Clinical characteristics of anti-glutamic acid decarboxylase antibody-positive fulminant type 1 diabetes

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Abstract. This research aimed to examine the relationship between anti-glutamic acid decarboxylase antibody (GADA) titers and clinical parameters at onset and to clarify the association between clinical severity and GADA titers in GADA-positive fulminant type 1 diabetes. This cross-sectional observational study included 20 cases with GADA-positive fulminant type 1 diabetes (4 cases from our hospital and 16 from cases reported in the literature). The association between GADA titers and clinical parameters [age, sex, body weight, body mass index, period from appearance of any prodromal symptoms to diagnosis, period from development of hyperglycemic symptoms to diagnosis, GADA titer, HbA1c level, blood pH and HCO₃⁻ level, serum levels of ketone bodies and pancreatic exocrine enzymes] were analyzed. Spearman’s rank correlation coefficient (rₛ) was used for the correlation analysis. The results showed that there was a significant inverse correlation between GADA titers and the “period from appearance of any prodromal symptoms to diagnosis” (rₛ = −0.559, p < 0.05). Moreover, GADA titers were inversely correlated with blood pH and HCO₃⁻ level (rₛ = −0.576, p < 0.05; rₛ = −0.578, p < 0.05, respectively), and positively correlated with serum levels of total ketone bodies, acetoacetate, and 3-hydroxybutyrate (rₛ = 0.661, p < 0.05; rₛ = 0.700, p < 0.05; and rₛ = 0.782, p < 0.01, respectively). These findings suggest that higher GADA titers may be linked to more severe clinical severity of GADA-positive fulminant type 1 diabetes at onset. This association may be attributed to possible pre-existence of autoimmunity-related β-cell damage before the onset of fulminant type 1 diabetes.

Key words: Anti-glutamic acid decarboxylase antibody, Clinical characteristics, Fulminant type 1 diabetes

Fulminant type 1 diabetes is a novel subtype of type 1 diabetes and is characterized by a relatively low HbA1c level at the time of onset, despite the abrupt development of marked hyperglycemia with ketosis or ketoacidosis [1]. A nationwide survey performed in Japan revealed that this type of diabetes accounts for 20% of newly diagnosed type 1 diabetes cases accompanied by hyperglycemia and diabetic ketosis/ketoacidosis [2]. Fulminant type 1 diabetes was initially classified as non-autoimmune diabetes, because it was considered that islet-associated autoantibodies, such as anti-glutamic acid decarboxylase antibody (GADA), were rarely detected even at onset. However, with the accumulation of cases of fulminant type 1 diabetes, many cases positive for islet-associated autoantibodies, mainly GADA, have recently been reported. Indeed, a study suggests that GADA-positive fulminant type 1 diabetes cases account for 9% of all fulminant type 1 diabetes cases [3]. These findings encouraged us to investigate the possibility that the involvement of islet-associated autoimmunity in the development of GADA-positive fulminant type 1 diabetes may produce some characteristic clinical pictures at onset. As far as we know, there has been no report investigating the clinical characteristics of GADA-positive fulminant type 1 diabetes. In this study, we therefore aimed to clarify the relationship between GADA titers and clinical parameters, especially clinical severity at onset, in GADA-positive fulminant type 1 diabetes.

Participants and Methods

Participants

This research project was conducted as a cross-sectional observational study. First, we tried to collect participants with GADA-positive fulminant type 1 diabetes who had been treated at our hospital (Saitama Medi-
Results

Participants’ clinical characteristics

Finally, 20 GADA-positive fulminant type 1 diabetes cases were included in this study (12 men, 8 women). The male-to-female ratio in this study was comparable with that in the classic fulminant type 1 diabetes cases reported in a previous nationwide survey that included a small number (7/142) of participants with GADA-positive fulminant type 1 diabetes [2]. The mean participant age was 43.4 ± 16.0 years, and the mean BMI was 21.1 ± 2.7 kg/m². These physical characteristics of the participants were comparable with those reported in the above-mentioned nationwide survey [2] (Table 1). There were 5 participants in this study with a history of hyperglycemia before diagnosis of GADA-positive fulminant type 1 diabetes. Human leukocyte antigen (HLA) genotype or serotype was examined in 14 out of 20 cases. As a result, HLA-DRB1*04:05 (or DR4) and HLA-DRB1*09:01 (or DR9), both of which are type 1 diabetes-associated HLA class II alleles in Japan [3], were presented in 5 and 6 out of 14 cases, respectively (Table 1, Supplementary Table 1).
Clinical symptoms just before or at onset of GADA-positive fulminant type 1 diabetes

