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Islet-Cell Antibodies and Beta-Cell Function in Insulin-dependent Diabetics

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Summary. Residual insulin secretion and islet-cell antibodies were studied in 399 insulin-dependent diabetics with age at onset of between 10–19.9 years (248 patients) or 30–39.9 years (151 patients). We found the prevalence of islet-cell antibodies to be independent of residual beta-cell function as measured by serum C-peptide and age at onset. The cause and role of the persistence of islet-cell antibodies in insulin-dependent diabetics remain obscure.

Key words: Insulin-dependent diabetics, beta-cell function, islet-cell antibodies.

A good deal of evidence has now accumulated concerning the possible aetiological role of both humoral [1, 2, 3, 4, 5] and cell mediatetd immunity [6, 7, 8, 9] in insulin-dependent diabetes.

Islet-cell antibodies (ICA) were first demonstrated in 1974 [1] in patients with polyendocrine autoimmune disease. The precise nature and location of the antigen remains to be elucidated, but it is a cytoplasmic component common to all four types of islet-cells [10]. The majority of patients have ICA at the time of onset of diabetes, but after 10 years of disease only 5–15% are still positive [11, 12, 13, 14]. We have also found that the prevalence of residual beta-cell function was almost 100% during the first two years of disease, and about 15% after 10 years of diabetes [15]. If the beta-cell is the antigenic stimulus to ICA-production, patients with residual beta-cell function would have a higher prevalence of ICA than those without beta-cells and hence no possibility for antibody stimulation. In one such study it was shown that only one out of 13 insulin-dependent patients with circulating ICA had demonstrable beta-cell function [16].

The purpose of the present study was to evaluate whether an association exists between residual beta-cell function and ICA in a larger population of insulin-dependent diabetics with onset of disease between the age of 10–19, or 30–39 respectively, i. e. a ten year span in each case. The difference in age at onset was chosen because of a previously demonstrated direct relationship between age at onset and prevalence of preserved beta-cell function [15].

Materials and Methods

Study Population

The study population (399 patients) was part of a larger series previously described [15]. It comprised 248 diabetic patients with age at onset 10–19, and 151 patients with age at onset 30–39. The average duration of diabetes was 16 years (range 0–52) in the early onset group and 13 years (range 0–42) in the late onset group. Patients were considered insulin-dependent if insulin treatment was started for initial hyperglycaemia with ketonuria, or became necessary within the first year after diagnosis. None of the patients were taking drugs known to influence immune response. Twenty patients had other endocrine or autoimmune disorders: Five had myxoedema, one with postadrenalectomy adrenocortical insufficiency, two with thyroiditis of which one also had pernicious anaemia, a further two with pernicious anaemia, and ten with previous or actual thyrotoxicosis of which one had concommitant pernicious anemia.

Patients with pancreatic disorders in addition to diabetes mellitus were excluded from the study. All patients gave informed consent to the investigation.

Methods

Residual beta-cell function was assessed by the C-peptide immunoreactivity (CPR) obtained following stimulation with 1 mg of glucagon or breakfast [17]. CPR was determined employing

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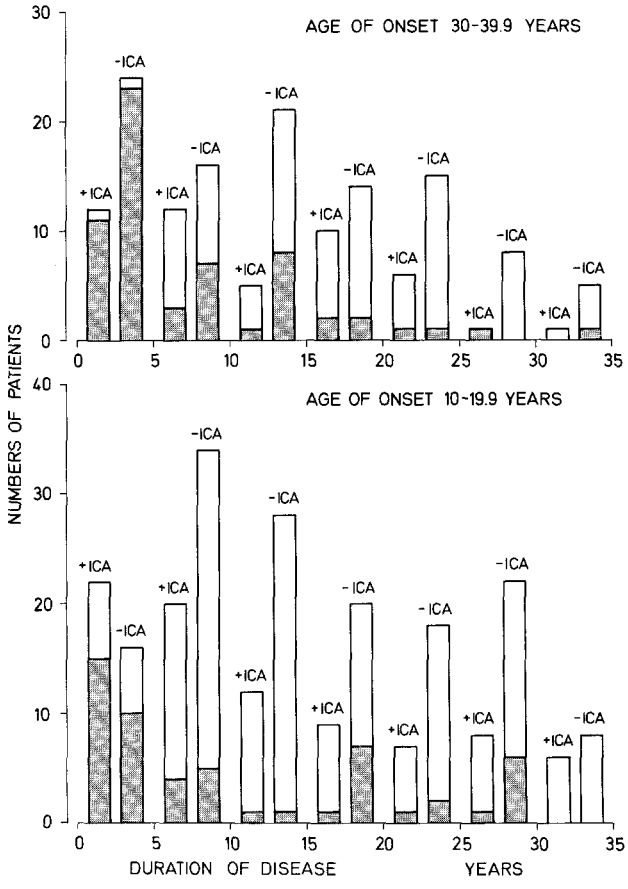

