

Clinical and Genetic Characteristics of Patients With Type 1 Diabetes Associated With Interferon Therapy

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OBJECTIVE—This study clarified characteristics of interferon-associated type 1 diabetes.

RESEARCH DESIGN AND METHODS—The study compared 12 patients with interferon-associated type 1 diabetes with 128 patients with type 1A diabetes with respect to clinical characteristics, and with 10 patients without diabetes despite interferon therapy and 136 normal controls with respect to HLA allele distributions.

RESULTS—Patients with interferon-associated type 1 diabetes retained higher levels of fasting serum C peptide as well as GAD65 antibodies than those with type 1A diabetes until 2 to 4 years after onset. *HLA-A*2402* was increased among patients with interferon-associated type 1 diabetes compared with those without diabetes, despite interferon therapy (odds ratio [OR] 4.00 [95% CI 1.09–17.26]). The haplotype of *DRB1*1302-DQA1*0102-DQB1*0604* was increased in these two groups combined compared with normal controls (OR 5.64 [95% CI 2.67–11.81]).

CONCLUSIONS—Interferon-associated type 1 diabetes is characterized clinically by high titers of GAD65 antibodies and preserved β -cell function, and genetically by addition of *HLA-A*2402* to *DRB1*1302-DQA1*0102-DQB1*0604*.

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Interferon α is used to treat several diseases, including chronic hepatitis C (1), and rarely causes type 1 diabetes (2–4). We examined the clinical characteristics and HLA associations of interferon-associated type 1 diabetes.

RESEARCH DESIGN AND METHODS

We enrolled 12 consecutive patients (four men, eight women) in whom type 1 diabetes developed during or after interferon therapy for chronic hepatitis C from 1998 to 2009, during which 1,250 patients with chronic hepatitis C were treated with interferon. For comparison of clinical features, 128 patients with type 1A diabetes (77 men and 51 women) in whom anti-GAD65 antibodies or fasting serum C-peptide levels were measured at least once during the 4

years after the onset of type 1 diabetes were enrolled from previous studies (5). The number of patients for whom data were available on GAD65 antibodies, fasting serum C peptide, or insulin dosage at each designated time point is presented in Supplementary Table 1. As genetic controls, 10 patients who did not develop diabetes and were negative for GAD65 antibodies after interferon therapy for chronic hepatitis C (eight men and two women) were enrolled. In addition, 136 normal controls were also enrolled (5). This study was approved by the institutional ethics committee. All patients gave informed consent for DNA analysis.

Levels of GAD65 antibodies were measured using an immunoprecipitation assay (Cosmic Co., Tokyo, Japan), and titers of GAD65 antibodies >1.5 units/mL

(mean + 3 SD of normal controls) were judged as positive. C-peptide assay, typing of *HLA-A*, *-DRB*, *-DQA*, and *-DQB* alleles, and subsequent determination of the *DRB1-DQA1-DQB1* haplotype were performed as previously described (5). As an index of glycemic control during the first 5 years of the disease, mean A1C (6) was calculated when onset was later than 1994.

In the case-control study, the odds ratio (OR) and their 95% CIs were calculated by logistic regression. The Mann-Whitney *U* test was used to compare unpaired data. Difference of frequency between the two groups was assessed by the Fisher exact probability test. Results are expressed as the means \pm SD except for titers of GAD65 antibodies, which are presented as median (range).

RESULTS—Type 1 diabetes occurred during interferon therapy in seven patients, within 3 months after interferon therapy in three patients, and 1 or 5 years after interferon therapy in two patients. Of 12 patients with interferon-associated type 1 diabetes, 10 (83.3%) showed ketosis at the onset and 11 (91.7%) needed insulin therapy within 3 months after the onset of diabetes.

Titers of GAD65 antibodies as well as levels of fasting serum C-peptide were higher in the patients with interferon-associated type 1 diabetes than those with type 1A diabetes at onset, 1 year, and 2–4 years after the onset of diabetes (Fig. 1A and B). The insulin dose required did not differ between the two groups at onset, but was lower at 1 year and at 2–4 years in the patients with interferon-associated type 1 diabetes (Fig. 1C). Mean A1C levels during the first 5 years did not differ between the two groups (7.47 ± 0.97 [$n = 12$] vs. $7.88 \pm 1.38\%$ [$n = 41$], $P = 0.51$).

