LESSON OF THE MONTH

Hereditary caeruloplasmin deficiency: clinicopathological study of a patient

T Kawanami, T Kato, M Daimon, M Tominaga, H Sasaki, K Maeda, S Arai, Y Shikama, T Katagiri

Abstract
A 58 year old patient with dementia, oral dyskinesia, and diabetes mellitus is described. He had an undetectable concentration of serum caeruloplasmin, as an autosomal recessive trait. Brain MRI disclosed a pronounced hypointensity in the bilateral putamina, caudate, and dentate nuclei on both T1 and T2 weighted images. Pathological findings were mainly in those regions of the brain and consisted of neuronal cell loss with gliosis, heavy iron deposition, and spheroids. Visceral organs also had iron deposition, especially severe in the liver and pancreas. The present patient and other recorded cases constitute a clinicopathological entity of hereditary caeruloplasmin deficiency, different from Wilson's disease.

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Keywords: hereditary caeruloplasmin deficiency; dementia; diabetes mellitus; iron deposition

Hereditary caeruloplasmin deficiency is a newly recognised disorder first described by Miyajima et al in 1987. At the present time, there are three reports1-3 on the disease. The patients had neurological and systemic symptoms such as dementia, involuntary movements, and diabetes. Iron deposition in the brain and liver is a feature of the disorder as well as serum caeruloplasmin deficiency. Caeruloplasmin deficiency in those patients is an autosomal recessive phenotype and recent investigations4 showed mutations of the caeruloplasmin gene on chromosome 3q that differ from the Wilson's disease gene, which is localised on chromosome 13q. The hereditary haemochromatosis gene localised to chromosome 6p. Nielson et al5 reported a case of hereditary haemochromatosis with iron accumulation in the basal ganglia and cerebellum. This pattern of iron deposition in the brain is so similar to hereditary caeruloplasmin deficiency that the question arises as to what differences exist between those disorders.

We report a necropsy of a patient with hereditary caeruloplasmin deficiency with a mutation of the caeruloplasmin gene. Our clinicopathological findings and the three previous reports1-3 further confirm this recently emerging disease. In addition, we present neuropathological features of our patient, which had some similarities to Hallervorden-Spatz syndrome.6-8

Case report
The patient was a 58 year old Japanese man with a 13 year history of diabetes mellitus. His wife noticed his depressive mood and forgetfulness; this had appeared insidiously and worsened slowly for two years. Neurological examination showed oral dyskinesia although the rest of the cranial nerve functions were intact. No motor or sensory disturbances were noted. The results of neuropsychiatric examinations were consistent with subcortical dementia: the WAIS full scale was IQ 69, verbal IQ 80, and performance IQ 62. Ophthalmological examination disclosed retinal degeneration and there was no Kayser-Fleischer ring in the cornea. Laboratory examination showed serum iron concentration of 16 (normal 90–180) µg/dl, total iron binding capacity 193 (normal 250–390) µg/dl, and ferritin 3200 (normal 80–220) ng/dl. Serum total protein was 6-5 g/dl and caeruloplasmin concentration was < 2 mg/dl (the lowest detectable concentration by immunoassay; normal 18–372 mg/dl). Copper concentration was 7 (normal 78–181) µg/dl in the serum and his 24 hour urinary excretion ranged from 5-6 to 7-2 (normal 4-2–33-0) µg. Plasma glucose concentration was 245 mg/dl in the fasting state and 468 mg/dl two hours after 75 g oral glucose loading, consistent with diabetes mellitus. Haematological examination showed microcytic anaemia (red blood cells 402 × 10^6/µl, haemoglobin 10-8 g/dl, packed cell volume 33-2%, mean corpuscular volume 83 µm^3) and normal white blood cell and thrombocyte counts. Erythrocyte sedimentation rate, liver and renal function tests, and serum concentrations of sodium, potassium, and calcium were normal. A cranial CT showed a high density of the bilateral putamina and caudate nuclei. The putamen, caudate, and cerebellar dentate nuclei were hypointense on both T1 and T2 weighted MRI (figure, A).