As shown in Table 1 and Supplementary Table 1, prodromal symptoms were observed in all 20 participants, and the period from development of the symptoms to the diagnosis of fulminant type 1 diabetes was 4.9 ± 2.7 days. The prodromal symptoms included flu-like symptoms (6 participants; 30.0%), abdominal symptoms (12 participants; 60.0%), and general fatigue (4 participants; 20.0%). Although statistical analysis could not be performed, the mean incidence rates of both flu-like and abdominal symptoms were lower than those in the classic fulminant type 1 diabetes cases reported in the nationwide survey [2]. Meanwhile, hyperglycemic symptoms (hyperglycemic symptoms (Yes/No)) were observed in 16 participants (80.0%), with a mean period of 3.1 ± 2.2 days from the development of these symptoms to diagnosis.

Table 1  Summary of participants’ clinical data

| Clinical characteristics                                  | N    | GADA-positive fulminant type 1 diabetes in the present study | Classic fulminant type 1 diabetes reported by a nationwide survey [2] |
|-----------------------------------------------------------|------|-------------------------------------------------------------|---------------------------------------------------------------------|
| Age (years)                                               | 19   | 43.4 ± 16.0                                                 | 39.1 ± 15.7                                                         |
| Sex (Male/Female)                                         | 20   | 12/8                                                       | 83/78                                                              |
| Body mass index (kg/m²)                                   | 19   | 21.1 ± 2.7                                                 | 20.7 ± 3.9                                                         |
| Clinical symptoms at the onset of fulminant type 1 diabetes |      |                                                            |                                                                     |
| Prodromal symptoms                                        |      |                                                            |                                                                     |
| Flu-like symptoms (Yes/No)                               | 20   | 30.0% (6/14)                                               | 71.7%                                                             |
| Abdominal symptoms (Yes/No)                              | 20   | 60.0% (12/8)                                              | 72.5%                                                             |
| General fatigue (Yes/No)                                 | 20   | 20.0% (4/16)                                              | —                                                                  |
| Hyperglycemic symptoms (Yes/No)                           | 20   | 80.0% (16/4)                                              | 93.7%                                                             |
| Period from development of any prodromal symptoms to diagnosis (days) | 19   | 4.9 ± 2.7                                                 | —                                                                  |
| Period from development of hyperglycemic symptoms to diagnosis (days) | 16   | 3.1 ± 2.2                                                 | 4.4 ± 3.1                                                         |
| Laboratory findings                                       |      |                                                            |                                                                     |
| Plasma glucose level (mg/dL)                             | 20   | 933 ± 471                                                  | 800 ± 360                                                          |
| HbA1c (%)                                                 | 18   | 6.6 ± 0.5                                                  | 6.4 ± 0.9                                                          |
| GADA titers (RIA) (U/mL)                                 | 19   | 22.1 ± 11.6                                               | —                                                                  |
| GADA titers (ELISA) (U/mL)                               | 1    | 7.5                                                       | —                                                                  |
| GADA positivity (positive/negative)                       | 20   | 20/0                                                      | 7/138                                                              |
| Serum amylase (U/L)                                       | 18   | 282.2 ± 297.0                                             | —                                                                  |
| Serum lipase (U/L)                                        | 17   | 197.4 ± 236.3                                             | —                                                                  |
| Serum elastase-1 (U/L)                                   | 12   | 2,251.9 ± 1,597.0                                         | —                                                                  |
| Blood pH                                                  | 17   | 7.153 ± 0.160                                             | 7.125 ± 0.125                                                      |
| Blood HCO₃⁻ (mmol/L)                                     | 17   | 9.2 ± 5.8                                                 | —                                                                  |
| Serum total ketone body (µmol/L)                         | 10   | 8,432.3 ± 5,633.4                                         | —                                                                  |
| Serum acetoacetate (µmol/L)                              | 9    | 1,710.3 ± 1,222.7                                         | —                                                                  |
| Serum 3-hydroxybutyrate (µmol/L)                         | 10   | 6,163.5 ± 3,908.7                                         | —                                                                  |
| Presence of type 1 diabetes-associated HLA class II (Yes/No) | 14   | 9/5                                                       | —                                                                  |

