SHORT REPORT

A new neurological entity manifesting as involuntary movements and dysarthria with possible abnormal copper metabolism

A Tagawa, S Ono, M Shibata, T Imai, M Suzuki, N Shimizu

Abstract
A few patients with an affected CNS involving abnormalities in copper metabolism have been described that do not fit any known nosological entities such as Wilson’s disease or Menkes’ disease.

Three sporadic patients (two men and one woman) were examined with involuntary movements and dysarthria associated with abnormal concentrations of serum copper, serum ceruloplasmin, and urinary copper excretion. The onset of neurological symptoms occurred at the age of 15 to 17 years. The common clinical symptoms were involuntary movements and dysarthria. The involuntary movements included dystonia in the neck, myoclonus in the shoulder, athetosis in the neck, and rapid orobuccal movements. The dysarthria consisted of unclear, slow, and stuttering speech. Two of the three patients did not have dementia. A cousin of the female patient had been diagnosed as having Wilson’s disease and had died of liver cirrhosis. Laboratory findings showed a mild reduction in serum copper and ceruloplasmin concentrations, whereas urinary copper excretion was significantly reduced in all three patients.

Two of the three patients showed a high signal intensity in the basal ganglia on T2 weighted brain MRI. In conclusion, the unique findings of involuntary movements, dysarthria, and abnormal serum copper and urinary copper concentrations suggest that the three patients may constitute a new clinical entity that is distinct from either Wilson’s or Menkes disease.

Keywords: Wilson’s disease; serum copper; serum ceruloplasmin; urinary copper excretion

Abnormalities in copper metabolism have been described in some diseases affecting the CNS, including Wilson’s disease,1 Menkes’ disease,2 aceruloplasminaemia,3 and other unclassified disorders.1-5 We describe three patients with involuntary movements, dysarthria, and mildly low concentrations of serum copper and ceruloplasmin. These three patients also showed a significant reduction in urinary copper excretion suggesting an abnormal copper metabolism. Two of the patients exhibited abnormal signal intensities in the basal ganglia on T2 weighted brain MRI. The patients described here do not resemble other previously described patients.

Case 1
A 35 year old woman had had a tremor in her right upper limb and dysostia in the neck for 18 years. She was admitted to our hospital after developing dysarthria and oral dyskinesia. On admission, she was fully conscious. A Weschler adult intelligence scale (WAIS-R) test disclosed a verbal IQ of 70, a performance IQ of 69, and a full scale IQ of 66. She exhibited a slow speech pattern, mild oral dyskinesia, and action tremors in the upper limbs. Her neck had a dystonic posture, and her muscle tone was moderately increased. Kayser-Fleisher rings were not seen. The optic fundus was normal. Laboratory findings showed a haemoglobin concentration of 9.5 g/dl, and a depressed serum iron concentration of 40 µg/dl. Liver function was normal. Her serum copper concentration was mildly depressed at 88 µg/dl (normal values 103–159 µg/dl), and her ceruloplasmin concentration was 24.9 mg/dl (normal values 14.9–38.4 mg/dl). Conversely, her ceruloplasmin concentration was 24.9 mg/dl (normal values 14.9–38.4 mg/dl). Urinary copper excretion decreased to less than than 20 µg/day. An abdominal ultrasonography and abdominal CT showed no abnormalities, and a liver biopsy showed no accumulation of copper. T2 weighted brain MRI showed a slightly high signal intensity in bilaterally in the putamen (fig 1). Her cousin had been diagnosed as having Wilson’s disease at another hospital and had died from liver cirrhosis at the age of 20 years. A consanguineous marriage had occurred among her relatives.

Case 2
A 37 year old man had been healthy until the age of 22, when he developed muscle rigidity in his right leg and an action tremor in his right hand. He began to stutter and speech became monotonous. He visited another hospital for a consultation and was suspected of having Wilson’s disease because his serum copper and ceruloplasmin concentrations were slightly low and abnormal intensity in the basal ganglia was

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seen on a brain MRI. Oral penicillamine therapy was started. Although his urinary copper excretion had been depressed during his basal condition, no obvious increase was found after the initiation of penicillamine therapy. No deterioration in clinical symptoms was seen. Twelve years later, he visited our hospital for a re-examination. At this time, his mental status was normal. He stuttered and had a monotonous speech pattern. Mild muscle rigidity and slight clumsiness were seen in the right upper and lower limbs. He sometimes showed myoclonic involuntary movements in his shoulder and athetotic movements of the neck when he wrote. Kayser-Fleischer rings were not seen. The optic fundus showed no abnormalities. Thyroid and liver functions were normal, as was his serum iron concentration. His serum copper concentration was depressed to 65 µg/dl (normal: 80–130 µg/dl), and ceruloplasmin concentration was 15.5 mg/dl (normal: 16.0–31.0 mg/dl). After the withdrawal of penicillamine, his urinary copper excretion decreased significantly to less than 10 µg/day. An abdominal CT showed no signs of abnormalities and a liver biopsy disclosed no abnormal deposits of copper. T2 weighted brain MRI showed a high signal intensity that was dominant in the left caudate nucleus and the lateral margin of the putamen (fig 2). A genetic study showed no mutation in the genes responsible for Wilson’s disease. His symptoms remain unchanged.