His five siblings had no physical or neurological abnormalities. Their parents were first cousins who were dead at the time of the family study. Four of the siblings had decreased

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serum concentrations of caeruloplasmin, which were consistent with heterozygotes of an autosomal recessive phenotype.

The patient was found dead in his home and necropsy was performed 20 hours postmortem. Representative specimens from the brain and the visceral organs were processed for histopathological examination after fixing in 20% formaldehyde. Several specimens were examined histochemically with Perls’ stain for iron and rhodanine and Shikata’s stains for copper.

**Necropsy results**

**NEUROPATHOLOGY**

The brain weighted 1300 g and appeared normal externally. Macroscopic sections of the brain disclosed symmetric red-brown discolouration in the putamen, caudate nucleus, and cerebellar dentate nucleus (figure, B). Microscopic examination of those regions disclosed neuronal cell loss with reactive astrocyesis and deposition of many pigment granules (figure, C). Those granules yielded a strong reaction with Perls’ stain, showing iron deposition in residual neurons, astrocytes, and neurons around blood vessels (figure, D). Eosinophilic, round to oval non-nucleated structures consistent with spheroids were occasionally noted (figure, C). Astrocytosis in those lesions consisted mainly of hypertrophic astrocytes and many of them had iron pigments (figure, D). There were a few Alzheimer type II cells; Opalski cells were not seen. Rhodanine and Shikata’s stains for copper did not show any positive results in the above regions. Microscopic examination of other regions of the brain showed mild Purkinje cell loss in the cerebellum and mild to moderate iron deposition in all lobes of the cerebral cortex and cerebellar Purkinje cell layer. There was no apparent neuronal cell loss in the globus pallidus, substantia nigra, hippocampus, thalamus, and the Meynert nucleus, although there was mild iron deposition. No copper deposition was detectable histochemically in those regions of the brain. Gross and microscopic examination of the brain did not show any cerebrovascular lesions. The main arteries of the brain had no atheromatous thickening. Histopathological examination showed only mild arteriosclerotic changes and the basal ganglia did not show any lacunae or small infarcts.
Clinical features of hereditary caeruloplasmin deficiency

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient age sex</th>
<th>Mood of inheritance</th>
<th>Mutation of the caeruloplasmin gene</th>
<th>Neurological findings</th>
<th>Systemic findings</th>
<th>Laboratory findings†</th>
<th>Caeruloplasmin</th>
<th>Iron</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyajima et al1 (1987)</td>
<td>52 M 5-Base pair insertion†</td>
<td>Autosomal recessive</td>
<td>Blepharospasm, oral spasm</td>
<td>Retinal degeneration anaemia</td>
<td>&lt; 0-6</td>
<td>24</td>
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<td></td>
<td>47 F (III-5)</td>
<td></td>
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<td>Retinal degeneration</td>
<td>&lt; 0-6</td>
<td>30</td>
<td>2000</td>
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<tr>
<td></td>
<td>45 F (III-6)</td>
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<td></td>
<td>Retinal degeneration</td>
<td>0-8 (17-37 mg/dl)</td>
<td>32</td>
<td>(70-150 μg/dl)</td>
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<td>Logan et al1 (1994)</td>
<td>58 M (VII)</td>
<td>Autosomal recessive</td>
<td>Unknown‡ (linkage to 3q25)</td>
<td>Dementia</td>
<td>Diabetes, retinal degeneration</td>
<td>&lt;0-02</td>
<td>5</td>
<td>1530</td>
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<td>55 M (VIII)</td>
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<td>Diabetes</td>
<td>&lt;0-02</td>
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<td>63 F (III-1)</td>
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<td>Diabetes, anaemia</td>
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<td>55 F (III-2)</td>
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<td>Diabetes, retinal degeneration</td>
<td>&lt; 1</td>
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<td>40 M (III-8)</td>
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<td>Diabetes</td>
<td>&lt; 1</td>
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<td>(F 29-164 μg/dl)</td>
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<td>(M 25-280 ng/ml)</td>
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<td>(F 10-120 ng/ml)</td>
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<td>Our case</td>
<td>58 M†</td>
<td>Autosomal recessive</td>
<td>Point mutation‡</td>
<td>Dementia, oral dyskinesia, ataxia</td>
<td>Diabetes</td>
<td>&lt; 16</td>
<td>(90-180 μg/dl)</td>
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<td>(89-220 ng/ml)</td>
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Numbers in parentheses = pedigree numbers in the original articles, indicating that they are brothers or sisters. Units and normal ranges of measurements from the original papers are indicated in parentheses.

