logistic regression analysis.** Based on a multiple logistic regression analysis, 2C-peptide values at onset ≥0.540 nmol/l and HbA1c levels at onset ≥8.0% were recognized as independent variables for discriminating fulminant type 1 diabetes from acute-onset type 1 diabetes; the odds ratio of 2C-peptide was 16.2 (95% CI 4.0 – 65.1; P < 0.0001), and the odds ratio of HbA1c was 11.5 (2.8 – 47.4; P = 0.0007). Using the criterion where patients whose 2C-peptide values at onset were ≥0.540 nmol/l and HbA1c levels at onset were ≥8.0% were diagnosed as fulminant type 1 diabetes, sensitivity and specificity were 92.0% (23/25 [95% CI 74.0 – 99.0]) and 99.0% (99/100 [94.6 – 100.0]), respectively, and positive and negative predictive values were 95.8% (23/24 [78.9 – 100.0]).
99.9]) and 98.0% (99/101 [93.0–99.7]), respectively.

To assess which variables are significant independent ones in the absence of ΣC-peptide values, which were sometimes hard to obtain in clinical practice, a further multiple logistic regression analysis was done after excluding ΣC-peptide values. In this case, fasting C-peptide levels at onset ≤0.033 nmol/l and HbA$_{1c}$ levels at onset ≤8.0% were recognized as independent variables; the odds ratio of fasting C-peptide was 11.4 (95% CI 3.4–38.4; $P = 0.0001$), and the odds ratio of HbA$_{1c}$ was 7.7 (2.2–26.7; $P = 0.0013$). Using the criterion where patients whose fasting C-peptide levels at onset were ≤0.033 nmol/l and HbA$_{1c}$ levels ≤8.0% were diagnosed as fulminant type 1 diabetes, sensitivity, specificity, positive predictive value, and negative predictive value were 92.0% (23/25 [95% CI 74.0–99.0]), 98.0% (98/100 [93.0–99.8]), 92.0% (23/25 [74.0–99.0]), and 98.0% (98/100 [93.0–99.8]), respectively.

**CONCLUSIONS** — In previous studies (3,5), the diagnosis of fulminant type 1 diabetes was based on negative findings of type 1 diabetes–related autoantibodies, including ICA, GADA$eta$, IA-2$eta$, and IAA, and aggressive mode of onset. However, type 1 diabetes–related autoantibodies in classical acute-onset type 1 diabetes are sometimes negative even at onset of diabetes (24–26). Very few hospital laboratories can assay diabetes-related autoantibodies, including ICA, GADA$eta$, IA-2$eta$, and IAA. Measurement of C-peptide levels can be easily carried out during routine practice. In the present study, we clearly demonstrate that the measurement of serum C-peptide values at onset is highly effective for diagnosis of fulminant type 1 diabetes without measuring pancreatic autoantibodies. The serum C-peptide values at onset were also highly predictive for further change of serum C-peptide levels. Low serum C-peptide levels at onset (fasting C-peptide ≤0.033 nmol/l or ΣC-peptide ≤0.540 nmol/l) can discriminate fulminant type 1 diabetes from acute-onset type 1 diabetes with high sensitivity and specificity (Table 1). Because acute-onset type 1 diabetes is much more common than fulminant type 1 diabetes, the possibility cannot be
Criteria of fulminant type 1 diabetes

Table 1—Discriminating criteria of fulminant type 1 diabetes from acute-onset type 1 diabetes and the sensitivity, specificity, positive predictive value, and negative predictive value for each discriminating criterion

