Hypoceruloplasminemia in Neurological Diseases

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Hereditary ceruloplasmin deficiency (HCD) (also termed aceruloplasminemia) is a late-onset neurodegenerative disease with a complete absence of serum ceruloplasmin (Cp) (1). This disease is caused by homoallelic mutations of the Cp gene (1, 2) and is characterized by adult-onset diabetes mellitus (DM) followed by neurological symptoms including dementia, involuntary movements, and cerebellar ataxia (1). A heteroallelic mutation of the Cp gene has not been considered to produce clinical symptoms. Recently, however, a patient with DM has been reported to have a heteroallelic Cp gene mutation, suggesting that even a heteroallelic mutation of the Cp gene does cause late-onset DM (3). Thus the question arises, whether or not neurological symptoms occur even in individuals with a heteroallelic Cp gene mutation. The present study was undertaken to search for such cases among patients with a variety of neurological symptoms.

Informed consent was obtained from 276 outpatients (142 men and 134 women; the mean age±SD, 58.7±15.5 years) in the neurology division of our hospital. These included 13 patients with essential tremor, 39 with parkinsonism, 42 with cerebrovascular diseases, 19 with cerebellar ataxia, 7 with epilepsy and 157 with other neurological manifestations. Serum Cp levels were measured by radial immunodiffusion assay using a Boehringer nephelometer analyzer. The mean±SD of serum Cp levels was 27.8±5.8 mg/dl in the 276 patients examined (normal range, 18–35 mg/dl). Serum Cp levels had a tendency to increase with aging (Fig. 1). No significant difference of serum Cp levels was observed among neurological disorders. Two patients (0.7%) had a decrease in serum Cp level. Case 1 was a 76-year-old woman with a three-year history of postural tremor of both hands. No other symptoms including dementia, cerebellar signs, sensory disturbance, or autonomic dysfunction were observed. Her serum Cp, copper, and ferritin levels were 12 mg/dl, 46 μg/dl (normal range, 78–131), and 244.2 mg/dl (normal range, 80–220), respectively. Thyroid function tests and glucose tolerance test were all normal. Brain MR images showed a decreased intensity of the bilateral basal ganglia on echo-planar imaging. Genetic analysis revealed a heteroallelic mutation, A82T, in exon 1 of the Cp gene, resulting in the substitution of Ile (ATT) for Phe (TTT). Her son, 51 years old, also showed a decrease in serum Cp level (11 mg/dl) and a low signal intensity in the basal ganglia on MR images, although no apparent neurological symptoms were observed (details of the case are described in ref. 4). The other patient (case 2) was a 79-year-old man with a serum Cp level of 14 mg/dl. He presented with an insidious onset of numbness of both feet in 1997. This symptom extended throughout his legs and up to the umbilical level in one year. His fasting blood glucose was 99 mg/dl. Motor nerve conduction velocity was 39 m/sec in the posterior tibial nerve. The patient did not want to undergo further clinical examination or MR imaging.

Serum Cp has been reported to be increased in several conditions, such as some inflammatory diseases, collagen diseases, malignant tumors, obstruction of bile duct, anemia and administration of estrogen (5). The increase in serum Cp with aging observed in normal subjects has been reported to be attenuated in diabetic subjects (6). In the present study, we revealed that an increase in serum Cp with aging was observed in the individuals with neurological diseases as is the case with normal subjects (Fig. 1). An abnormally low level of serum Cp was encountered in 2 (0.7%) out of 276 patients with neurological manifestations. The frequency of individuals with a low level of serum Cp was reported to be 0.1% in a certain area of Japan (7). The frequency of 0.7% in the present patients with neurological manifestations therefore was higher than that of the normal Japanese population (0.1%). This raises the possibility that hypoceruloplasminemia may not be coincidental with neurological presentations in those patients.
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References