SHORT REPORT

Relapsing hypocupraemic myelopathy requiring high-dose oral copper replacement

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J Neurol Neurosurg Psychiatry 2006;**77**:1092–1093. doi: 10.1136/jnnp.2006.096883

Adult-onset copper deficiency with neurological manifestations is a newly recognised syndrome. Long-term oral copper replacement therapy has been the mainstay of treatment in the literature. A case of relapsing hypocupraemic myelopathy responsive to increased doses of copper replacement is reported. Standard doses of copper may not be sufficient for all patients.

Acquired copper deficiency in adults has been known to cause anaemia and neutropenia.[1] Recently, a neurological syndrome caused by acquired copper deficiency has been recognised in adults. The symptoms comprised of central nervous system demyelination, polyneuropathy, myeloneuropathy, myelopathy and optic neuritis.[2–10] The clinical manifestations and radiological findings of this syndrome resemble those associated with vitamin B_{12} deficiency.[8 11 12] Most cases have been treated with long-term copper supplementation using about 2 mg copper/day,[4 6–10] with variable results in terms of neurological improvement. In some instances, higher doses were used either for limited periods[3 13] or in the context of relatively poor adherence.[5] We report on a patient with hypocupraemic myelopathy who relapsed neurologically and biochemically despite ongoing oral copper replacement therapy at the most commonly used dose.

A 52-year-old woman presented with progressive numbness and weakness in the lower extremities over the previous 6 months. She had undergone a gastric restriction procedure for obesity 24 years earlier. According to the records, the procedure performed was a non-laparoscopic vertical-banded gastroplasty. On examination, she was found to have pallor, tachycardia, hyperactive reflexes, bilateral ankle clonus with extensor plantar responses, increased tone in both upper and lower extremities, markedly decreased vibratory and joint position sense at the toes, ankles and knees, and an extremely ataxic gait, which required the use of a walker. The haemoglobin concentration was 10.2 g/dl (normal 12–16 g/dl), mean corpuscular volume 103 fl (normal 82–99 fl), white cell count 1.9×10^3/μl (normal $4–10\times10^3$/μl) and platelet count 192×10^3/mm^3 (normal $150–300\times10^3$/mm^3). Bone marrow examination showed only ringed sideroblasts. Copper and ceruloplasmin concentrations were markedly decreased in the serum at 5 μg/dl (normal 70–155 μg/dl) and 3.4 mg/dl (normal 7.9–53.3 mg/dl), respectively. Zinc concentration in serum was 102 μg/dl (normal 70–150 μg/dl). Other laboratory tests including levels of vitamin B_{12}, heavy metals, paraproteins, antinuclear antibodies and antibodies to human T cell lymphoma virus-I, HIV, *Treponema pallidum* and *Borrelia burgdorferi* were normal or negative. Analysis of the spinal fluid showed a myelin basic protein concentration of 1.8 ng/ml (normal <0.5 ng/ml), with normal results for the cerebrospinal fluid cell count, protein level, immunoglobulin G (IgG) index, rate of IgG synthesis, determination of oligoclonal band and venereal disease research laboratory test. Nerve conduction studies and somatosensory-evoked potentials were normal. Magnetic resonance imaging studies of the brain and cervical and thoracic spine were unremarkable.

The patient's treatment was initiated with a daily multivitamin containing 2 mg of elemental copper. In 3 months, the haemogram, copper and ceruloplasmin levels returned to normal. After 6 months of continued treatment, she noted a marked improvement in sensory symptoms and was able to ambulate without help. Examination showed considerable improvement in vibratory sense and gait. On the basis of our previous experience,[4] we elected to continue long-term oral copper supplementation and followed her up in clinic every 3–4 months.

After 14 months, the patient noted increased numbness and paraesthesias in both feet. No changes were found on neurological examination or on repeat nerve conduction studies. Repeat laboratory data, however, showed that the copper concentration in serum had decreased to 38 μg/dl and the ceruloplasmin concentration to 11.3 mg/dl. The haemoglobin, white blood cell count, platelet count and zinc level in the serum remained normal. The patient's adherence with treatment was confirmed by her husband and also by social workers and adult protective services. The daily dose of elemental copper was increased to 4 mg by the addition of a copper acetate solution. As there was no improvement in clinical or laboratory data noted after 3 months, the copper acetate dose was raised further so that she received 6 mg of elemental copper daily. The copper and ceruloplasmin levels in serum returned to normal in 2 months and the new neurological symptoms remitted 1 month later. Without a change in her copper intake, all laboratory studies, including the haemogram, remained normal over the next 10 months. Neurological findings at her last examination were limited to brisk reflexes, extensor plantar responses, mildly decreased vibratory and position sense in the toes and ankles, and mild increase in tone in the lower extremities.

DISCUSSION

In the absence of excess zinc ingestion or total parenteral nutrition lacking copper,[1] the aetiology of adult-onset copper deficiency remains elusive. Although some of the patients who were previously reported to have this deficiency have had raised zinc levels in serum,[4–6 8 9 14] our patient did not develop hyperzincaemia during our observation period. Similar to our case, a history of gastric surgery has been reported in some patients presenting with neurological manifestations of copper deficiency,[7 8 10 15] suggesting a malabsorption syndrome. In addition, the laboratory and clinical improvement noted in most of the previous cases treated with oral copper supplements suggests an abnormality at the gastrointestinal uptake level.

The treatments described in the literature consist of copper supplementation and efforts to decrease zinc ingestion when applicable. In contrast with previous experience, the case presented in our study shows that the initial response to copper replacement may not be sustained over time and a relapse may occur during continued oral treatment even in a compliant person.

Although periodic monitoring of copper levels in serum in this syndrome seems prudent, the re-emergence of neurological symptoms should prompt repeated studies on copper level in the serum, even if replacement therapy has not been discontinued. It is of interest that in our patient, neurological dysfunction was a more sensitive indicator of the change in copper metabolism than the peripheral blood cell count. Early detection and treatment of similar cases may prevent the onset of haematological and neurological complications and increase the quality of life considerably in these patients. Further studies are needed to determine the optimal dose, preparation and duration of copper replacement in patients with neurological manifestations of acquired copper deficiency.

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Competing interests: None declared.

Informed consent was obtained for publication of the patient's details described in this report.

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Received 2 May 2006
Revised version received 15 May 2006
Accepted 17 May 2006

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