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

Akihisa Imagawa[1†], Toshiaki Hanafusa[2‡*], Takuya Awata[3], Hiroshi Ikegami[4], Yasuko Uchigata[5], Haruhiko Osawa[6], Eiji Kawasaki[7], Yumiko Kawabata[4], Tetsuro Kobayashi[8], Akira Shimada[9], Ikki Shimizu[10], Kazuma Takahashi[11], Masao Nagata[12], Hideichi Makino[13], Taro Maruyama[14]

ABSTRACT

We have revised a part of the diagnostic criteria for fulminant type 1 diabetes. The new criteria were set both to express the essence of this disease of rapid increase of patients' blood glucose and to be highly sensitive to reduce the misdiagnosis. After analyzing the data of 382 patients with newly-diagnosed fulminant type 1 diabetes, we adopted the glycated hemoglobin (HbA_{1c}) level of 8.7% (National Glycohemoglobin Standardization Program [NGSP] value). The new criterion indicates 100% of sensitivity and the best value by receiver operating characteristic curve analysis. In addition, we added a comment that 'This value (HbA_{1c} <8.7% in NGSP) is not applicable for patients with previously diagnosed glucose intolerance' in the new criteria and also a comment that 'Association with human leukocyte antigen *DRB1*04:05-DQB1*04:01* is reported' as a related finding. We did not revise the screening criteria and the other part of the diagnostic criteria, because they are still reliable. (J Diabetes Invest doi: 10.1111/jdi.12024, 2012)

KEY WORDS: Criteria, Diagnosis, Fulminant

INTRODUCTION

Fulminant type 1 diabetes is an independent subtype within type 1 diabetes that was discovered and clinically characterized in Japan. The following findings are clinical characteristics observed in this subtype: markedly rapid onset of hyperglycemia with ketoacidosis, near normal glycated hemoglobin (HbA_{1c}) levels despite remarkable hyperglycemia, negative status of islet-related autoantibodies, an absence of insulin secreting capacity even at disease onset and elevation of serum pancreatic enzyme levels[2].

The Japan Diabetes Society (JDS) set up a research committee, carried out a nationwide survey and reported the detailed characteristics of this new clinical entity in 2004[3,4]. Based on that report, the society introduced two sets of criteria; one was for screening so that affected patients would not be missed, and the other was established for the diagnosis of the disease (Tables 1 and 2). These criteria have now been widely used, not only in Japan, but also worldwide.

The Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus started to re-evaluate the criteria after the transition of HbA_{1c} from the JDS value to the National Glycohemoglobin Standardization Program (NGSP) value was made by the JDS in 2012[5–19].

[1]Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, Suita, [2]Department of Internal Medicine (I), Osaka Medical College, Takatsuki, [3]Department of Endocrinology and Diabetes, Saitama Medical University, [14]Department of Internal Medicine, Saitama Social Insurance Hospital, Saitama, [4]Department of Endocrinology, Metabolism and Diabetes, Kinki University School of Medicine, Osaka, [5]Diabetes Center, Tokyo Women's Medical University School of Medicine, [9]Department of Internal Medicine, Saiseikai Central Hospital, Tokyo, [6]Department of Laboratory Medicine, Ehime University School of Medicine, [13]Diabetes Center, Shiraishi Hospital, Ehime, [7]Department of Metabolism/Diabetes and Clinical Nutrition, Nagasaki University Hospital, Nagasaki, [8]Third Department of Internal Medicine, University of Yamanashi School of Medicine, Yamanashi, [10]Department of Internal Medicine, The Sakakibara Heart Institute of Okayama, Okayama, [11]Department of Diabetes and Metabolism, Iwate Medical University, Morioka, and [12]Department of Internal Medicine, Kakogawa Municipal Hospital, Kakogawa, Japan
*Corresponding author. Toshiaki Hanafusa Tel.: +81-72-683-1221 Fax: +81-72-685-1655
E-mail address: hanafusa@poh.osaka-med.ac.jp
†Secretariat
‡Chairman

In 2012, the Japan Diabetes Society established the Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus, which published a committee report in *J Jpn Diabetes Soc* 2012; **55**: 815–820 (in Japanese)[1]. This is the English version of that report
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METHODS

Our re-evaluation was carried out based on the records of 382 patients with newly-diagnosed fulminant type 1 diabetes and those collected from other published findings[5–17]. The records had been submitted to the committee for the past 12 years. We also evaluated 122 patients with classical autoimmune type 1A diabetes from the nationwide survey carried out in 2004.

