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NIDDM With a Ceruloplasmin Gene Mutation

NIDDM is a common disorder characterized by hyperglycemia caused by defects in insulin secretion and action (1). Although the causes of NIDDM are not well understood, it is thought to result from the joint action of genetic and environmental factors. To date, several genes have been reported as responsible for the disease (2). The mitochondrial gene mutations are observed in relatively high ratio (about 1%), while the mutations of the insulin, insulin receptor, and glucokinase genes are observed in very limited population. We propose here that the ceruloplasmin (Cp) gene is another gene responsible for NIDDM.

The Cp gene has been shown to be responsible for hereditary ceruloplasmin deficiency (HCD) (3–4), which is an autosomal-recessive disease characterized by complete Cp deficiency, neurological abnormalities such as progressive cerebral degeneration, and excessive storage of iron in the systemic organs such as brain, liver, and pancreas (5). In many HCD cases, NIDDM is the first symptom, and 5–20 years later at age 40–60 years, neurological abnormalities occur (3–5). The carriers of the defective Cp genes (heterozygotes) have been considered as asymptomatic. Here, we make a working hypothesis that in these carriers the pathogenic changes related to HCD occur very slowly and reach only to the levels of developing NIDDM at later ages. In other words, among many NIDDM patients, there are some who are a heterozygote for the defective Cp genes. To prove this, we measured serum Cp level in all NIDDM outpatients in our clinic (328 individuals). The level of Cp was 29.9 ± 6.1 mg/dl (normal range 18–37). A 71-year-old patient with NIDDM showed low serum level of Cp (14), suggesting that he is a heterozygote for the defective Cp gene. Indeed, genetic analysis revealed that he had the same Cp gene mutation we have previously reported in a HCD patient (4). This NIDDM patient had been in good health until diabetes was diagnosed at age 61. Oral antihyperglycemic agent (sulfonylurea) therapy was started 8 years after the diagnosis and his diabetes was controlled well. Magnetic resonance imaging (MRI) of his brain showed a slightly low signal intensity in the striata on T2-weighted images, compatible with the findings of HCD, although he had no neurological symptoms. This indicates that pathological changes related to HCD were developing in his brain. So, pathological changes of HCD are also expected to be developing in his pancreas, which seem to be the cause of his diabetes. His diabetes was indistinguishable from "common" NIDDM by routine examinations for diabetes. His younger sister (65 years old), who does not have the defective Cp gene, showed normal glucose tolerance. So, these clinical and laboratory observations support our hypothesis.

Because the Cp gene defect may be responsible for NIDDM in more than a few patients, we strongly recommend the measurement of serum Cp level to detect NIDDM patients with a Cp gene mutation, especially among the population of NIDDM patients who developed the disease at later ages.

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Clinical Hypoglycemia Before Diabetes Is Rare

A study of identical twins

Hypoglycemia is one of the metabolic changes described before the onset of both IDDM and NIDDM, but there are no prospective studies to show whether it is a feature of the prediabetic phase (1,2). To determine whether symptomatic hypoglycemia can be a feature of the prediabetic period, we studied prospectively a large cohort of nondiabetic identical twins of diabetic twins (1–3).

We followed 162 nondiabetic identical twins of diabetic patients (117 with IDDM; 45 with NIDDM) for a mean of 12.7 years (range 0.1–30.1) until they either developed diabetes or for at least 5 years (4). Also, 30 twins of IDDM patients and 25 twins of NIDDM patients developed diabetes under observation. Twins were seen at least annually for the first 6 years from diagnosis of the index case and had oral glucose tolerance tests at each visit; all twins remain under review with frequent communication with family physicians (4). Symptoms noted by nondiabetic twins were recorded at each visit, although we deliberately did not ask about hypoglycemic symptoms. A hypoglycemic episode was documented

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 prediabetic 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 ± 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