Data are shown as mean ± standard deviation (SD). Exceptionally, GADA titers are presented as mean ± standard error (SE). ELISA, Enzyme-Linked ImmunoSorbent Assay; GADA, anti-glutamic acid decarboxylase antibody; HLA, human leukocyte antigen; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program; RIA, radioimmunoassay.

*NGSP value (%) = 1.02 × JDS value (%) + 0.25 (%) [20]

Clinical symptoms just before or at onset of GADA-positive fulminant type 1 diabetes

As shown in Table 1 and Supplementary Table 1, prodromal symptoms were observed in all 20 participants, and the period from development of the symptoms to the diagnosis of fulminant type 1 diabetes was 4.9 ± 2.7 days. The prodromal symptoms included flu-like symptoms (6 participants; 30.0%), abdominal symptoms (12 participants; 60.0%), and general fatigue (4 participants; 20.0%). Although statistical analysis could not be performed, the mean incidence rates of both flu-like and abdominal symptoms were lower than those in the classic fulminant type 1 diabetes cases reported in the nationwide survey [2]. Meanwhile, hyperglycemic symp-
Symptoms before diagnosis were observed in 16 participants, and the period from development of the symptoms to the diagnosis of fulminant type 1 diabetes was 3.1 ± 2.2 days, which was comparable with that in the classic fulminant type 1 diabetes cases reported in the nationwide survey (4.4 ± 3.1 days; Table 1) [2].

Next, we investigated the correlation between GADA titers and the “period from development of any prodromal symptoms to diagnosis of fulminant type 1 diabetes.” There was a significantly inverse correlation between the two factors ($r_s = -0.559, p < 0.05$) (Table 2, Fig. 1a). In contrast, when we investigated the correlation between GADA titers and the “period from development of hyperglycemic symptoms to diagnosis of fulminant type 1 diabetes,” there was no significant correlation between the two factors (Table 2).

**Laboratory findings**

As shown in Table 1 and Supplementary Table 2, the blood test at onset revealed HbA1c of 6.6 ± 0.5%, a plasma glucose level of 933 ± 471 mg/dL, and a GADA-RIA titer of 22.1 ± 11.6 U/mL. HbA1c and plasma glucose levels were comparable with those in the classic fulminant type 1 diabetes cases reported in the nationwide survey (Table 1) [2]. The mean serum levels of 3 pancreatic exocrine enzymes (i.e., amylase, lipase, and elastase-1) were elevated.

Blood gas analysis revealed pH of 7.153 ± 0.160 and HCO$_3^-$ of 9.2 ± 5.8 mmol/L. The pH level was comparable with that in the classic fulminant type 1 diabetes cases reported in the nationwide survey [2]. Moreover, a marked increase in the serum ketone bodies level was observed (Table 1, Supplementary Table 2). These findings suggested a severe clinical severity of diabetic ketoacidosis at the onset of GADA-positive fulminant type 1 diabetes.

Next, we investigated the correlation between GADA titers and various clinical laboratory findings. GADA titers were significantly and inversely correlated with blood pH and HCO$_3^-$ levels ($r_s = -0.576, p < 0.05$ and $r_s = -0.578, p < 0.05$, respectively) (Table 2, Fig. 1b and c). In addition, GADA titers were significantly and positively correlated with serum levels of total ketone bodies, acetoacetate, and 3-hydroxybutyrate ($r_s = 0.661, p < 0.05$ and $r_s = 0.700, p < 0.05$, respectively) (Table 2, Fig. 1d). For reference, GADA titers tended to be positively correlated with HbA1c levels, though it did not reach statistical significance ($r_s = 0.365, p = 0.15$) (Table 2). Meanwhile, no significant correlations were found between the serum levels of the three pancreatic exocrine enzymes and GADA titers (Table 2 and Supplementary Fig. 1).