RESULTS

A histogram of the HbA_{1c} values of 382 patients with fulminant type 1 diabetes and 122 patients with classical type 1A diabetes are shown in Figure 1. The candidate cut-off value, and the sensitivity and specificity using each value are shown in Table 3. The HbA_{1c} (NGSP) value was 6.8% on average in the 382 patients with fulminant type 1 diabetes, and was below 7.0% in 70.2% of those patients.

DISCUSSION

Based on these data, we decided to use 'HbA_{1c} <8.7% (NGSP)' in the new diagnostic criteria (Table 4). A simple conversion of HbA_{1c} (JDS) <8.5% in the previous diagnostic criteria to the HbA_{1c} (NGSP) value resulted in HbA_{1c} (NGSP) <8.9%. In this case, the sensitivity was 100%, and the specificity 97.5%. When we established the previous criteria for fulminant type 1 diabetes in 2004, we emphasized the prevention of a misdiagnosis that would directly result in the death of the patient. This meant that the sensitivity had to be 100%. In contrast, the presence of a low HbA_{1c} value despite a high blood

Table 1 | Criteria for screening of fulminant type 1 diabetes mellitus (2004)

1) Ketosis or ketoacidosis within 1 week after the onset of hyperglycemic symptoms
2) Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) at first visit

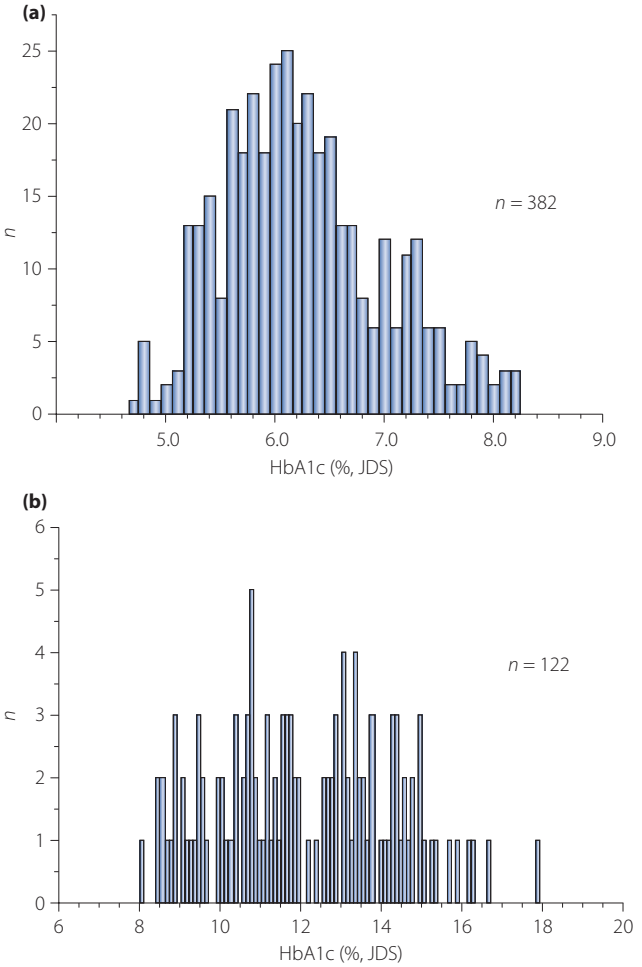

Figure 1 | Glycated hemoglobin (HbA_{1c}) concentrations at onset in (a) 382 patients with fulminant type 1 diabetes and (b) 122 patients with classical acute onset type 1A diabetes. JDS, Japan Diabetes Society.

Table 2 | Criteria for definite diagnosis of fulminant type 1 diabetes mellitus (2004)

Fulminant type 1 diabetes mellitus is confirmed when all the following three findings are present:

1) Occurrence of diabetic ketosis or ketoacidosis soon (approximately 7 days) after the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketone bodies at first visit)
2) Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and glycated hemoglobin level <8.5% (Japan Diabetes Society value) at first visit
3) Urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucagon (or after meal) load at onset

Other findings in fulminant type 1 diabetes mellitus:

A) Islet-related autoantibodies, such as antibodies to glutamic acid decarboxylase, islet-associated antigen 2 and insulin are undetectable in general
B) Duration of the disease before the start of insulin treatment can be 1–2 weeks
C) Elevation of serum pancreatic enzyme levels (amylase, lipase or elastase-1) is observed in 98% of the patients
D) Flu-like symptoms (fever, upper respiratory symptoms, etc.) or gastrointestinal symptoms (upper abdominal pain, nausea and/or vomiting, etc.) precede the disease onset in 70% of patients
E) The disease can occur during pregnancy or just after delivery

