SPECIAL REPORT

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, Toshiaki Hanafusa, Takuya Awata, Hiroshi Ikegami, Yasuko Uchigata, Haruhiko Osawa, Eiji Kawasaki, Yumiko Kawabata, Tetsuro Kobayashi, Akira Shimada, Ikki Shimizu, Kazuma Takahashi, Masao Nagata, Hidei Makino, Taro Maruyama

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 (HbA1c) 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 (HbA1c <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 ketoadidosis, near normal glycated hemoglobin (HbA1c) levels despite remarkable hyperglycemia, negative status of islet-related autoantibodies, an absence of insulin secretory capacity even at disease onset and elevation of serum pancreatic enzyme levels.

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. 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 HbA1c from the JDS value to the National Glycohemoglobin Standardization Program (NGSP) value was made by the JDS in 2012.
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 findings5–17. 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 HbA1c 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 HbA1c (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 ‘HbA1c <8.7% (NGSP)’ in the new diagnostic criteria (Table 4). A simple conversion of HbA1c (JDS) <8.5% in the previous diagnostic criteria to the HbA1c (NGSP) value resulted in HbA1c (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 HbA1c value despite a high blood

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

| 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 |

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

© 2012 The Japan Diabetes Society
Table 3 | Candidate cut-off values, and their sensitivity and specificity

| HbA1c (NGSP) | HbA1c (JDS) | Specificity | Sensitivity |
|-------------|-------------|-------------|-------------|
| 8.5         | 8.1         | 1000        | 98.4        |
| 8.6         | 8.2         | 99.2        | 99.2        |
| 8.7         | 8.3         | 99.2        | 1000        |
| 8.8         | 8.4         | 99.2        | 1000        |
| 8.9         | 8.5         | 99.2        | 1000        |
| 9.0         | 8.6         | 97.5        | 1000        |
| 9.1         | 8.7         | 95.9        | 1000        |

HbA1c, glycated hemoglobin; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program.

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. 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 2.917.

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 included 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, 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.

ACKNOWLEDGEMENTS

The authors thank Dr M Ohkubo (Toranomon Hospital), Dr Y Kajo and Dr K Yasuda (National Center for Global Health and Medicine), Dr H Kamoi (Nagaoka Red Cross Hospital),...
Dr J Satoh (Iwate Medical University), Dr S Tanaka (University of Yamanashi School of Medicine), Dr K Nakanishi (Okinawa Memorial Institute for Medical Research), Dr S Fujii (Ishikawa Prefectural Central Hospital), Dr J Miura (Tokyo Women’s Medical University School of Medicine) and Dr S Murao (KKR Takamatsu Hospital) for giving us important suggestions as collaborators in the subcommittee on Fulminant and Acute Type 1 diabetes, Committee on Type 1 diabetes, Japan Diabetes Society. We also thank Dr T Hirata (Kyoto University), Dr C Tsutsumi (Osaka Medical College), Dr H Takaike (Tokyo Women’s Medical University School of Medicine), Dr M Koga (Kinki Central Hospital) and Dr K Nakamura (Nagasaki University) who took part in the committee’s studies, and Ms S Mitsui and Ms S Ikeda (Osaka Medical College) for their excellent secretarial assistance. The authors declare no conflicts of interest.

REFERENCES

1. Imagawa A, Hanafusa T, Awata T, et al. Report of the Committee of Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus: New Diagnostic Criteria of Fulminant Type 1 Diabetes Mellitus. J Jpn Diabetes Soc 2012; 55: 815–820 (Japanese).

2. Imagawa A, Hanafusa T, Miyagawa J, et al. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. N Engl J Med 2000; 342: 301–307.

3. Imagawa A, Hanafusa T, Uchigata Y, et al. Fulminant type 1 diabetes: a nationwide survey in Japan. Diabetes Care 2003; 26: 2345–2352.

