The Prevalence of Islet-Cell Antibodies and Complement-Fixing Islet-Cell Antibodies in Japanese Diabetics

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Abstract

The presence of complement-fixing islet-cell antibodies (CF-ICA) and islet-cell antibodies (ICA) was examined in 355 patients with different types of diabetes mellitus in the Japanese population by an indirect immunofluorescence test (IFT).

The overall prevalence of ICA, which were stained as a homogenous cytoplasmic fluorescence in islet cells, was 7 per cent (5/67) in insulin-dependent (Type I) diabetics, 4 per cent (6/137) in noninsulin-dependent (Type II) diabetics treated with insulin and 2 per cent (1/58) in Type II diabetics treated with oral hypoglycemic agents. None of 84 Type II diabetics receiving diet alone and 9 diabetics associated with chronic pancreatitis had ICA. CF-ICA, which were stained as a "ring-shaped" fluorescence in a part of the cytoplasma, were demonstrated in 5 out of 12 cases (42%) whose sera possessed ICA.

The lower prevalence and remarkably shorter persistence of ICA and CF-ICA in Japanese diabetics than those observed in Caucasian diabetics may be explained by the heterogenous immunological response in different races or possible heterogeneity of Type I diabetics.

The autoantibodies to pancreatic islet cell cytoplasm, namely islet-cell antibodies (ICA), were found by Bottazzo et al. (1974) in the sera of patients with autoimmune endocrinopathies (AIE) with or without diabetes mellitus. Lendrum et al. (1976) reported that ICA were also present in 85 per cent of newly diagnosed patients with insulin-dependent diabetes mellitus and they became less common with prolonged duration of disease. Furthermore, Irvine et al. (1976, 1977a) showed that ICA-positive diabetics who were initially treated with oral hypoglycemic agents (OHA) or diet alone required insulin after a few years. Recently, Bottazzo et al. (1980) reported the existence of ICA having complement fixing abilities (complement-fixing ICA: CF-ICA). This result suggested that CF-ICA reflected the damage of pancreatic beta cells more selectively than conventional ICA.

These reports imply that ICA and CF-ICA have not only a pathognomonic value for insulin-dependent diabetics but also prognostic value for potential diabetics. Almost all studies concerning ICA and CF-ICA have been performed in Caucasians (Irvine et al., 1977; Del Prete et al., 1977; Neufeld et al., 1980) and blacks (Oli et al., 1980). The prevalence of ICA in Japanese
has not been studied in large numbers of the patients with different types of diabetes except for one report by Nagaoka et al., (1978) in insulin-dependent diabetes. Furthermore, no report concerning CF-ICA in Japanese diabetics has appeared as far as we know. We therefore examined CF-ICA and ICA using an indirect immunofluorescence test (IFT), and demonstrated the presence and prevalence of CF-ICA as well as ICA in various types of diabetes mellitus in the Japanese population.

Materials and Methods

Sera were obtained from 355 Japanese diabetics (sex: 230 males, 125 females, age: 3-80 years, duration: 1 month-30 years) including 67 insulin-dependent diabetics (Type I), 279 noninsulin-dependent diabetics (Type II) (137 patients treated with insulin, 58 patients treated with OHA, 84 diabetics receiving diet alone), 9 diabetics associated with chronic pancreatitis, and 144 age-matched non-diabetic controls. Among these diabetics, 5 patients were concomitantly afflicted with AIE (2 patients with chronic thyroiditis, 2 patients with Graves’ disease and 1 patient with pernicious anemia).

The detection of ICA was performed by an IFT using fluorescein-conjugated specific goat anti-human IgG, IgA and IgM sera (Meloy Labs.). CF-ICA were detected by a three-layered IFT, the second layer of which consisted of undiluted fresh normal human serum as a source of complement followed by fluorescein-conjugated goat anti-human C1 serum (Meloy Labs.) diluted 1:10.

IFT was performed on unfixed 5 μm cryostat sections of fresh specimens of non-diabetic human pancreas obtained from blood O-group patients. In ICA-positive sera, gastric parietal cell antibodies and thyroid microsomal antibodies were examined by IFT and Microsome Test (Fujizooki Co. Ltd.), respectively.