Table 3 | Candidate cut-off values, and their sensitivity and specificity

HbA_{1c} (NGSP)	HbA_{1c} (JDS)	Specificity	Sensitivity
8.5	8.1	100.0	98.4
8.6	8.2	99.2	99.2
8.7	8.3	99.2	100.0
8.8	8.4	99.2	100.0
8.9	8.5	99.2	100.0
9.0	8.6	97.5	100.0
9.1	8.7	95.9	100.0

HbA_{1c}, glycated hemoglobin; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program.

glucose level at the same time indicates a rapid deterioration of the blood glucose level, which is the most important aspect of fulminant type 1 diabetes. The average value at the time of onset was 6.4% (JDS; = 6.8% [NGSP]). It is therefore reasonable to use a lower value of HbA_{1c} in the diagnostic criteria. In the present study, the cut-off value of the HbA_{1c} was set as the minimum value to maintain the 100% sensitivity, which was 'HbA_{1c} <8.7% (NGSP)'. This value was also the optimal value identified in the receiver operating characteristic curve analysis.

In the new criteria, we have added a comment that, 'This value (HbA_{1c} <8.7% in NGSP) is not applicable for patients with previously diagnosed glucose intolerance'. Shimada *et al.* reported that in 18 patients with previously diagnosed glucose intolerance who showed rapid onset of hyperglycemia suggestive of fulminant type 1 diabetes, the mean value of HbA_{1c} was 8.5% (JDS), and it was more than 8.5% (JDS) in five patients (27.8%; 8.5% [JDS] = 8.9% [NGSP])[20]. This finding suggests that the HbA_{1c} concentration is higher in patients with previously diagnosed glucose intolerance than in patients without it in cases of fulminant type 1 diabetes.

We also added a new comment in the new criteria: 'Association with human leukocyte antigen (HLA) *DRB1*04:05-DQB1*04:01* is reported' as a related finding. Kawabata and Ikegami have published this association as a committee report[14]. Imagawa and Ikegami have also reported that *DRB1*04:05-DQB1*04:01* was seen in 32.6% of 207 fulminant type 1 diabetic patients, and this prevalence was remarkably higher than that in healthy control subjects (14.2%), with an odds ratio of 2.9[17].

In contrast, we concluded that it was not necessary to revise the cut-off value for the serum and urine C-peptide levels based on the data for the newly-diagnosed cases submitted to the committee during the past 8 years (data not shown). We also did not revise the other part of the diagnostic criteria and 'Other findings in fulminant type 1 diabetes mellitus', except for the addition of class II HLA, because the other parts of the previous criteria are still reliable. We agreed, as part of the present committee, that the 'Criteria for screening of fulminant type 1 diabetes mellitus (2004)' is still effective to be used in the future.

Based on the new lines of evidence, we have revised the diagnostic criteria for fulminant type 1 diabetes and include it as 'Criteria for definite diagnosis of fulminant type 1 diabetes mellitus (2012)'. We hope that these criteria will be widely used in various clinical and experimental situations, and will contribute to achieving a better understanding of this clinical entity. As we mentioned in the first committee report[4], fulminant type 1 diabetes, if disregarded or not diagnosed, directly results in the death of the patient. We hope that these new criteria will help save the lives of patients with this rapidly-progressing type of diabetes.

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Table 4 | Criteria for definite diagnosis of fulminant type 1 diabetes mellitus (2012)

Fulminant type 1 diabetes mellitus is confirmed when all the following three findings are present:

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3) Urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucagon (or after meal) load at onset

Other findings in fulminant type 1 diabetes mellitus

A) Islet-related autoantibodies, such as antibodies to glutamic acid decarboxylase, islet-associated antigen 2 and insulin, are undetectable in general
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D) Flu-like symptoms (fever, upper respiratory symptoms, etc.) or gastrointestinal symptoms (upper abdominal pain, nausea and/or vomiting, etc.) precede the disease onset in 70% of patients
E) The disease can occur during pregnancy or just after delivery
F) Association with HLA *DRB1*04:05-DQB1*04:01* is reported

†This value is not applicable for patients with previously diagnosed glucose intolerance. HLA, human leukocyte antigen, NGSP, National Glycohemoglobin Standardization Program.

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