The *HLA-A*2402* allele was present in 12 of 24 (50%) of those with interferon-associated type 1 diabetes compared with four of 20 (20%) in those without diabetes despite interferon therapy (OR 4.00 [95% CI 1.09–17.26]; $P = 0.045$; Supplementary Table 2). Details of interferon therapy did not differ between these

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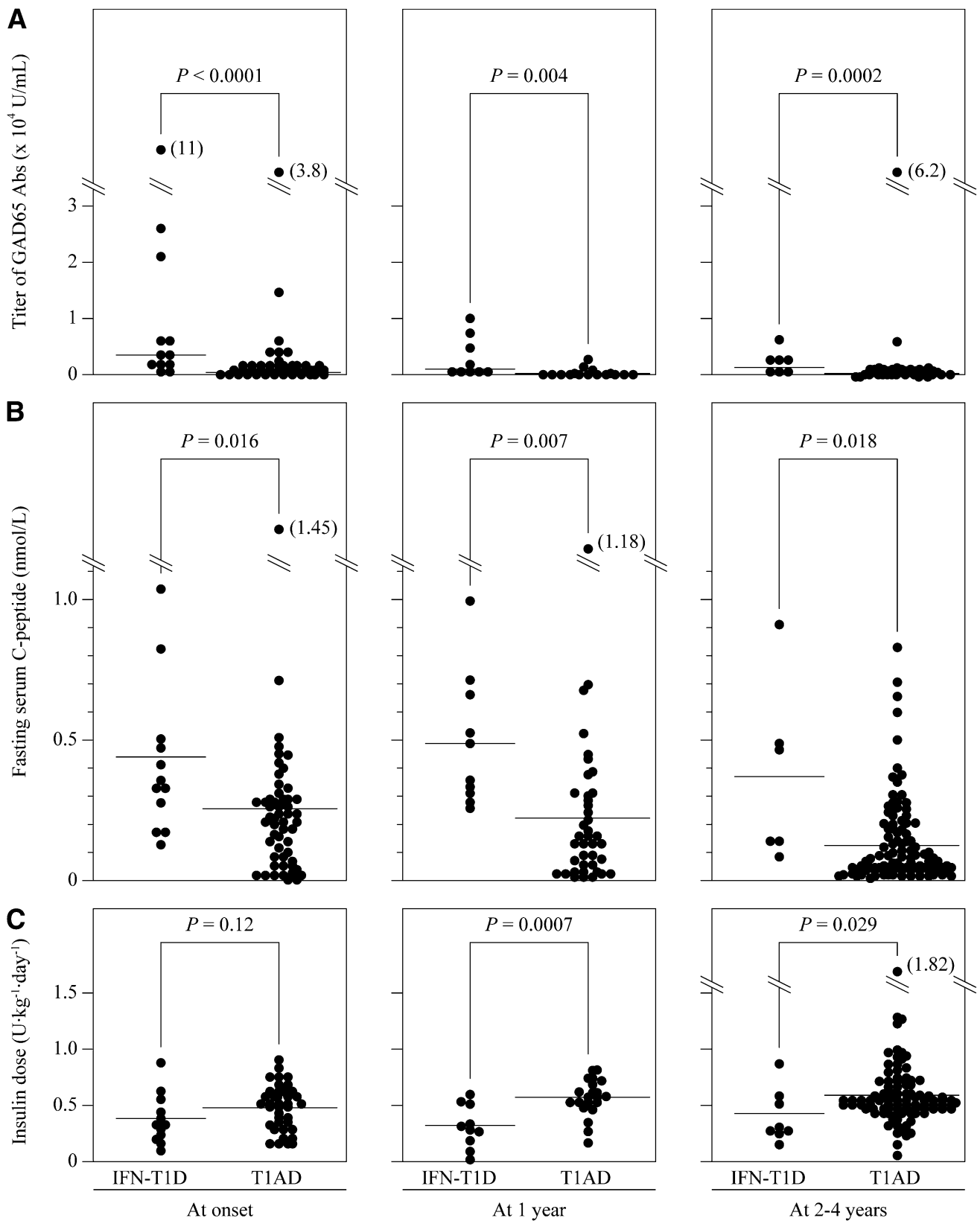


