Diabetes mellitus is a heterogeneous disease, only a few types of which a specific etiology or pathogenesis has been identified (1). Of non-insulin dependent diabetes (NIDDM), the mutations of mitochondrial DNA, proinsulin gene, glucokinase gene and insulin receptor gene have been proven to be causative (1). Other potential gene mutations for diabetes may exist in patients with myotonic dystrophy, Prader-Willi’s syndrome, Werner’s syndrome and polycystic ovary syndrome. All of these cases, however, account for less than 5%, merely the tip of the iceberg, of NIDDM. Recent progress in medicine is gradually dispelling this misty area. In this journal, a new face of diabetes is presented.

The paper “Late onset diabetes in patients with hereditary ceruloplasmin deficiency” (or more commonly termed, hereditary ceruloplasmin deficiency) by Miyajima et al in this issue (2) contributes to establish a new clinical entity by adding diabetes as a new criterion. Diabetes in this disease was first noted by Logan et al (3) and was also reported in subsequent 4 papers (5–8). The earlier report by Miyajima et al (2) did not mention the presence or absence of diabetes in their cases; now all of these cases have diabetes.

Miyajima et al (2) first reported 2 cases of this disease and considered it as a unique disease entity by demonstrating an autosomal recessive mode of inheritance, characteristic clinical features, laboratory findings and specific localization of iron deposition in the liver and brain. They clearly distinguished this disorder from Wilson’s disease based on the following points: the accumulation of iron but not copper in the liver; no liver cirrhosis; urinary excretion of copper is low in this disease, although high in Wilson’s disease. Of special note is that they already suggested the cause of this disease to be ceruloplasmin deficiency. The discovery of this new disease is definitely one of the distinguished works performed in Japan. Therefore, I would like to propose that the term Miyajima’s disease is used for this disorder.

Regarding genetic studies, Logan et al (3) have focused the causative locus on the ceruloplasmin gene on chromosome 3q25 by positional cloning technique. To date at least 3 types of mutations (5, 6, 8, 9) and one dinucleotide repeat polymorphism (10) of the ceruloplasmin gene have been detected in this disease.

The prominent clinical features were first noted in the field of neurology: retinal pigment degeneration, extrapyramidal signs (blepharospasm, oral dyskinesia, grimacing or tic), cerebellar ataxia and progressive dementia. Due to lack of or only mild symptoms, many investigators did not give importance to diabetes. In all of the cases diabetes occurred at an age of over 20 years, 10 to 20 years before neurological manifestations (3–9) and therefore diabetes was the initial and cardinal symptom. Hence the clinical criteria for this disease consists of diabetes and neurological signs and symptoms with or without mild anemia. Laboratory findings in the plasma are also noticeable: undetectably low level of ceruloplasmin and copper, low iron and extremely high ferritin concentrations (3–9). Liver function tests are within the normal limits, despite massive accumulation of iron in the liver. Ceruloplasmin catalyzes $Fe^{2+}$ to $Fe^{3+}$ which forms transporting iron by binding to apotransferrin (11), and thus ceruloplasmin deficiency causes iron deposition to a variety of organs and tissues. Also noteworthy is that in the brain iron deposition is localized to the putamen, caudate nucleus and cerebellar dentate nucleus. This distribution is clearly demonstrable by MRI and completely different from that of hemochromatosis and Hallervorden-Spatz syndrome (12). Microscopic examination revealed loss of neuronal cells with spheroid formation and reactive astrocytosis in addition to iron deposition in those areas (13). Morita et al (7) demonstrated a wider distribution of iron deposition to the brain and revealed that neuronal cell loss was more severe in the areas with more massive deposition of iron. Therefore, most neurological manifestations can be explained by a massive accumulation of iron (3, 4, 7, 13) and loss of antioxidant function due to ceruloplasmin deficiency. Another possibility is that these specific neurological manifestations might be caused by intrinsic genetic or metabolic defect(s), irrespective of iron deposition.

Regarding diabetes, a decrease in insulin secretion is evident by the estimation of insulin and C-peptide levels in this late onset type of diabetes. One can easily consider that diabetes results from massive deposition of iron to the pancreas similar to hemochromatosis. Thereby many investigators (3, 7) have speculated that the simple mechanical damage to the islets, or chemical damage by excessive oxidant formation due to the iron deposition or ceruloplasmin deficiency or both, may be the cause. However, no study has reported the pancreatic islets of these cases in detail. We found a massive deposition of iron in the exocrine portion of the pancreas, but none or little in the islets. Nevertheless, a marked reduction in insulin-containing cells was revealed in the islets without degeneration, necrosis or cell infiltration. Most non-insulin containing cells in the islets were positive for glucagon or somatostatin immunostaining.
Insulin deficiency therefore could not be the result of iron deposition itself, but could be a congenital disposition in this disorder. In such predisposed patients diabetes may develop with the aging process (14).

In any case, late onset type of diabetes is a hallmark of this disease.

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