4. Hanafusa T, Imagawa A, Iwahashi H, et al. Report of Japan Diabetes Society Committee on fulminant type 1 diabetes mellitus research: epidemiological and clinical analysis and proposal of diagnostic criteria. J Jpn Diabetes Soc 2005; 48(Suppl. 1): A1–A13 (Japanese).

5. Imagawa A, Hanafusa T, Uchigata Y, et al. Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus. Diabetologia 2005; 48: 294–300. Erratum in: Diabetologia 2008; 51: 524–526.

6. Shimizu I, Makino H, Hanafusa T, et al. Immunogenetic characteristics of fulminant type 1 diabetes mellitus associated with pregnancy: a nationwide survey. J Jpn Diabetes Soc 2005; 48(Suppl. 1): A15–A19 (Japanese).

7. Shimizu I, Makino H, Imagawa A, et al. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. J Clin Endocrinol Metab 2006; 91: 471–476.

8. Shimizu I, Makino H, Imagawa A, et al. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy: Report of the Japan Diabetes Society Committee on Fulminant Type 1 Diabetes Mellitus Research. J Jpn Diabetes Soc 2006; 49: 755–760 (Japanese).

9. Kawasaki E, Shimizu I, Hanafusa T, et al. Nationwide survey on the prevalence of type 1 diabetes associated with pregnancy. Diabetes Pregnancy 2006; 6: 104–107 (Japanese).

10. Hanafusa T, Imagawa A, Iwahashi H, et al. Report of the committee of the Japan Diabetes Society on research on fulminant type 1 diabetes mellitus: analysis of HLA serotype and diabetic microangiopathy. J Jpn Diabetes Soc 2007; 50: 825–833 (Japanese).

11. Hanafusa T, Imagawa A, Iwahashi H, et al. Report of the Japan Diabetes Society’s Committee on fulminant type 1 diabetes mellitus: analysis of antiviral antibodies at disease onset. J Jpn Diabetes Soc 2008; 51: 531–536 (Japanese).

12. Imagawa A, Hanafusa T, Iwahashi H, et al. Uniformity in clinical and HLA-DR status regardless of age and gender within fulminant type 1 diabetes. Diabetes Res Clin Pract 2008; 82: 233–237.

13. Takaike H, Uchigata Y, Iwamoto Y, et al. Nationwide survey to compare the prevalence of transient elevation of liver transaminase during treatment of diabetic ketoacidosis in new-onset acute and fulminant type 1 diabetes mellitus. Ann Med 2008; 40: 395–400.

14. Kawabata Y, Ikegami H, Awata T, et al. Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. Diabetologia 2009; 52: 2513–2521.

15. Koga M, Murai J, Saito H, et al. Serum glycated albumin to haemoglobin A1C ratio can distinguish fulminant type 1 diabetes mellitus from type 2 diabetes mellitus. Ann Clin Biochem 2010; 47: 313–317.

16. Nakamura K, Kawasaki E, Imagawa A, et al. Type 1 diabetes and interferon therapy: a nationwide survey in Japan. Diabetes Care 2011; 34: 2084–2089.

17. Tsutsumi C, Imagawa A, Ikegami H, et al. On behalf of the Japan Diabetes Society Committee on Type 1 Diabetes Mellitus Research. Class II HLA genotype in fulminant type 1 diabetes – a nationwide survey with reference to glutamic acid decarboxylase antibodies. J Diabetes Invest 2012; 3: 62–69.

18. Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. Diabetol Int 2012; 3: 8–10.

19. Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest 2012; 3: 39–40.

20. Hirata H, Shimada A, Imagawa A, et al. Clinical characteristics of cases that progress rapidly from type 2 diabetes to insulin deficiency like fulminant type 1 diabetes: subcommittee report on Fulminant and Acute Type 1 diabetes, Committee on Type 1 diabetes, Japan Diabetes Society. J Jpn Diabetes Soc 2012; 55: 505–511 (Japanese).