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The age of onset of diabetes and glutamic acid decarboxylase titer measured long after diagnosis are associated with the clinical stage of slow-onset type 1 diabetes

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ABSTRACT

Aims: Diabetes mellitus is divided into 3 clinical stages: not insulin requiring, insulin requiring for control, and insulin requiring for survival. We investigated the clinical characteristics of patients with slow-onset type 1 diabetes (T1D) to examine which clinical factors influence the clinical stage.

Methods: One hundred fifty patients with slow-onset T1D were divided into 3 groups based on disease stage, and clinical features were compared among these groups. The patients were also divided into 4 groups based on the age of onset and the glutamic acid decarboxylase antibody (GAD-Ab) titer, which was measured long after diagnosis (mean, 9.2 years). The frequencies of the 3 stages were compared among these 4 groups.

Results: The age of onset and the log (GAD-Ab) titer differed significantly among the 3 stages. The number of patients not requiring insulin was significantly higher and the number of those requiring insulin for survival was significantly lower in the group in which the age of onset was ≥50 and the log (GAD-Ab) titer <0.6, while the opposite pattern was observed in the group in which the age of onset was <50 and the log(GAD-Ab) titer ≥0.6.

Conclusions: Our results suggest that the combination of the age of onset and GAD-Ab titer measured long after diagnosis might predict the clinical stage of slow-onset T1D.

1. Introduction

Diabetes mellitus is subdivided regardless of its underlying cause into 3 clinical stages: not insulin requiring, insulin requiring for control, and insulin requiring for survival. Type 1 diabetes (T1D) results from β-cell destruction that may ultimately lead to the clinical stage in which insulin is required for survival [1]. T1D is divided into 3 prevalent subtypes: fulminant, acute-onset (“classic”), and slow-onset [2,3]. The first 2 subtypes are difficult to detect during the clinical stages in which insulin is not required or is required for control, while type 2 diabetes rarely reaches the clinical stage at which insulin is required for survival. However, all 3 clinical stages are readily detected in slow-onset T1D, as the anti-islet antibodies, which are most commonly directed against glutamic acid decarboxylase (GAD), can be measured. Both latent autoimmune diabetes in adults (LADA) and slowly progressive T1D (SPT1D) are forms of slow-onset T1D. Patients with LADA are typically adults (usually aged >30 years) at diagnosis, remain at the clinical stage at which insulin is not required for at least the first six months after

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diagnosis, and do not necessarily reach the stage of ''insulin requiring for survival''. Patients with SPT1D are diagnosed at varying ages and remain at the clinical stage at which insulin is not required for at least the first 12 months after diagnosis, but most eventually progress to ''insulin requiring for survival'' [4].

We investigated the clinical characteristics of patients with slow-onset T1D in order to examine which clinical factors are associated with each of 3 clinical stages: not insulin requiring, insulin requiring for control, and insulin requiring for survival. The first 2 subdivisions constitute non-insulin-deficient T1D, while the last corresponds to insulin-deficient T1D. We also examined the difference between insulin requirement and insulin deficiency in slow-onset T1D.

2. Patients and methods

2.1. Patients

The study enrolled 150 unrelated Japanese patients with slow-onset T1D who visited the Internal Medicine sections of the participating hospitals between 2001 and 2012. The participating hospitals were Ichinomiya Municipal Hospital (Ichinomiya, Japan), Kyoritsu General Hospital (Nagoya, Japan), and Okazaki City Hospital (Okazaki, Japan), all of which are in the Aichi prefecture. All of the patients fulfilled the World Health Organization criteria for diabetes [1]. Fulminant T1D was diagnosed according to the criteria proposed by Imagawa et al. [5], and the patients diagnosed with this disease were excluded from this study. Slow-onset T1D was distinguished from acute-onset T1D by the absence of an insulin requirement at diagnosis and for a minimum of 6 months after diagnosis and by the absence of ketoacidosis and weight loss upon clinical presentation. Slow-onset T1D was distinguished from type 2 diabetes by the presence of GAD antibodies (GAD-Ab), which are not found in patients with type 2 diabetes.