†Necropsied patient.

GENERAL PATHOLOGY

The liver showed a brown discolroration macroscopically and microscopic examination disclosed a heavy iron deposition in hepatocytes. There were otherwise no specific alterations such as cirrhotic changes. Other organs had microscopic iron deposition of varying degrees. The pancreas, kidney, and heart showed moderate to severe iron deposition, and the spleen, bone marrow, thyroid gland, and pituitary gland had mild iron deposition.

Discussion

The patient presented here and the other recorded patients1-3 represent a specific disorder characterised by serum caeruloplasmin deficiency. Although Wilson's disease shows a decrease in serum caeruloplasmin, it can be ruled out by the mutations of the caeruloplasmin gene in those patients (table), which is different from the Wilson's disease gene.6,11 The differences in clinical presentations are that the patients did not have Kayser-Fleischer rings, liver cirrhosis, or increased urinary copper excretion. Furthermore, our patient showed iron deposition in the brain and liver instead of copper accumulation. Patients with hereditary hypocaueruloplasminemia,12,13 which was first reported by Cox,12 showed decreased serum caeruloplasmin concentrations in affected members of the family but the members were reported to have no medical problems.12,13 It is uncertain whether they are heterozygotes for hereditary caeruloplasmin deficiency, because there are no chance matchings of members with hypocaueruloplasminemia from those families.13

The common features of the patients are familial caeruloplasmin deficiency and iron deposition in the brain and liver. Caeruloplasmin's role in iron metabolism has been established in animal studies14 and Miyajima et al1 proposed a pathomechanism of tissue iron deposition caused by caeruloplasmin deficiency in humans. Caeruloplasmin is a copper containing protein with ferroxidase activity that oxidises ferrous iron (Fe (II)) to ferric iron (Fe (III)).15 Because Fe III is the only iron form that can bind to apotransferrin and enter the bloodstream, caeruloplasmin deficiency would decrease recycling of iron from cell to plasma, resulting in cellular iron deposition.1 Laboratory findings for the recorded patients and ours (table) show decreased iron but greatly increased ferritin concentrations in the serum that could be due to caeruloplasmin deficiency.

The present pathological findings correlate well with the clinical features of the other recorded patients and our patient (table). Iron deposition and neuronal cell loss in the putamen and caudate nucleus can explain subcortical dementia13 and involuntary movements such as blepharospasm.1 Cerebellar Purkinje cell loss and the dentate nucleus lesion could result in cerebellar symptoms.3 Diabetes mellitus13 could be due to increased iron in the pancreas, resulting in impaired insulin secretion.16 The brain MRI findings can be explained by massive iron deposition to the cerebral basal ganglia and cerebellar dentate nucleus.17 The variation in clinical findings among the reported patients1-3 and the present one could be explained partly by the differences in the severity of iron deposition and subsequent tissue damage in affected organs of the body. Other factors such as differences in the mutations of the caeruloplasmin gene among the reported families15,16 could con-
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Hereditary deficiency: clinicopathological... These are different from diseases caused by iron overload, such as hereditary haemochromatosis.

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