Figure 1—Titers of GAD65 antibodies (Abs) (A), fasting serum C-peptide levels (B), and insulin doses (C) in patients with interferon-associated type 1 diabetes (IFN-T1D) and those with type 1A diabetes (T1AD) at onset, 1 year after onset, and 2–4 years after onset of type 1 diabetes. The horizontal bars (—) in panel A represent medians, exact values of which were 3,309 vs. 7.7 units/mL at onset, 347 vs. 1.6 units/mL at 1 year after onset, and 1,247 vs. 3.5 units/mL at 2–4 years after onset. The horizontal bars (—) in panels B and C represent means.

two groups (Supplementary Table 3). Haplotype frequency of *DRB1*1302-DQA1*0102-DQB1*0604* was increased in these two groups combined (36.4% [6/44]) compared with normal controls (9.2% [25/272], $P < 0.0001$; OR 5.64 [95% CI 2.67–11.81]) and those with type 1A diabetes (4.9% [10/206], $P < 0.0001$; OR 11.20 [95% CI 4.70–27.96]).

CONCLUSIONS—Chronic hepatitis C is strongly associated with type 2 diabetes (7), whereas the occurrence of type 1 diabetes in chronic hepatitis C is almost always associated with the use of interferon (2–4). The incidence rate of interferon-associated type 1 diabetes in chronic hepatitis C was 0.96% (12/1,250) in our institution. Compared with type 1A diabetes, interferon-associated type 1 diabetes was characterized by a higher level of GAD65 antibodies and preserved β -cell function, which led to a smaller dose of insulin despite comparable levels of A1C. However, the acute mode of onset and the need for similar doses of insulin at onset in interferon-associated type 1 diabetes compared with type 1A diabetes may be partly related to insulin resistance caused by interferon α (8).

Our preliminary examination showed high levels of serum interleukin (IL)-18 and undetectable serum IL-12 at the onset of interferon-associated type 1 diabetes (9). IL-18 enhances the Th2-driven immune response in the absence of IL-12 (10).

Furthermore, an inverse relationship exists between humoral and cellular immunity to GAD in type 1 diabetes (11). These situations may lead to a high titer of GAD antibodies along with relatively preserved β -cell function in interferon-associated type 1 diabetes. On the other hand, insulinoma-associated antigen-2 antibodies showed no difference in titers between seven patients with interferon-associated type 1 diabetes and 12 with type 1A diabetes (K.N., unpublished data).

*HLA-A*2402*, which is implicated in susceptibility to type 1 diabetes (12,13) and is related to early complete β -cell destruction in type 1 diabetes (5), was associated with occurrence of type 1 diabetes after exposure to interferon. In addition, the haplotype of *DRB1*1302-DQA1*0102-DQB1*0604* was associated with chronic hepatitis C that required interferon therapy regardless of the subsequent occurrence

of type 1 diabetes. *DRB1*13* was reported to be increased in Brazilian patients of Caucasian origin (14) and Turkish patients with chronic hepatitis C (15). The current study cannot determine whether the *DRB1*1302-DQA1*0102-DQB1*0604* haplotype is necessary for susceptibility to interferon-associated type 1 diabetes. However, type 1 diabetes occurs more frequently in patients treated for chronic hepatitis C than for other conditions (2), which suggests that the addition of *A*2402* to the *DRB1*1302-DQA1*0102-DQB1*0604* haplotype contributes to the susceptibility to interferon-associated type 1 diabetes. Nonetheless, these HLA associations, as well as the specific clinical features in interferon-associated type 1 diabetes, need to be confirmed in subsequent large-scale studies.

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K.N. researched the data and wrote the manuscript. S.S. contributed to the discussion and reviewed and edited the manuscript.

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