Copper Deficiency Masquerading as Subacute Combined Degeneration of the Cord and Myelodysplastic Syndrome

Copper deficiency is an increasingly reported but under-recognised cause of blood dyscrasias and neurological dysfunction. It can present to the neurologist as a myeloneuropathy that resembles subacute combined degeneration of the cord both clinically and radiologically. We describe a patient who presented initially to the haematologists with a myelodysplastic syndrome but went on to develop a myeloneuropathy triggering the recognition of copper deficiency as the unifying diagnosis. Copper supplementation completely reversed the haematological disorder and stopped his neurological deterioration.

Case report

A 69-year-old retired clergyman, who had undergone a partial gastrectomy for a duodenal ulcer in the 1960s, presented in late 2004 to his GP with fatigue. He was found to have a normocytic anaemia (Hb 7.7g/dl, MCV 88.5fl) and leukopenia (white cell count 1.1*10^9/l) in the presence of a normal platelet count and normal B12, folate and ferritin levels. He was referred to the haematologists at his local hospital where a bone marrow biopsy showed dyserythropoiesis with vacuolated erythroid precursors, left shift of granulopoiesis, and normal megakaryocytes. Perl's stain demonstrated normal iron stores and ring sideroblasts. A diagnosis of myelodysplastic syndrome was made.

He was managed supportively over the next 18 months with recurrent red cell transfusions, as required. His white cell count remained low, with neutrophils never exceeding 0.9*10^9/l (Figure 1).

He was first seen by neurology 12 months after initial assessment having complained of ascending numbness. Examination revealed a mild spastic paraparesis with brisk lower limb reflexes, bilaterally upgoing plantars and a soft sensory level at T11. He was fully ambulant. A compressive spinal cord syndrome was initially suspected. MRI of his spine was unremarkable and, apart from his known haematological abnormalities, all investigations were normal including repeated B12 and folate levels, autoantibody screen, antineutrophil cytoplasmic antibodies, antineuronal antibodies and serology for syphilis and human T-cell lymphoma viruses. CSF was acellular with a protein of 0.4g/l and no detectable oligoclonal bands.

Further neurological deterioration occurred over the next 6 months. By this time, the patient's numbness had ascended to the level of the mid-chest and to the elbows. He complained of feeling increasingly unsteady on his feet, and was having frequent falls, particularly at night. He was only able to mobilise a few steps with assistance. His sphincter function remained normal.

On examination, tone in the upper limbs was normal. In the lower limbs, tone was markedly increased with sustained clonus at both ankles. There was mild power loss (MRC 4- to 4) in all limbs in a pyramidal distribution.

Upper limb reflexes were diminished, while lower limb reflexes were pathologically brisk with bilateral extensor plantars. Sensation to light touch and pin prick was diminished up to the waist, with a flank-sparing extension to a level of T5, and in a glove pattern up to the elbows. Vibration sense was absent to the sternum. Proprioception was markedly impaired to the proximal interphalangeal joints in the upper limbs, and to the ankles in the lower limbs. There was pseudoathetosis and sensory ataxia. He was able to stand only with support.

The patient was admitted to the regional neurosciences centre for further investigation. Haemoglobin and white cell count remained low, though the red cells were now macrocytic (MCV 103fl). B12 and folate levels were again normal. ESR was 74. CSF was acellular but contained mildly high protein levels at 0.53g/l. Nerve conduction studies showed normal amplitudes, conduction velocities and distal latencies. MRI brain was normal, however MRI of the spinal cord now showed a longitudinally extensive high T2 signal lesion in the dorsal cord (Figure 2).

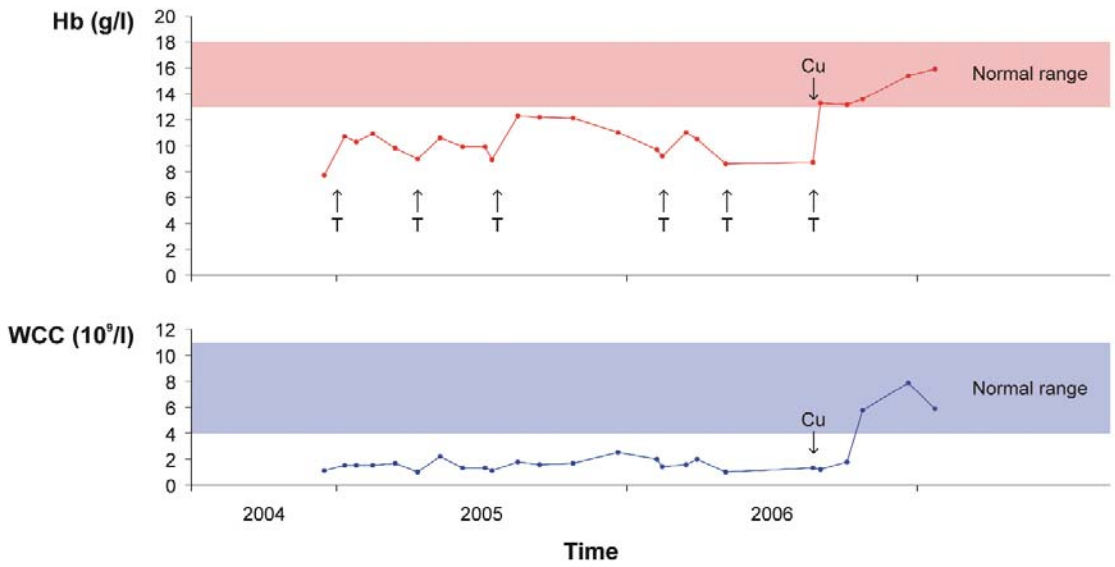
The clinical and radiological findings were reminiscent of subacute combined degeneration of the cord, and although B12 levels had been repeatedly normal, functional B12 deficiency was considered possible and