Results

In the first series of experiments, the prevalence of ICA in 355 patients with different types of diabetes mellitus was studied in the Japanese population. As shown in Fig. 1, ICA were stained as homogenous cytoplasmic fluorescence in islet cells by standard IFT. Twelve patients (7 males, 5 females) out of 355 diabetics had ICA. The prevalence of ICA in insulin-dependent diabetics and noninsulin-dependent diabetics treated with insulin was 7 per cent (5/67) and 4 per cent (6/137), respectively. Only 2 per cent (1/58) of diabetics treated with OHA had ICA, while ICA were not detected in any of 84 diabetics receiving diet therapy alone, 9 diabetics associated with chronic pancreatitis, 5 patients concomitantly suffering from overt AIE and 144 controls. ICA present in 4 (2 males, 2 females) out of 9 insulin-dependent diabetics (44%) during the first year of the disease, decreased during the subsequent 10 or more years (Fig. 2). ICA were invariably of IgG class in our study. Neither gastric parietal cell nor thyroid microsomal antibodies were detected in ICA-positive patients except for one case, in whom thyroid microsomal antibodies were positive.

In the next study, the complement fixing ability of ICA-positive sera was investigated. CF-ICA were stained as a “ring-shaped” fluorescent design in cytoplasm as shown in Fig. 3. It was demonstrated that CF-ICA existed in 5 of 12 ICA-positive serum samples (42%). The prevalence of CF-ICA was highest in the first year of the disease similar to ICA (Fig. 2).
Fig. 1. Islet-cell antibodies (ICA) showing diffuse cytoplasmic fluorescence over the pancreatic islet cells.

Fig. 2. The prevalence of islet-cell antibodies (ICA) and complement-fixing islet-cell antibodies (CF-ICA) in 67 insulin-dependent diabetics (IDDM) and 195 noninsulin-dependent diabetics (NIDDM) treated with insulin or oral hypoglycemic agents.
**Discussion**

In the present study we demonstrated the presence of CF-ICA in Japanese diabetics. This might be the first time that the presence of CF-ICA in Japanese population has been elucidated. Bottazzo et al. (1980) reported that CF-ICA were found in about half of ICA-positive serum samples. Riley et al. (1980) showed the presence of the antibodies in almost all cases with ICA-positive sera, suggesting that ICA and CF-ICA were identical. Our results were consistent with those of Bottazzo et al. (1980). The difference in the staining between ICA and CF-ICA obtained in the present study suggests the possibility that these two antibodies are different.

In this study we also showed the paucity and remarkably short persistence of ICA in Japanese diabetics as compared with those of insulin-treated Caucasian diabetics (Irvine et al., 1977b). Recently, there appeared one paper in collaboration with Irvine (Nagaoka et al., 1978) and two reports in abstract form (Tanae and Bottazzo, 1981; Shinjo, 1981) concerning ICA in smaller Japanese diabetic populations. In the first year of the disease, the prevalences of ICA in insulin-dependent diabetics reported by Nagaoka et al. (1978), and Tanae and Bottazzo (1981) were much lower than that observed in our study. Since the ICA in these studies was assayed in England, it might be possible that the sera obtained from Japanese did not match the Caucasian pancreas as the antigen used in the IFT. Shinjo...
(1981) found ICA in 18 out of 194 different types of diabetics, but the details are not yet fully reported. A few reports suggested that ICA persisted longer in patients with AIE (Irvine et al., 1978) and/or with HLA-B8 (Irvine et al., 1977; Bottazzo et al., 1978) in Caucasians. It has been shown that diabetes mellitus is rarely associated with AIE in Japan (Kitamuro et al., 1978) and that HLA-B8 is almost absent in Japanese diabetics (Wakisaka et al., 1976). These differences in immunological properties between Caucasian and Japanese diabetics may account for the low prevalence and remarkably short persistence of ICA demonstrated in our study.

References