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SPECIAL REPORT

Diagnostic criteria for acute-onset type 1 diabetes mellitus (2012): Report of the Committee of Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus

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ABSTRACT

Type 1 diabetes is a disease characterized by destruction of pancreatic β-cells, which leads to absolute deficiency of insulin secretion. Depending on the manner of onset and progression, it is classified as fulminant, acute-onset or slowly progressive type 1 diabetes. Here, we propose the diagnostic criteria for acute-onset type 1 diabetes mellitus. Among the patients who develop ketosis or diabetic ketoacidosis within 3 months after the onset of hyperglycemic symptoms and require insulin treatment continuously after the diagnosis of diabetes, those with anti-islet autoantibodies are diagnosed with 'acute-onset type 1 diabetes mellitus (autoimmune)'. In contrast, those whose endogenous insulin secretion is exhausted (fasting serum C-peptide immunoreactivity <0.6 ng/mL) without verifiable anti-islet autoantibodies are diagnosed simply with 'acute-onset type 1 diabetes mellitus'. Patients should be reevaluated after certain periods in case their statuses of anti-islet autoantibodies and/or endogenous insulin secretory capacity are unknown.

INTRODUCTION

Type 1 diabetes is a disease characterized by the destruction of pancreatic β-cells, which leads to absolute deficiency of insulin secretion. Depending on the manner of onset and progression, it is classified as fulminant, acute-onset or slowly progressive type 1 diabetes in Japan[1]. The diagnostic criteria for type 1 diabetes have not been established in Western countries, because the clinical characteristics of Caucasian patients with type 1 diabetes are relatively homogenous, and it is conjectured that type 1 diabetes has been recognized to be easily distinguished from other types of diabetes by their age of onset, the presence or absence of obesity, and mode of disease onset. However, with rising obesity rates in children, it has been reported that it is increasingly difficult to differentiate between type 1 diabetes and type 2 diabetes[2]. Therefore, it is speculated that, in the near future, investigation towards a decision on the diagnostic criteria or guidelines to discriminate between both types of diabetes will be made in Western countries.

†Chairman
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Although most cases of type 2 diabetes remain in a non-insulin-dependent state, it is known that some patients progress to an insulin-dependent state as a result of exhausting their endogenous insulin secretion. The term 'insulin-dependent state' means that insulin treatment is essential to sustain life, whereas patients whose conditions do not require insulin treatment for survival, but require insulin injections for glycemic control, are considered to be in a non-insulin-dependent state[1]. Therefore, the diagnostic criteria that can distinguish type 1 diabetes from type 2 diabetes with insulin-dependent state are important for general practitioners. Here, we propose the diagnostic criteria for acute-onset type 1 diabetes mellitus.

DIAGNOSTIC CRITERIA FOR ACUTE-ONSET TYPE 1 DIABETES MELLITUS (2012)

Table 1 shows the diagnostic criteria for acute-onset type 1 diabetes mellitus (2012). As previously reported diagnostic criteria for fulminant type 1 diabetes[3], it was taken as the 2012 version because of the possibility of revision. In order to establish the diagnostic criteria for 'typical acute-onset type 1 diabetes', which can be used easily by general practitioners and can be adapted to long-standing patients, we selected the following three conditions as criteria: (i) acute-onset type; (ii) the need for continuous insulin therapy; and (iii) anti-islet autoantibody status. Patients are diagnosed as having 'acute-onset type 1 diabetes mellitus (autoimmune)' if they are positive for anti-islet autoantibodies, whereas they are diagnosed simply as having 'acute-onset type 1 diabetes mellitus' if their endogenous insulin secretion is exhausted without verifiable anti-islet autoantibodies. However, reassessment is required after certain periods in case the statuses of anti-islet autoantibodies and/or endogenous insulin secretory capacity are unknown. Although patients are diagnosed as having 'acute-onset type 1 diabetes mellitus (idiopathic)' if they are negative for autoantibodies to glutamic acid decarboxylase (GADA), insulinoma-associated antigen 2 (IA-2A), insulin (IAA) and zinc transporter-8 (ZnT8A) at the onset of diabetes, this category was not included in the present diagnostic criteria, because it is difficult to measure all of these autoantibodies at the clinic. Based on the previous reports, the prevalence of acute-onset type 1 diabetes (idiopathic) is estimated to be <10% of patients with acute-onset type 1 diabetes in Japan[4–6].