Case 3
A 26 year old man presented with a 10 year history of frequent palpebrations. He developed orobuccal involuntary movements at the age of 20 years. He visited another hospital for a consultation and was found to have low serum copper and ceruloplasmin values. He was admitted to our hospital for further examination. He was alert on admission. A WAIS-R test disclosed a verbal IQ of 87, a performance IQ of 106, and a full scale IQ of 94. He exhibited rapid orofacial involuntary movements and slightly unclear speech. Muscle tone was normal in all limbs. Kayser-Fleischer rings were not seen. The optic fundus was normal. Liver and thyroid functions were also normal. His serum copper concentration was 61 µg/dl (normal: 82–134 µg/dl), and his ceruloplasmin concentration was 15.1 mg/dl (normal 20.0–37.0 mg/dl). His urinary copper excretion concentration was less than 10 µg/day. Brain MRI and abdominal CT showed no signs of abnormalities. A liver biopsy found no abnormal deposits of copper. His involuntary movements slightly improved with oral medication of pimozide.

Table 1 Clinical and laboratory features of the three patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)/sex</td>
<td>35/F</td>
<td>37/M</td>
<td>26/M</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>17</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Genetics</td>
<td>?</td>
<td>Sporadic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Involuntary movement</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dementia</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kayser-Fleischer rings</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deposits of copper in the liver</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum copper</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Serum ceruloplasmin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Urinary copper</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Abnormalities on T2 weighted brain MRI</td>
<td>+</td>
<td>-</td>
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</tr>
</tbody>
</table>

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Discussion

As shown in table 1, the common clinical and laboratory features of the present three patients were involuntary movements, dysarthria, slightly low concentrations of serum copper and ceruloplasmin, and a reduction in urinary copper excretion. These features suggested the presence of abnormal copper metabolism. Two of the three patients showed no signs of dementia, and liver function was normal in all three patients (table 1). The presence of a relative who had been diagnosed as having Wilson’s disease is significant in patient 1. Moreover, the high signal intensities in the basal ganglia on T2 weighted brain MRI in patients 1 and 2 imply that a mineral has been deposited in this area.

Copper is required for the catalytic activity of enzymes that play essential parts in neurobiological and pathogenesis, including tyrosinase for melanin synthesis, cytochrome-c oxidase for electron transport in the mitochondrial respiratory chain, Cu/Zn superoxide dismutase for antioxidant defence, dopamine hydroxylase for catecholamine biosynthesis, and ceruloplasmin for brain iron homeostasis. Some diseases affecting the CNS involve abnormalities in copper metabolism, such as Wilson’s disease, Menkes’ disease, aceruloplasminaemia, amyotrophic lateral sclerosis, Alzheimer’s disease, prion disease, and a few other diseases.

Patients with Wilson’s disease exhibit a high signal intensity on T2 weighted brain MRI due to abnormal copper deposition. Therefore, some of the clinical aspects and brain MRI findings seen in our patients are similar to those for Wilson’s disease. Wilson’s disease is an autosomal recessive disorder. Patients may be either homozygous or heterozygous, and various clinical manifestations have been reported. For instance, some patients do not show Kayser-Fleischer rings or have normal serum ceruloplasmin concentrations have been reported. Most patients with Wilson’s disease can show a raised concentration of urinary copper excretion and mild clinical symptoms; these features are strikingly different from those found in our patients. Some case reports describing normal urinary copper excretion concentrations under basal conditions in heterozygous and asymptomatic patients with Wilson’s disease have been made. In the 16 asymptomatic patients described by Marecek et al., urinary copper excretion was normal in the basal condition and increased significantly after penicillamine therapy. Unlike these findings, urinary copper excretion did not obviously increase after penicillamine therapy in patient 2. No case of Wilson’s disease associated with a decrease in urinary copper excretion has been reported. Therefore, the pathophysiological mechanism of our patients is distinct from that of Wilson’s disease.

Menkes’ disease is a disorder in which copper absorption in the gastrointestinal tract is disturbed. It is an X linked recessive disease that causes severe mental retardation and cerebellar ataxia in early childhood. The clinical features of Menkes’ disease are different from those of the patients described here.

Aceruloplasminaemia is an autosomal recessive disorder resulting from inherited mutations in the ceruloplasmin gene. Patients with aceruloplasminaemia do not have copper deposition in their organs, but have significantly increased iron concentrations in both their hepatocytes and the basal ganglia. The iron deposits produce an increase in low signal intensities in the basal ganglia on T2 weighted brain MRI, which is different from our findings.