**Discussion**

Fulminant type 1 diabetes is a novel subtype of type 1 diabetes characterized by a markedly rapid and almost complete destruction of pancreatic β-cells in a matter of days. A nationwide survey performed in Japan revealed that this type of diabetes accounts for 20% of newly diagnosed type 1 diabetes cases accompanied by hyperglycemia and diabetic ketosis/ketoacidosis [2]. Growing evidence suggest that both genetic factors, such as HLA, and environmental factors, such as viral infection, may contribute to the development of fulminant type 1 diabetes. Originally, anti-islet autoimmune processes were

| Table 2 | Spearman’s rank correlation coefficient ($r_s$) and significant $p$ values between GADA titers (RIA) and clinical parameters |
|-----------------|-----------------|-----------------|
| Period from development of any prodromal symptoms to diagnosis | $-0.559$ | $<0.05$ |
| Period from development of hyperglycemic symptoms to diagnosis | $-0.416$ | N.S. (0.12) |
| HbA1c | 0.365 | N.S. (0.15) |
| Blood pH | $-0.576$ | $<0.05$ |
| Blood HCO$_3^-$ | $-0.578$ | $<0.05$ |
| Serum total ketone body | 0.661 | $<0.05$ |
| Serum acetoacetate | 0.700 | $<0.05$ |
| Serum 3-hydroxybutyrate | 0.782 | $<0.01$ |
| Serum amylase | 0.465 | N.S. (0.06) |
| Serum lipase | 0.115 | N.S. (0.67) |
| Serum elastase-1 | 0.364 | N.S. (0.27) |

GADA, anti-glutamic acid decarboxylase antibody; N.S., not significant; RIA, radioimmunoassay; $r_s$, Spearman’s rank correlation coefficient.
thought to have a reduced contribution to fulminant type 1 diabetes compared to acute-onset type 1 diabetes; because the incidence of GADA-positive fulminant type 1 diabetes is very low; further, even when the result of the GADA test is positive, the titer tends to be very weakly positive. Rather, it is believed that both viral infection and subsequent non-autoimmune inflammatory reactions in genetically susceptible individuals directly cause β-cell destruction, leading to the development of ‘classic’ (non-autoimmune) fulminant type 1 diabetes [4].

However, there have been some recent studies regarding the possible involvement of autoimmune processes in fulminant type 1 diabetes. For example, a previous histological analysis demonstrated the infiltration of macrophages and T cells in the pancreatic islets (i.e., existence of insulitis) and exocrine pancreatic tissues in participants shortly after the onset of fulminant type 1 diabetes, suggesting that autoimmune processes may contribute to ‘classic’ fulminant type 1 diabetes [5]. In addition, several cases with fulminant type 1 diabetes induced by anti-programmed cell death-1 (PD-1) antibody treatment, such as nivolumab, against malignancies have been reported [6-9]. PD-1, an immunoreceptor, is expressed on T cells and pro-B cells, and interacts with its ligands to inhibit T cell activation and proliferation, inducing immunological self-tolerance. Thus, an anti-PD-1 antibody blocks PD-1 and can restore anticancer immune responses by abrogating PD-1 pathway-mediated T cell inhibition. Conversely, anti-PD-1 antibody treatment could lead to autoimmune adverse events. It is likely that anti-PD-1 antibody-induced fulminant type 1 diabetes may also develop through anti-islet autoimmune responses. These findings suggest that some autoimmune processes may be at least in part involved in the development of fulminant type 1 diabetes.