Table 1 | Diagnostic criteria for acute-onset type 1 diabetes mellitus (2012)

1. Occurrence of diabetic ketosis or ketoacidosis around <3 months after the onset of hyperglycemic symptoms (thirst, polydipsia, polyuria, weight loss)†
2. Need for continuous insulin therapy after the diagnosis of diabetes mellitus‡
3. Positive test result for anti-islet autoantibodies§
4. Presence of endogenous insulin deficiency without verifiable anti-islet autoantibodies¶

'Acute-onset type 1 diabetes mellitus (autoimmune)': fulfilled criteria 1, 2 and 3.

'Acute-onset type 1 diabetes mellitus': fulfilled criteria 1, 2 and 4.

Re-evaluation is required after a certain period in case the status of anti-islet autoantibodies and/or endogenous insulin secretory capacity is unknown.

†The presence of ketosis should be confirmed by the elevation of urine and/or serum ketone bodies. Diabetic ketosis or ketoacidosis might not be seen in patients in whom insulin therapy was started immediately after the occurrence of hyperglycemia and/or hyperglycemic symptoms. ‡'Continuous insulin therapy' includes restart of insulin therapy after a transient period of being able to withdraw insulin therapy after initiation of treatment (honeymoon period). §'Positive test result for anti-islet autoantibodies' is defined as when one or more of the following autoantibodies are positive at any time during the course of the disease; islet cell autoantibodies, glutamic acid decarboxylase autoantibodies, insulinoma-associated antigen 2 autoantibodies or insulin autoantibodies. However, insulin autoantibodies should be evaluated before or shortly after insulin therapy is initiated. ¶'Endogenous insulin deficiency' is defined as fasting serum C-peptide immunoreactivity <0.6 ng/mL. Patients should be diagnosed as having fulminant type 1 diabetes when its diagnostic criteria are fulfilled. Monogenic diseases need to be discriminated.

As described in the 'Notes' in these criteria, a state of ketosis should be confirmed by the elevation of urine and/or serum ketone bodies. It is noted that diabetic ketosis or ketoacidosis might not be seen in patients in whom insulin therapy was started immediately after the occurrence of hyperglycemia and/or hyperglycemic symptoms. Furthermore, we added a comment on the 'honeymoon period', which is observed in approximately 30% of patients with acute-onset type 1 diabetes[7]. We also described a comment that 'IAA should be evaluated before or shortly after insulin therapy is initiated', because IAA and insulin antibodies developed by exposure to exogenous insulin are currently indistinguishable.

CUT-OFF LEVEL FOR ENDOGENOUS INSULIN DEFICIENCY

In the present diagnostic criteria, we defined 'endogenous insulin deficiency' as fasting serum C-peptide immunoreactivity (CPR) <0.6 ng/mL. The bases on this definition are as follows. As we have not found any clear evidence demonstrating the definition of endogenous insulin deficiency in Japan, we created a cut-off value based on CPR data collected from our hospitals and literature previously reported from outside of Japan.

