

ISLET CELL ANTIBODIES IN DIABETES MELLITUS

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The existence of autoantibodies reactive with the endocrine pancreas was first reported in 1974 when Islet Cell Antibodies (ICAs) were detected in patients with diabetes mellitus together with autoimmune polyendocrine deficiencies¹, and in diabetics with coexistent autoimmune disease². Several other reports ensued in the following years³⁻⁷, indicating a high incidence of ICAs in Insulin-Dependent Diabetes Mellitus (IDDM). ICAs are seldom found in normal persons (less than 1%) or in patients with non-insulin-dependent diabetes mellitus (NIDDM) (about 15%). The percentage of patients with ICAs in their circulation decreases with time and less than 25 per cent have detectable levels of this antibody two years after diagnosis^{4,6-8}. Initially, ICAs were thought to be of IgG class only and were shown to react with both cytoplasmic and cell surface determinants present in cells of the islet of Langerhans^{9,10}, but later, it was reported that ICAs are distinct from Islet Cell Surface Antibody (ICSA)". In a study conducted on patients with IDDM, it was proved that only the serum from ICSA-positive patients was cytotoxic to islet cell¹¹. Serum from ICA-positive but ICSA-negative patients was noncytotoxic to islet cells. Thus, claiming that ICAs are directed against cytoplasmic antigens and are noncytotoxic to viable islet cells while ICSAs are directed against cell surface antigens and in presence of complement are cytotoxic to viable islet cells¹¹. In the same study¹¹, about 25 per cent of non-diabetic first degree relatives were found to be positive for cytotoxic ICSA. This simple presence of ICSA is not sufficient to produce diabetes since non-diabetic relatives have been found to be ICSA- positive and not all IDDM patients have cytotoxic ICSAs.

There are three possible mechanisms of the production of ICSAs in patients with IDDM:

- i. That ICSA is not the cause but the result of beta cell injury perhaps secondary to environmental insult (e.g. viruses or chemicals¹²⁻²¹)
- ii. That ICSAs are the host's immune response to foreign antigens that cross-react with surface antigens on beta cell - a form of molecular mimicry^{3-5,22,23}; and/or;
- iii. The ICSAs precede the development of diabetes and result from genetically programmed and/or environmentally induced immunoregulatory disorder¹¹. The potential for cytotoxic ICSAs as markers for the identification of risk of diabetes mellitus or autoimmune disorder remain controversial until further large scale trials are conducted in heterogeneous populations. The broad division of diabetes mellitus into Type 1 (IDDM) and Type 2 (NIDDM) is widely accepted. Some investigators have proposed two subtypes of the Type 1 (IDDM). Type 1a, the more common juvenile form^{4,24} thought to be initiated by viruses^{12,18} and type 1b^{7,25} found in polyendocrine patients in whom viral etiology is less conspicuous and an immune anomaly is likely. Evidence came from the work of Bottazzo et al²⁵ on sixty-eight patients with longstanding diabetes and persistent ICAs and thirty-five with coexistent diabetes and Graves' disease or primary myxedema. The hypothesis of a primary autoimmune diabetes mellitus was supported by the findings that this group is distinct from the "juvenile" type (Type 1a) diabetes mellitus by having a female predominance, a later onset of diabetes, and a strong family history of autoimmune endocrinopathy. In contrast, in the typical "juvenile" type diabetic (Type 1a), there is a slight male predominance, a generally earlier age of onset (11-13 years old), constant seasonal variation, temporary pancreatic autoimmunity and a weak correlation with thyrogastic antibodies. They²⁵ further reported that the overall incidence of ICA was 53 per cent with a higher incidence (64%) in patients with diabetes and Grave's disease than in those diabetics with primary myxedema (44%). All patients with persistent ICAs had evidence of other organ-specific

