

only 1) if symptoms suggestive of hypoglycemia were of sufficient severity to seek medical advice; 2) if whole venous blood glucose levels were <2.5 mmol/l at the time of symptoms; 3) if symptoms were relieved by eating carbohydrate.

Of the 162 nondiabetic twins, 5 sought medical advice with hypoglycemic symptoms relieved by carbohydrate; hypoglycemia was confirmed on extensive testing in only 3 of them. All 3 subjects were twins of IDDM patients, 2 of these 3 twins subsequently developed diabetes. However, in one (S.C.), hypoglycemia was probably due to self-injection of insulin since she was admitted unconscious to the hospital at age 15 years with a blood glucose of 0.9 mmol/l and normal serum C-peptide level (0.049 nmol/l), despite an extremely high serum insulin level (1,380 pmol/l) indicating an exogenous source of insulin. This twin already had impaired glucose tolerance, islet cell antibodies (ICA), and glutamic acid decarboxylase 65 (GAD65) antibodies but had no insulin autoantibodies; IDDM developed at age 19 years. Thus, spontaneous clinical hypoglycemia was detected in just 1 of the 55 twins who developed diabetes under observation. This twin (V.S.), started having symptomatic hypoglycemia after large meals (blood glucose on three occasions of 2.0 mmol/l) at age 34 years. She developed diabetes 4 years later with GAD65 antibodies and decreased first-phase insulin response. Her diabetes is controlled by diet alone at present. The third twin (C.A.) with documented hypoglycemia (blood glucose on three occasions <2.5 mmol/l) remains nondiabetic without antibodies and is, we estimate, unlikely to develop diabetes.

Symptoms of hypoglycemia before the onset of NIDDM have been reported to be common (5) but alone are not sufficient to establish the diagnosis. Furthermore, low blood glucose levels may occur without symptoms (6). By strict diagnostic criteria, spontaneous hypoglycemia occurred in only 2 of 162 twins (1.2%) and then only in twins of IDDM patients. Extrapolating from our observations in twins, we conclude that clinical hypoglycemia, whether fictitious or real, is not a feature of the pre-diabetic period.

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Autoantibody Against ICA512 Did Not Improve Test Sensitivity for Slowly Progressive IDDM in Adults

Recently, the test for the autoantibody against islet cell antigen (ICA) 512 (ICA512Ab) has been described as a useful screening tool for IDDM in combination with the test for the autoantibody against GAD65 (GAD65Ab) (1). GAD65Ab is frequently detected in slowly progressive IDDM (SPIDDM [2,3]). The ICA512Ab is detected mainly in young (age <15 years) Caucasian IDDM subjects (1); therefore, it would be interesting to investigate whether ICA512Ab can be detected in SPIDDM, which is frequently seen over the age of 15 years (4).

Sera from 104 recent-onset IDDM patients (<2 years), who fulfilled the National Diabetes Data Group (NDDG) criteria for IDDM, were collected from our

hospitals. These patients were then subclassified as 78 abrupt-onset IDDM (with ketoacidosis at onset) and 26 SPIDDM subjects. The criteria for SPIDDM were defined as follows: 1) patients with good control of blood glucose at least 6 months from the onset of the disease without insulin therapy and 2) gradual dependence on insulin and patients becoming ketosis-prone without insulin therapy (3). The ages (mean \pm SD) were 19.2 ± 10.0 and 47.0 ± 13.3 years for abrupt-onset IDDM and SPIDDM, respectively.

GAD65Ab or ICA512Ab were detected by a radioligand-binding assay (3) using a clone of the full-length human islet GAD65 (clone pEx9, provided by A.E. Karlsen and C.E. Grubin) or the carboxyl part (amino acid 256-979) of full-length human IA-2 (clone ICA512bdc, provided by G.S. Eisenbarth). In the First Combinatorial Autoantibody Workshop (Immunology of Diabetes Society, 1995), our GAD65Ab assay showed 74.4% sensitivity and 98.0% specificity, and our ICA512Ab assay showed 60.5% sensitivity and 98.0% specificity with normal ranges <0.020 and <0.010 (mean + 3 SD), respectively.

Among abrupt-onset IDDM, 48% (37:78) were positive for ICA512Ab and 69% (54:78) for GAD65Ab, while each antibody was individually detected in two different healthy subjects (1:78, 1.3%). The positivity for ICA512Ab was higher among younger patients (age ≤ 15 years, 65%, 26:40) than older (29%, 11:38), while the frequency of GAD65Ab was unaffected (70 and 68%). Among the younger patients, ICA512Ab, in combination with GAD65Ab, significantly improved sensitivity (70-90%, $P < 0.05$ tested by χ^2 test). Among patients with SPIDDM, GAD65Ab was frequently detected (65%, 17:26), while ICA512Ab was less frequent (12%, 3:26, $P < 0.00001$). Because none of the nine GAD65Ab-negative patients were ICA512Ab-positive, ICA512Ab did not improve sensitivity for SPIDDM.

Our study demonstrates that ICA512Ab autoantibody was frequently detected by the radioligand-binding assay in Japanese IDDM subjects. We further confirmed previous observations in Caucasian subjects (1) that ICA512Ab is more frequently detected in younger patients. In SPIDDM, ICA512Ab did not improve sensitivity in combination with GAD65Ab. We should further investigate better combinations of the antibodies to improve the

sensitivity and the positive predictive value for SPIDDM.

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