Dr Stephan R Jaiser graduated MA, MB, BChir (2002), from Cambridge University. Early medical training at Addenbrooke's Hospital, Cambridge and Queen's Medical Centre, Nottingham. Academic specialist registrar at Newcastle General Hospital, Newcastle-upon-Tyne from 2006.

Dr Martin Duddy graduated MB, BCh, BAO, (1992), and MD (2000), from Queen's University Belfast. Clinical and research fellowship in neuroimmunology 2001-2 at Montreal Neurological Institute. Consultant Neurologist with special interest in multiple sclerosis at Royal Victoria Infirmary, Newcastle-upon-Tyne from 2003.

Correspondence to:
Dr Stephan R Jaiser,
Department of Neurology,
Newcastle General Hospital,
Westgate Road,
Newcastle-upon-Tyne,
NE4 6BE, UK.
E. stephanjaiser@gmx.net

Figure 1: haemoglobin and white cell count against time. T=transfusion. Cu=initiation of copper replacement.



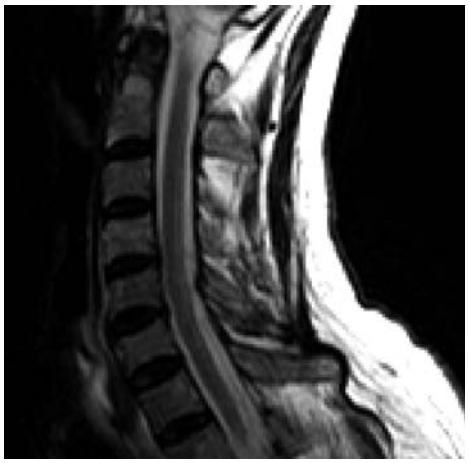


Figure 2: sagittal T2-weighted MRI demonstrating a longitudinal high signal lesion in the dorsal cervical cord.

B12 replacement was initiated. Concurrently, a literature search using the terms 'subacute combined degeneration' and 'myelodysplasia' led to case reports of copper deficiency. The patient's copper and caeruloplasmin levels were found to be undetectable, thus confirming a copper deficiency state. Zinc levels were slightly high at 24µmol/l (normal 9-19).

Oral copper supplementation equivalent to 8mg of elemental copper per day resulted in prompt haematological recovery (Figure 1) and cessation of neurological deterioration, but without functional improvement to date (now eight months into therapy).

Discussion

Copper is a micronutrient essential to the function of nervous system and bone marrow as a prosthetic group in many key enzymes, including cytochrome oxidase (respiratory chain), superoxide dismutase (antioxidant defence), dopamine β-hydroxylase (catecholamine synthesis) and methionine synthase (folate metabolism). It is contained in many common foodstuffs including meat, fish, nuts, seeds and legumes, and pure dietary deficiency is rare. Absorption occurs in the stomach and proximal duodenum. While the bulk of absorbed copper is excreted into the bile, a small proportion is incorporated into caeruloplasmin for transport to extrahepatic tissues.

Despite the recognition of copper deficiency as a cause of anaemia and neutropenia for over 30 years,[1] there is still limited awareness of copper deficiency as a cause of cytopenias. The anaemia is most commonly macrocytic, but may be normocytic or microcytic. Thrombocytopenia is rare.[2] Bone marrow assessment often shows morphological characteristics suggestive of myelodysplastic syndrome, such as ring sideroblasts and nuclear maturation changes of erythroid and myeloid precursors. As a rare and poorly recognised cause of sideroblastic myelodysplastic syndrome, copper deficiency is not listed as a differential in many current haematology textbooks[3] and the neurologist seeing such cases may be the first to make the connection.

The commonest neurological manifestation of acquired copper deficiency is a myeloneuropathy with sensory ataxia. Spinal cord MRI typically shows increased T2 signal in the dorsal cord.[4] The syndrome is thus clinically and radiologically similar to subacute combined degeneration of the cord seen with vitamin B12 deficiency, and both conditions may potentially coexist.[5]

Copper deficiency myelopathy was first described in 2001,[6] and a total of 36 cases have been reported to date.[5-16] It predominantly affects females (F:M 3.6:1), with age at presentation ranging from 36 to 78 years. The most frequent cause is previous upper gastrointestinal surgery, which has been implicated in almost half the cases.[5-11] Whilst the majority of these cases had a remote history of partial gastrectomy for peptic ulcer disease, three of them occurred following bariatric gastric surgery. The increasing use of such bariatric interventions may leave a growing number of patients at risk of copper deficiency in the future.