autoimmunity, and 75 per cent were positive for HLA-B8. Most of the patients had thyroid antibodies. Thyroid microsomal antibodies were found in 93 per cent ICA-positive patients with thyrotoxicosis against 71 per cent in those ICA-positive patients with myxedema. Gastric parietal cell antibodies were found in 53.5 per cent of patients compared with 30 per cent of subjects with uncomplicated thyroid disorders. The pathogenetic role of the ICAs is uncertain in view of the distribution of the autoantigen in the cytoplasm of all four types of endocrine cells within the islets, while the immune damage is focussed entirely upon beta cells. Cell surface antibodies are more likely to directly mediate immune damage, since they may be directed against insulin-secreting cells¹⁰. However, besides access to the target organ in vivo, antibodies must possess certain properties in order to damage cells. IgG molecules cannot produce cytotoxic effects on their own but initiate cell lysis either by attachment to 'killer' cells as in antibody-dependent cellular cytotoxicity²⁶ or by binding complement. Bottazzo, Dean et al²⁷ described their findings about the variable complement-fixing (CF) capacity of ICAs. They provided evidence that CF-ICAs are a separate subspecies, independent of the IgG subclasses, and that their appearance in the circulation may be more closely related to the clinical onset of diabetes than that of conventional ICAs (i.e. CF-ICAs appeared in circulation later than ICA-IgG), and they tend to disappear more rapidly after onset of clinical diabetes. The CF-ICAs may reflect pancreatic beta cell damage more selectively and may be preferable as a marker in Type 1 diabetes. They further reported that among the ICA-positive non-diabetic endocrine patients, cases who actually became diabetic were either positive for CF-ICAs from the beginning of the observation or else acquired CF-ICAs during the follow-up, whereas all patients who only had ICA-IgG remained clinically well. Repeated tests in established diabetics showed that thyroid or gastric antibodies were more prevalent in those with persistent CF-ICAs than in those who became sero-negative for CF-ICAs.

Following is the incidence of CF-ICAs in ICA-positive individuals reported in the above²⁷ study:

- i. About 50 per cent of all ICA-positive sera were also positive for CF-ICAs in each of Type 1 diabetics, diabetic children, unaffected relatives of Type 1 diabetics and those with polyendocrine disease.
 - ii. At the diagnosis of disease, 78 per cent of ICA-positive patients also had CF-ICAs. This proportion dropped to 66 per cent at one year and to 413 per cent at 15 years or more after diagnosis; and
 - iii. Thyroid or gastric antibodies were detected in 58 per cent of patients with persistent CF-ICAs.
- Rotter and Rimoin²⁸ confirmed a strong association of ICAs with IDDM (38%), compared with 5.3 per cent in NIDDM and 1.7 per cent in non-diabetics in Caucasian patients. Few studies have been conducted in non-Caucasian populations which reveal a paucity of ICAs in association with diabetes. The prevalence of ICAs was found to be low in non-Caucasian diabetics from Nigeria²⁹, and in Pima Indians from Arizona, USA³⁰. This indicates a predominance of the Type 2 diabetes mellitus or the Mature-onset Diabetes of the Young (MODY) which is distinct from juvenile-onset diabetes mellitus (Type 1). In a recent study in Saudi Arabia³¹ which has a high incidence of diabetes mellitus among its natives^{32,33}, frequencies of ICAs as well as CF-ICAs and thyroid, stomach, and antinuclear antibodies were assessed in newly diagnosed diabetics. In the Saudi Arabian population³¹, the incidence of ICAs was 13 per cent (18/138) in diabetics diagnosed within six months of onset of symptoms. The frequency of CF-ICAs was one-third of the total ICA-positive cases. In addition, ICA association was noted, in patients of 35 years or above, during onset of disease, suggesting a subgroup of late-onset diabetes^{34,35} distinguished by ICA positivity. In contrast to Caucasian groups, none of the ICA-positive Saudi patients had other organ-specific autoantibodies. Among the more recent studies, Richter et al³⁶ have reported isolation of IgG-ICA-producing B lymphocytes from peripheral blood of Type 1 diabetics, and an ICA-positive non-diabetic individual. Another prototype study by Buschard et al³⁷ investigated effect of diabetes mellitus on the fetus. All of the fifty five children observed were in utero, at the time of onset of IDDM in their mothers. All the children were found to be nondiabetic and

seronegative for ICAs. From this study the mothers' ICAs appear not to cause any damage to fetal islet cells. Although IgG can pass the placental barrier, it is unlikely that CF-ICAs cytotoxic ICAs or substantial numbers of ICA-producing B lymphocytes can do so. In retrospect, immunological studies in patients with diabetes mellitus have shown that, at the time of diagnosis, a circulating antibody directed against all components of the islet of Langerhans can be found in a substantial number of patients. The precise nature of the ICAs has been observed³⁸. Although ICAs³⁹ and cytotoxic ICAs²⁷ have been shown to have a role in precinical pathogenesis of diabetes, ICAs which fix complement²⁷ apparently are the most specific markers for incipient Type 1 diabetes. Furthermore, the sub classification of Type 1 diabetes is facilitated with the pattern of incidence and persistence of ICAs⁴⁰. It appears that there is a subgroup (Type 1b) in which there is primary autoimmune damage to the insulin-producing cells. In the majority (Type 1a), the presence of ICAs is probably an epiphenomenon. Caucasian and non-Caucasian populations show variability in incidence of ICAs another related autoantibodies and the Saudi Arabian patients described fall halfway between the two groups. Future large scale trials in heterogeneous populations are necessary to elucidate the exact role and significance of ICAs in the pathogenesis and immunology of diabetes mellitus.

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