<table>
<thead>
<tr>
<th>Discriminating criterion*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
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<tbody>
<tr>
<td>$\Sigma$C-peptide $\leq$ 0.540 nmol/l</td>
<td>96.0 (79.7-99.9)</td>
<td>94.0 (87.4-97.8)</td>
<td>80.0 (61.4-92.3)</td>
<td>98.9 (94.3-100.0)</td>
</tr>
<tr>
<td>Fasting serum C-peptide $\leq$ 0.033 nmol/l</td>
<td>96.0 (79.7-99.9)</td>
<td>94.0 (87.4-97.8)</td>
<td>80.0 (61.4-92.3)</td>
<td>98.9 (94.3-100.0)</td>
</tr>
<tr>
<td>Age at onset $&gt; 20$ years</td>
<td>100.0 (86.2-100.0)</td>
<td>20.0 (12.7-29.2)</td>
<td>23.8 (16.0-33.1)</td>
<td>100.0 (83.2-100.0)</td>
</tr>
<tr>
<td>BMI $&gt; 19.1$ kg/m$^2$</td>
<td>76.0 (54.9-90.6)</td>
<td>64.0 (53.8-73.4)</td>
<td>34.5 (22.2-48.6)</td>
<td>91.4 (82.3-96.8)</td>
</tr>
<tr>
<td>Duration $\leq$ 80.0 days</td>
<td>96.0 (79.7-99.9)</td>
<td>88.0 (80.0-93.6)</td>
<td>66.7 (49.0-81.4)</td>
<td>98.9 (93.9-100.0)</td>
</tr>
<tr>
<td>Glucose $&gt; 33.6$ mmol/l</td>
<td>76.0 (54.9-90.6)</td>
<td>81.0 (71.9-88.2)</td>
<td>50.0 (33.9-66.6)</td>
<td>93.1 (85.6-97.4)</td>
</tr>
<tr>
<td>$HbA_1c$ $\leq$ 8.0%</td>
<td>96.0 (79.7-99.9)</td>
<td>89.0 (81.2-94.4)</td>
<td>68.6 (50.7-83.2)</td>
<td>98.9 (94.0-100.0)</td>
</tr>
<tr>
<td>Arterial pH $\leq$ 7.21</td>
<td>84.0 (63.9-95.4)</td>
<td>74.0 (64.3-82.3)</td>
<td>44.7 (30.2-59.9)</td>
<td>94.9 (87.4-98.6)</td>
</tr>
<tr>
<td>Amylase $&gt; 345$ IU/l</td>
<td>68.0 (46.5-85.1)</td>
<td>92.0 (84.8-96.5)</td>
<td>68.0 (46.5-85.1)</td>
<td>92.0 (84.8-96.5)</td>
</tr>
<tr>
<td>Lipase $&gt; 173$ U/l</td>
<td>64.0 (42.5-82.0)</td>
<td>92.0 (84.8-96.5)</td>
<td>66.7 (44.7-84.4)</td>
<td>91.1 (83.8-95.8)</td>
</tr>
<tr>
<td>Elastase one $&gt; 231$ ng/dl</td>
<td>80.0 (59.3-93.2)</td>
<td>91.0 (83.6-95.8)</td>
<td>69.0 (49.2-84.7)</td>
<td>94.8 (88.3-98.3)</td>
</tr>
</tbody>
</table>

Data are percent (95% CI). *Discriminating criterion of fulminant type 1 diabetes ($n = 25$) from acute-onset type 1 diabetes ($n = 100$) was devised from the optimum cutoff value obtained using ROC curve analysis of each clinical or laboratory finding at onset of diabetes. Normal range of amylase, 111–536; normal range of lipase, 25–170; normal range of elastase 1, 22–221.

We have prospectively demonstrated that patients with fulminant type 1 diabetes had extremely low C-peptide response during OGTT at onset, at 1 year after onset, and at 2 years after onset when compared with patients with acute-onset type 1 diabetes. Characteristically, none of patients with fulminant type 1 diabetes had improvement of $\Sigma$C-peptide values, i.e., $>0.331$ nmol/l (1.0 ng/ml) increase of $\Sigma$C-peptide values after onset (1 year and 2 years) when compared with the values at onset. In contrast, in more than one-third of acute-onset type 1 diabetic patients, improvement of $\Sigma$C-peptide values as demonstrated by OGTT at 1 year after onset was recognized. These findings are in line with previous reports that a high C-peptide level at diagnosis has been associated with a higher C-peptide level during the first year of follow-up (28, 29). No recovery of residual $\beta$-cell function after onset is another characteristic feature of fulminant type 1 diabetes. An inverse correlation has been reported between residual $\beta$-cell function and the degree of glycemic instability (30). We previously demonstrated that a negative relationship between preserved $\beta$-cell function and progression of diabetes complications exists (12). This indicates that patients with fulminant type 1 diabetes have higher risks of developing diabetes complications than patients with acute-onset type 1 diabetes. Therefore, fulminant type 1 diabetic patients might have a need for accurate diagnosis followed by intensive insulin therapy to attain good and stable glycemic control.

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References


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