Further causes include malabsorption[5] and zinc overload.[5,12-16] Despite hyperzincaemia, no external source of excess zinc may be evident. Zinc induces the expression of the intracellular chelator metallothionein in enterocytes. Copper has a higher affinity for metallothionein than zinc, and thus displaces zinc from metallothionein. Copper remains bound in the enterocytes which are then sloughed into the lumen and eliminated (a mechanism exploited when using zinc as a treatment for Wilson's disease). Despite adequate investigation, approximately 25% of cases remain idiopathic.[5]

Treatment involves stopping any excessive zinc intake, and administering copper supplements. No studies have addressed the most appropriate dose, route and duration of supplementation. Several previous cases were treated with oral supplements equivalent to 2mg of elemental copper per day. A relapse was reported with this dose in a patient with a past history of gastric surgery,[9] and we therefore opted for a higher dose. Although deficiency is usually due to impaired absorption, oral supplementation is effective, and is more practical than parenteral supplements.

Haematological abnormalities resolve rapidly and completely, while the neurological decline can usually only be halted but not reversed. Where neurological recovery occurs, it tends to be limited to a subjective improvement in sensory symptoms.[6,9]

Conclusion

Copper deficiency represents a rare but treatable cause of neurological disability, which should be considered in individuals presenting with undiagnosed myelopathy. The coexistence of haematological abnormalities and a history of gastric surgery may suggest the diagnosis.

Acknowledgements

We are indebted to Gavin Winston for his help with the literature review.

References

1. Dunlap WM, James GW 3rd, Hume DM. *Anemia and neutropenia caused by copper deficiency.* Ann Intern Med 1974;80(4):470-6.
2. Wasa M, Satani M, Tanano H, Nezu R, Takagi Y, Okada A. *Copper deficiency with pancytopenia during total parenteral nutrition.* JPEN J Parenter Enteral Nutr 1994;18(2):190-2.
3. Gregg XT, Reddy V, Prchal JT. *Copper deficiency masquerading as myelodysplastic syndrome.* Blood 2002;100(4):1493-5.
4. Kumar N, Ahlskog JE, Klein CJ, Port JD. *Imaging features of copper deficiency myelopathy: a study of 25 cases.* Neuroradiology 2006;48(2):78-83.
5. Kumar N. *Copper deficiency myelopathy (human s wayback).* Mayo Clin Proc 2006;81(10):1371-84.
6. Schleper B, Stuerenburg HJ. *Copper deficiency-associated myelopathy in a 46-year-old woman.* J Neurol 2001;248(8):705-6.
7. Bartner R, Will M, Conrad J, Engelhardt A, Schwarz-Eywill M. *Pancytopenia, arthralgia and myeloneuropathy due to copper deficiency.* Med Klin (Munich) 2005;100(8):497-501.
8. Tan JC, Burns DL, Jones HR. *Severe ataxia, myelopathy, and peripheral neuropathy due to acquired copper deficiency in a patient with history of gastrectomy.* J Parenter Enteral Nutr 2006;30(5):446-50.
9. Prodan CI, Bottomley SS, Holland NR, Lind SE. *Relapsing hypocupraemic myelopathy requiring high-dose oral copper replacement.* J Neurol Neurosurg Psychiatry. 2006;77(9):1092-3.
10. Everett CM, Matharu M, Gawler J. *Neuropathy progressing to myeloneuropathy 20 years after partial gastrectomy.* Neurology 2006;66(9):1451.
11. Wu J, Ricker M, Muench J. *Copper deficiency as cause of unexplained hematologic and neurologic deficits in patient with prior gastrointestinal surgery.* J Am Board Fam Med 2006;19(2):191-4.
12. Hedera P, Fink JK, Bockenstedt PL, Brewer GJ. *Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin: further support for existence of a new zinc overload syndrome.* Arch Neurol 2003;60(9):1303-6.
13. Greenberg SA, Briemberg HR. *A neurological and hematological syndrome associated with zinc excess and copper deficiency.* J Neurol 2004;251(1):111-4.
14. Rowin J, Lewis SL. *Copper deficiency myeloneuropathy and pancytopenia secondary to overuse of zinc supplementation.* J Neurol Neurosurg Psychiatry 2005;76(5):750-1.
15. Yaldizli O, Johansson U, Gizewski ER, Maschke M. *Copper deficiency myelopathy induced by repetitive parenteral zinc supplementation during chronic hemodialysis.* J Neurol 2006;253(11):1507-9.
16. Goodman BP, Chong BW, Patel AC, Fletcher GP, Smith BE. *Copper deficiency myeloneuropathy resembling B12 deficiency: partial resolution of MR imaging findings with copper supplementation.* Am J Neuroradiol 2006;27(10):2112-4.