The male/female ratio of the patients was 74/76. The values for all patient characteristics represent the mean and standard deviation. The patients' age of onset of diabetes was 51.5 ± 14.1 years (range, 15–80 years), the duration of diabetes was 11.3 ± 8.8 years, the body mass index (BMI) (kg/m^2) was 23.0 ± 4.3. The time between the onset of diabetes and the diagnosis of the clinical stage of ''insulin requiring for control'' (corresponding to the duration of non-insulin-requirement) was 7.6 ± 7.0 years. The time from the onset of diabetes to the measurement of GAD-Ab was 9.2 ± 8.4 years. All patients had positive GAD-Ab titers. Insulin deficiency was defined as a urinary C-peptide level of <6.6 nmol/day (20 μg/day), a serum 2-h C-peptide level of <0.33 nmol/L (1.0 ng/mL), or a serum fasting C-peptide level of <0.17 nmol/L (0.5 ng/mL). The transitional period from the clinical stage of ''insulin requiring for control'' to the clinical stage of ''insulin requiring for survival'' was determined retrospectively as the period in which the daily insulin injection dose was greater than 0.5 units/kg. If the daily insulin injection dose had been below 0.5 units/kg, the transitional period was determined retrospectively as the period in which multiple daily insulin injection therapy was initiated.

2.2. Analytical methods

GAD-Ab titers were determined as previously described [6]. The cut-off value and coefficients of variation (CV) for GAD-Ab were 1.5 U/mL and 5.29%, respectively. Both the specificity and sensitivity of GAD-Ab measurement were 100% according to the Second and Third GAD Proficiency Test Results Evaluations (University of Florida, Gainesville, FL). The urinary and serum C-peptide levels were determined using a commercially available enzyme immunoassay kit (Eiken C-peptide Kit; Eiken Chemical Co., Ltd., Tokyo, Japan). The intra-assay CVs of the C-peptide assay at C-peptide concentrations of 0.24, 1.59, and 5.64 nmol/L were 2.29%, 1.96%, and 2.97%, respectively. The inter-assay CV values at C-peptide concentrations of 0.25, 1.53, and 5.50 nmol/L were 2.60%, 2.23%, and 1.06%, respectively.

2.3. Statistical analysis

Results are shown as the mean ± SD unless otherwise indicated. Statistical analysis was performed using PASW Statistics 20.0 (SPSS, Inc., Chicago, IL). Inter-group comparisons of clinical parameters were performed using 1-way ANOVA, unpaired t tests, or the χ^2-test, as appropriate. The level of statistical significance was defined as $P < 0.05$ or the absolute value of adjusted residual >1.96.

3. Results

3.1. Clinical characteristics of the patients

The patients were divided into 3 groups according to their clinical stages. Forty-six patients with slow-onset T1D were ''not insulin requiring'' (stage I), 64 ''insulin requiring for control'' (stage II), and 40 ''insulin requiring for survival'' (stage III). Table 1 shows the clinical characteristics of the patients in each stage. The age of onset of diabetes, BMI, duration of diabetes, time from onset of disease to GAD-Ab measurement, common logarithm of the GAD-Ab titer [log (GAD-Ab)], 2-h postprandial serum C-peptide level, and fasting serum C-peptide level differed significantly among the 3 groups ($P < 0.0001$, $P = 0.0040$, $P = 3.0E{-}04$, $P = 0.0031$, $P = 1.5E{-}04$, $P < 0.0001$, and $P = 0.0023$, respectively). The age of onset of diabetes and the 2-h postprandial and fasting serum C-peptide levels were significantly lower in stage III patients than in stages I and II patients. The duration of diabetes was significantly longer in stage III patients than in stages I and II patients ($P = 1.8E{-}04$ and 0.0297, respectively). The BMI was significantly lower in stage III patients than in stage I patients ($P = 0.0028$). The time from onset of disease to GAD-Ab measurement was significantly longer in stage III patients than in stage I patients ($P = 0.0021$). The log (GAD-Ab) was significantly lower in stage I patients than in stages II and III patients ($P = 0.0211$ and 0.0439, respectively).

The daily insulin dosage and number of daily insulin injections were significantly higher in stage III patients than in stage II patients ($P < 0.0001$ and $P < 0.0001$, respectively). The 24-h urinary C-peptide level was significantly lower in stage III patients than in stage II patients ($P < 0.0001$). The gender distribution, duration of non-insulin-requirement,