First, 123 patients (56 males, 65 females and two unknown) whose duration of hyperglycemic symptoms before the initiation of insulin therapy was <3 months and who did not meet the diagnostic criteria for fulminant type 1 diabetes were selected from our previous study[8]. Of these 123 patients, fasting serum CPR values were available in 48 patients and were used to determination the cut-off value. As shown in Figure 1, the fasting serum CPR value was distributed from <0.1 to 1.4 ng/mL, and the mean level was 0.61 ± 0.42 ng/mL (mean ± standard deviation). Furthermore, the median level and 10th, 25th, 50th, 75th and 90th percentiles were 0.55 ng/mL, and 0.10,

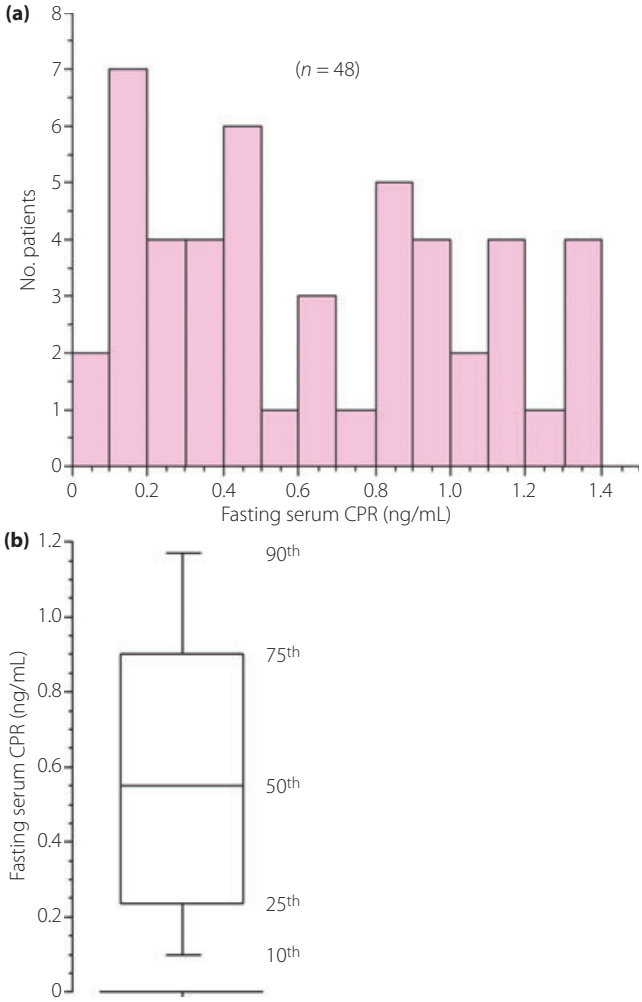

Figure 1 | Distribution of fasting serum C-peptide immunoreactivity (CPR) levels in patients with acute-onset type 1 diabetes. (a) Histogram. (b) Box plot.

0.24, 0.55, 0.90 and 1.17 ng/mL, respectively. In Caucasian patients with diabetes, Gjessing *et al.*[9] reported that fasting serum CPR <0.2 nmol/L (0.6 ng/mL) gives a good distinction between ketosis-onset type 1 and type 2 diabetes, and the positive and negative predictive values were 83% (95% confidence interval [CI] 70–93%) and 86% (95% CI 76–92%) in patients including recent-onset diabetes. and 97% (95% CI 86–100%) and 86% (95% CI 76–93%) in patients with a duration of diabetes >2 years. Furthermore, in Taiwanese patients with childhood-onset type 1 diabetes, Tung *et al.*[10] reported that median fasting serum CPR level was 0.2 nmol/L (0.6 ng/mL) at disease onset. Based on these data, we decided to use 'fasting serum CPR <0.6 ng/mL' as a definition of endogenous insulin deficiency. The assay procedure for determination of CPR levels has been improved, and sensitive CPR immunoassays, which do not cross-react with proinsulin, have recently come into wide use instead of the conventional radioimmunoassay method. The evaluation of the cut-off value for endogenous insulin deficiency might be required using newly developed assays in the future.