A few patients similar to ours have been reported in the literature; these patients showed signs of CNS involvement and the existence of an abnormality in copper metabolism different from that found in Wilson’s disease and Menkes’ disease. The patients described by Ono and Kurisaki and Godwin-Austen et al. were sporadic and showed mildly low concentrations of serum copper and ceruloplasmin. As in our patients, urinary copper excretion was reduced, and the accumulation of copper was not found. However, two of our patients showed no dementia, unlike the patients reported by Ono and Kurisaki and Godwin-Austen et al.

Haas et al. and Willvonsder et al. reported a new X linked recessive disorder resulting in an abnormal copper metabolism that was distinct from Menkes’ disease. Their cases showed dysarthria, involuntary movements and mildly reduced serum copper and ceruloplasmin concentrations. However, all of their patients showed dementia, and the patients described by Willvonsder et al. exhibited normal concentrations of urinary copper excretion. Thus, the findings of the above studies are quite different from ours.

Our three unique patients showing dysarthria, involuntary movements, and abnormal serum and urinary copper values may constitute a new clinical entity distinct from Wilson’s disease and other previously described disorders.

The subthalamic nucleus and Jules Bernard Luys (1828–97)

The 1860s was an interesting time in the development of clinical and anatomical knowledge, particularly that relating to degenerative diseases. In 1863, Nikolaus Friedreich described progressive hereditary degenerative CNS disorder (Friedreich's ataxia). A year later Hughhings Jackson portrayed traumatic aphasia. More fundamental was the differentiation of dendrites and axons by Otto Friedrich Karl Deiters in 1865, and the detailed histological analysis of the cerebral cortex in 1867 by Theodore Meynert. The stage was set for further research, and the identification of the subthalamic nucleus and the centrum median by Jules Bernard Luys.

Bernard Luys was a French neurologist born in Paris. His doctorate thesis in 1857 was on the microscopic pathology of tuberculosis. In 1862, he was Médecin des Hôpitaux and Chef de Service at the Salpêtrière and the Charité, and succeeded Marcé as Director of the Maison de Santé Esquirol at Ivery-sur-Seine. He was also Director of the lunatic asylum ativy. He was an excellent artist and one of the early photographers. He employed these skills in his three dimensional illustrations that are found in his first and most important book. The subthalamic nucleus he described as the “bandelette accessoire de l’olive supérieure.” thus showing its spatial relation with the red nucleus which he labelled the “olive supérieure” (fig 1).

However, Meynert in 1872 thought that it was a subdivision of the substantia nigra, and in 1884 referred to it as the discus lentiformis. It was Forel in 1877, who provided the term corpus Luysii to this nucleus for posterity. Its clinical significance was not appreciated until Martin and Alcock showed that lesions of the nucleus were associated with hemiballismus, a word devised by Kussmaul or possibly von Economo. Knowledge of the function of the thalamus was virtually unknown until the Dane, SAW Stein's dissertation of 1834 revealed the anatomy and the connections with the optic nerves, and cortex, confirmed in RB Todd's Cyclopaedia (vol 3, 1835) as “the principal foci of sensibility”. In the 1860s, Luys importantly recognised four centres, each mediating one of the senses: the anterior or olfactory centre, the middle or optic centre, the median or somesthetic centre, and the posterior or acoustic centre. He carefully studied the arrangement of white matter fibres, but thought that the thalamus was the sensorium commune and the corpus striatum the subcortical motor centre, A biographer wrote “Luys’s synthesis... gave ‘une impulsion nouvelle et durable.’”

Luys's subthalamic nucleus lies ventromedially to the globus pallidus within the diencephalon. It has a reciprocal connection with the globus pallidus. It completes a loop with the pallidum, since the subthalamic nucleus gets input inhibitory input from those areas of the globus pallidus, which excite motion. The subthalamic nucleus sends excitatory efferents to the areas of the globus pallidus, which inhibit motion. It is thus justified to attribute to the subthalamic nucleus or an inhibitory effect on movement.

In 1874 appeared his book1 on physiology and reflex cerebral activity, and soon after his Le cerveau et ses fonctions, which was translated into English.2 Luys was a large and imposing man with impressive sideburns. He was a clinician and studied insanity, hysteria, and hypnotism on which he wrote extensively. Unfortunately, they yielded little of scientific value, and he was thought to have been misled or duped by his patients. Respected by his colleagues, he was elected to membership of the Academy of Medicine in 1877 and awarded the Legion d’Honneur the same year, being promoted to officer in 1895. He founded and edited L’Encéphale, a journal devoted to nervous diseases. As he grew older, his scientific contributions fell away and his reputation declined, although his integrity was not in question. He became increasingly deaf in old age, but continued to attend meetings at the Académie de Médicine.

3 Stein SAW. De thalamo et origine nervi optici. Copenhagen: S Trier, 1834.
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