GADA is one of the important islet cell-associated autoantibodies and a critical marker for helping to diagnose autoimmune type 1 diabetes. In other words, the presence of GADA in people with diabetes generally indicates the possible involvement of autoimmune processes in the development of diabetes. As shown in Supplemental Tables 1 and 2, there have been some reports of cases with GADA-positive fulminant type 1 diabetes, and autoimmune processes may be involved in the development of this type of fulminant type 1 diabetes.
Harrison et al. previously demonstrated an inverse correlation between GADA titers and T cell reactivity to GAD in subjects at risk of type 1 diabetes, suggesting that higher titers of GADA are associated with slower progression to type 1 diabetes [10]. Therefore, we initially anticipated a milder onset pattern of fulminant type 1 diabetes with higher titers of GADA. However, contrary to our expectations, this study showed a significant inverse correlation between GADA titers and blood pH (inversely), HCO$_3^-$ (inversely), and serum ketone bodies levels (positively), all of which may reflect the clinical severity of fulminant type 1 diabetes at onset, suggesting that higher titers of GADA may be linked to more severe injury to β-cells and lower insulin secretion capability. These findings may further support the possible involvement of islet-associated autoimmune processes in GADA-positive fulminant type 1 diabetes. To establish more details, histological analyses will be needed in the future.

A previous study demonstrated that HLA-DRB1*04:05 (or DR4) and DRB1*09:01 (or DR9) are the main HLA alleles which confers susceptibility to autoimmune type 1 diabetes [3]. In contrast, only DRB1*04:05, but not DRB1*09:01, was associated with (classic) fulminant type 1 diabetes [3]. However, according to another study, it became obvious that DRB1*09:01 was strongly associated with GADA-positive fulminant type 1 diabetes [11]. Indeed, DRB1*09:01 was observed in 6 out of 14 cases in this study. Considering that our previous study showed that GAD-responsive interferon-γ-secreting CD4 T cells were increased in the periphery of participants with GADA-positive acute-onset type 1 diabetes with HLA-DR9 compared to those without it [12], GAD-related T cell autoimmunity may also be involved in the development of GADA-positive fulminant type 1 diabetes with HLA-DR9. To establish more details, further studies including GAD-specific T cell assays will be needed.

As an environmental factor, viral infection has been believed to be a main trigger of the development of fulminant type 1 diabetes. Indeed, the previous nationwide survey described above revealed that flu-like symptoms as prodromal symptoms are observed in about 70% of fulminant type 1 diabetes participants [2], although the rate of identification of specific viruses is low [2]. In some reports, histological examination revealed the possible existence of enterovirus in the endocrine and exocrine pancreas of ‘classic’ fulminant type 1 diabetes participants [5, 13]. These findings suggest the following; firstly that direct infection of viruses in β-cells leads to destruction of β-cells, and secondly that infection of viruses in the pancreas activates local innate immunity, leading to the destruction of β-cells by activated macrophages and other immune cells. In contrast, our study revealed a low incidence in flu-like symptoms as prodromal symptoms (30.0%), suggesting that unknown triggers other than viral infection may be associated with the onset of GADA-positive fulminant type 1 diabetes.

In cases of acute-onset type 1 diabetes, islet-associated autoantibodies, such as GADA, are reported to appear in the blood before the onset of diabetes [14, 15]. This finding indicates the possibility that destruction of β-cells was already underway before the development of overt hyperglycemia. Thus, in cases of GADA-positive fulminant type 1 diabetes, there is the possibility of the existence of GADA and some destruction of β-cells prior to the disease onset. In fact, 5 out of the 20 participants examined were found to have a history of hyperglycemia before their disease onset. Three out of the 5 participants had been diagnosed with impaired glucose tolerance, and 1 out of the remaining 2 participants had been diagnosed with slowly progressive insulin-glucose tolerance, and 1 out of the remaining 2 participants had been diagnosed with diabetes mellitus (SPIDDM) or latent autoimmune diabetes in adults (LADA). Although the remaining 1 participant had been diagnosed with diabetes before the onset of fulminant type 1 diabetes according to the relevant case report, the details remain unknown because of insufficient clinical information. These findings suggest the possibility that the destruction of β-cells to some extent precedes the onset of GADA-positive fulminant type 1 diabetes, leading to the pre-existence of impaired glucose tolerance before the onset of this disease. It is likely that more β-cells are destroyed in participants with a higher titer of GADA, leading to a positive correlation between GADA titers and HbA1c levels, though it did not reach statistical significance (Table 2).