Fig. 1. Distribution of patients in the early- and late-onset groups by 5-year intervals of duration of diabetes up to 35 years. Black areas illustrate number of patients with residual beta-cell function in relation to persistence of islet-cell antibodies

antibody M 1230 [18], and residual beta-cell function was considered present when CPR in plasma was equal to or exceeded 0.06 pmol/ml, which is the detection limit of the assay.

Islet-cell antibodies were detected by the indirect immunofluorescence test on undiluted serum as previously described [1].

All probability values were derived by use of the chi-squared test.

Results

Residual beta-cell function was present in 54 patients (21.7%) with early onset diabetes and in 61 (40.4%) with late onset ($p < 0.01$). The prevalence was almost 100 per cent during the first 2 years of disease and thereafter lower in diabetics with early onset and up to 15 years of disease (Fig. 1). About 15% of all patients who had had the disease between 15 and 35 years had measurable C-peptide.

Ninety patients (36.3%) in the early onset group were positive for ICA, compared with 47 patients (31.1%) in the late onset group ($p > 0.05$). Islet-cell antibody prevalence fell with increasing duration of disease in both groups of patients. Antibodies were not demonstrated in the few patients who had had diabetes for more than 51 years in the early onset group and 33 years in the late onset group.

In both groups, irrespective of the duration of disease, there was no difference in the prevalence of ICA in patients with or without residual beta-cell function (fig.).

Of the 20 (5%) patients with concommitant other endocrine disorders only two had demonstrable beta-cell function and 10 circulating ICA. Out of 10 actual or previously thyotoxic patients 8 showed circulating ICA.

Discussion

The present study fails to demonstrate any correlation between measurable C-peptide and the presence of ICA, irrespective of the age of onset of diabetes. This is in accordance with Theophanides et al. [16] who in 122 long-term insulin-treated patients found seventeen to be positive for ICA. Thirteen of these 17 patients were tested for residual insulin secretion, which was found in one.

It has been demonstrated that residual beta-cell function as determined by C-peptide response to glucose, glucagon or a meal is present in many insulin-dependent diabetics for several years after the onset of clinical symptoms [15]. An important question is whether persistence of ICA represents a state of gradual beta-cell destruction associated with a constant immunogenic stimulus. If this was the case, it should be expected that residual beta-cell function should correlate with the presence of ICA.

The findings, however, are perhaps not surprising if one considers some of the possible alternatives. It is known that ICA reacts with a cytoplasmic antigen which is common to the four different islet-cells [10]. In support of this concept is the existence of a common antigen to all three layers of the adrenal cortex reacting with the autoantibody of Addison's disease, in which the functional deficit is related mainly to the zona fasciculata [20]. In the islets of newly diagnosed insulin-dependent diabetics, morphometric studies have shown an increase in glucagon, somatostatin [19] and pancreatic polypeptide secreting cells [21], implying that there is no active destruction of these cells. This is borne out by metabolic studies which have demonstrated a normal or elevated glucagon response to arginine infusion in ICA positive cases [22]. Furthermore the persistence of an autoantibody in classical autoimmune disease may be associated with an apparent lack of residual organ specific anti-

gen. For example, long-term Hashimoto's thyroiditis or Addisonian patients may show strong antibody reactions despite complete atrophy of the corresponding endocrine gland [20].

The results from the present study thus suggest that ICA have no direct role in beta-cell destruction. It is speculated that active damage results from an abnormal immune response involving specific cell surface antibodies and cell mediated immunity. Although this initial mechanism is still unclear, the long-term production of cytoplasmic antibodies may reflect an intrinsic genetic defect in the immune system possibly related to T-suppressor mechanisms.

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