DISCUSSION

Japanese patients with type 1 diabetes are classified into fulminant, acute-onset or slowly progressive type 1 diabetes depending on the manner of onset and progression. Diagnostic criteria for fulminant type 1 diabetes, which were established in 2004 and revised in 2012, are widely used in general medicine[8]. We are also in the process of establishing diagnostic criteria for slowly progressive type 1 diabetes. One of the reasons we decided to establish diagnostic criteria for acute-onset type 1 diabetes is that there are no tools that general practitioners can use to appropriately and easily diagnose type 1 diabetes. As the treatment of type 1 diabetes has changed in recent years, such as the introduction of dietary therapy using carbohydrate counting and the development of new insulin analogs, it would be desirable for suitable treatment to be based on the correct diagnosis of type 1 diabetes. Furthermore, as it is also important to start insulin treatment immediately when type 1 diabetes is suspected, diagnostic criteria that can be used easily are urgently required. In contrast, establishment of diagnostic criteria for 'typical' cases enables discussions using the same criteria in the research fields, which is important for the investigation of the pathogenesis of type 1 diabetes.

In establishing these diagnostic criteria, we discussed which is more suitable, between <3 months and <6 months as the period from the onset of hyperglycemic symptoms to initiation of insulin therapy, and concluded to use the former from a view point of the criteria of typical cases with acute-onset type 1 diabetes. Furthermore, we made a criterion, 'Need for continuous insulin therapy after the diagnosis of diabetes mellitus', because insulin-treated diabetic patients do not necessarily have type 1 diabetes, and patients with 'soft-drink ketosis' have acute-onset diabetes, but can withdraw insulin therapy after several months. As anti-islet autoantibodies, which are the hallmark of autoimmunity, can disappear after years of diabetes being present, it is important to prove endogenous insulin deficiency in patients with long-standing diabetes if they have no anti-islet autoantibodies. 'Acute-onset type 1 diabetes mellitus' can be diagnosed when endogenous insulin deficiency is proved, even if anti-islet autoantibodies are negative, but reassessment is required after a certain period in patients with preserved endogenous insulin secretion. Patients should not be diagnosed as having 'acute-onset type 1 diabetes mellitus (idiopathic)' even if their GADA, IA-2A, IAA and ZnT8A are all negative during the follow up, except for the case where those autoantibodies were measured at the onset of diabetes. This is because we cannot exclude the possibility that anti-islet autoantibodies were positive soon after the development of type 1 diabetes. Tanaka *et al.*[11] recently reported for the Committee on Type 1 Diabetes, Japan Diabetes Society that the prevalence of anti-islet autoantibody-negative type 1 diabetic patients with

duration of <5 years was 12.5% (8/64) and 13.8% (8/58) when six patients with fulminant type 1 diabetes were excluded. However, it should be noted that there is a possibility that autoantibody-negative patients might include patients whose anti-islet autoantibodies were positive at disease onset, but became negative within 5 years.

It is well known that genetic factors including human leukocyte antigen genes are associated with the development of type 1 diabetes. Kawabata *et al.*[12] reported as a report of the Committee on Type 1 Diabetes, Japan Diabetes Society that *DRB1*04:05-DQB1*04:01*, *DRB1*08:02-DQB1*03:02* and *DRB1*09:01-DQB1*03:03* were positively associated, and *DRB1*15:01-DQB1*06:02* and *DRB1*15:02-DQB1*06:01* were negatively associated with Japanese patients with acute-onset type 1 diabetes. We did not include the criteria on human leukocyte antigen, because the presence of susceptible haplotypes in patients with suspected acute-onset type 1 diabetes does not lead to a definite diagnosis, and the presence of protective haplotypes cannot exclude type 1 diabetes completely.

Although serum and urinary CPR have been conventionally used for the assessment of endogenous insulin secretory capacity, we have omitted urinary CPR from these diagnostic criteria as measurement of serum CPR is currently an international standard[13]. Furthermore, we used fasting serum CPR because tolerance tests, such as intravenous glucagon stimulatory test or mixed meal test, are difficult to manipulate in general practice.

CONCLUSION

We proposed diagnostic criteria for acute-onset type 1 diabetes mellitus (2012). We hope that acute-onset type 1 diabetes will be diagnosed precisely using these new criteria both in clinical medicine and research fields.

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