Sasamori et al. recently revealed that unlike that in the participants with acute-onset type 1 diabetes and SPIDDM, pancreatic volume (PV) was not decreased in the participants (mainly) with classic fulminant type 1 diabetes, irrespective of disease duration, as compared with that in the control participants [16]. These findings suggest the possibility of no pre-existence of pancreatic inflammation until just before the onset of fulminant type 1 diabetes. However, if a decrease in PV is demonstrated in the participants with GADA-positive fulminant type 1 diabetes but not in those with classic fulminant type 1 diabetes, we could argue about the possibility of pre-existence of autoimmunity in the pancreas before the onset of GADA-positive fulminant type 1 diabetes. Unfortunately, any data on PV in our subjects could not be obtained in this study. In the future, we would like to make a comparison of PV between participants with autoimmune and non-autoimmune fulminant type 1 diabetes to exam-
ine the possibility of a pre-existence of autoimmunity in the pancreas of GADA-positive fulminant type 1 diabetes.

This study includes several limitations. Because this research was conducted mainly using published clinical data from cases reported in the literature, there were limitations to collect some important clinical parameters, such as body weight change just before the diagnosis of fulminant type 1 diabetes and serum glucagon level. As a sudden weight loss just before a diagnosis of fulminant type 1 diabetes is believed to reflect the degree of pre-existing ketosis, we could have revealed more about the association of GADA titers and the clinical severity of GADA-positive fulminant type 1 diabetes from the viewpoint of body weight loss. Meanwhile, histological evidence demonstrated that not only β-cells but also α-cells of pancreatic islets were reduced in number in fulminant type 1 diabetes [17], and a recent study revealed impaired glucagon secretion in individuals with fulminant type 1 diabetes [18]. These findings suggest that a decrease in serum glucagon level at diagnosis of fulminant type 1 diabetes may reflect the degree of islet destruction, which is probably useful for evaluating the clinical severity of the disease. In the future, we would like to focus on serum glucagon levels in GADA-positive fulminant type 1 diabetes at diagnosis. In addition, the clinical parameters, especially the period from development of any prodromal symptoms to diagnosis, the period from development of hyperglycemic symptoms to diagnosis, and so on, may differ depending on the timing of the participants’ visits, which varies among participants. As a result, the degree of association between clinical parameters and the clinical severity of the disease may also vary among participants, consequently hindering an accurate evaluation regarding the association. Moreover, a portion of cases had incomplete data regarding clinical parameters including serum levels of ketone bodies, possibly leading to an obstacle to accurate analyses. Accumulation of similar cases will be needed for details in a future. In this study, we focused on the positivity of GADA, but not other islet-associated autoantibodies, such as anti-insulinoma-associated antigen-2 (IA-2) antibody or anti-zinc transporter 8 (ZnT8) antibody. According to a previous report, the incidence of positivity of islet-associated autoantibodies other than GADA is considered to be extremely very low in fulminant type 1 diabetes [19]. To clarify the details regarding such fulminant type 1 diabetes, a nationwide survey will be required in a future. Finally, to our knowledge, no data specific to the clinical characteristics of GADA-negative (classic) fulminant type 1 diabetes are available. Indeed, to compare the clinical characteristics between GADA-positive and classic non-autoimmune fulminant type 1 diabetes cases in this study, we used the data from the previous nationwide survey on fulminant type 1 diabetes cases, including a small number of GADA-positive cases as classic fulminant type 1 diabetes cases [2]. Ideally, use of data specific to fulminant type 1 diabetes cases in which GADA measurements are negative is deemed desirable.

In conclusion, higher GADA titers may be linked to greater clinical severity of GADA-positive fulminant type 1 diabetes at onset. This finding may be attributed to possible pre-existence of islet-associated autoimmunity-related β-cell damage before the onset of GADA-positive fulminant type 1 diabetes. Thus, this type of fulminant type 1 diabetes may have a unique mechanism of development different from the ‘classic’ (non-autoimmune) fulminant type 1 diabetes. More similar cases will be needed to establish greater detail in the future.

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