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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