Published in final edited form as:
*Arch Neurol*. 2009 August ; 66(8): 1025–1027. doi:10.1001/archneurol.2009.70.

# Acute and Bilateral Blindness Due to Optic Neuropathy Associated With Copper Deficiency

**Robert T. Naismith, MD**, **James B. Shepherd, MD**, **Conrad C. Weihl, MD, PhD**, **Nhial T. Tutlam, MPH**, and **Anne H. Cross, MD**
Departments of Neurology (Drs Naismith, Weihl, and Cross and Mr Tutlam) and Ophthalmology (Dr Shepherd), Washington University, St Louis, Missouri.

## Abstract

**Background—**Acquired copper deficiency in adults is associated with a subacute to chronic progressive myeloneuropathy and optic neuropathy.

**Objective—**To describe an individual after gastric bypass surgery who developed a chronic progressive myeloneuropathy, an acute optic neuropathy, along with anemia and leukopenia.

**Design—**Case report.

**Setting—**Academic center.

**Patient—**A 55-year-old woman, following gastric bypass surgery 22 years earlier, developed progressive numbness, weakness, and sphincter disturbance over 6 years. She awoke one morning with bilateral blindness. Examination findings showed evidence of severe myelopathy and peripheral neuropathy.

**Main Outcome Measures—**Magnetic resonance imaging, optical coherence tomography, electrophysiologic studies, nerve and muscle biopsy specimens, and vision testing.

**Results—**Over 1 year of follow-up, copper infusion therapy seemed to stabilize the progressive myeloneuropathy and improved leukopenia and anemia. It had no effect on the optic neuropathy. Optic nerve tissue injury was observed on magnetic resonance diffusion tensor imaging and on optical coherence tomography.

**Conclusions—**Copper deficiency should be considered in cases of atypical optic neuropathy. Serum copper levels should be monitored in patients with a compatible neurologic syndrome who



**Correspondence:** Robert T. Naismith, MD, Department of Neurology, Washington University, Campus Box 8111, 660 S Euclid Ave, St Louis, MO 63110 (naismithr@neuro.wustl.edu)..

**Author Contributions:** Dr Naismith had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. *Study concept and design:* Naismith. *Acquisition of data:* Naismith, Shepherd, Weihl, and Tutlam. *Analysis and interpretation of data:* Naismith, Shepherd, Weihl, and Cross. *Drafting of the manuscript:* Naismith. Critical revision of the manuscript for important intellectual content: Naismith, Shepherd, Weihl, and Cross.

**Financial Disclosure:** Dr Naismith is a participant in clinical trials for Fampridine SR by Acorda Therapeutics. He has received consulting fees and speaking honoraria from Bayer Healthcare, Biogen Idec, and Teva Neurosciences. His research funding is through the National Institutes of Health (NIH) and the National Multiple Sclerosis Society USA. Dr Shepherd has received speaking honoraria from Pfizer Pharmaceuticals. Dr Cross has received research funding, clinical trial funding, honoraria, or consulting fees from the NIH, National Multiple Sclerosis Society USA, Consortium of Multiple Sclerosis Centers, Genentech, Inc, Bayer Healthcare, Biogen Idec, Teva Neurosciences, Acorda Therapeutics, Serono, Pfizer, and BioMS.

**Disclaimer:** The views expressed in this article are solely those of the authors and do not necessarily represent the official view of the NCRR or the NIH.

**Additional Information:** Information on the NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://rihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

have undergone gastric bypass surgery. Although visual acuity did not improve after copper infusion in our patient, prompt recognition of copper deficiency may prevent further deterioration.

COPPER DEFICIENCY CAN BE associated with myelo-optic neuropathy and pancytopenia. The clinical course ranges from subacute to chronic, with similarities to cobalamin deficiency. Optic neuropathy has been reported rarely and is not well characterized. We describe an individual with the full disease phenotype who awoke one morning with bilateral blindness associated with a low serum level of copper. Copper repletion, albeit delayed, did not improve her condition after 1 year of follow-up.

## REPORT OF A CASE

A 55-year-old woman who had undergone gastric bypass surgery 22 years earlier awoke one morning with bilateral painless loss of vision. Six years previously, gradual progression of numbness in the feet led to a diagnosis of unspecified neuropathy. Over the next 5 years, progressive weakness and imbalance necessitated the use of a cane and then a walker to ambulate up to 15 m. She experienced constant lower extremity paresthesias. She reported urinary urgency with incontinence twice per week. Cyanocobalamin injections had been administered twice per month since the gastric bypass surgery.

After the vision loss, her visual acuity was tested individually in each eye, resulting in 20/800 OU. The optic discs and retina were normal, with no afferent pupillary defect. Strength was 4+/5 throughout the upper extremities. Symmetric weakness in the lower extremities included 2/5 for hip flexors and 4/5 for knee extensors/flexors and plantar flexors. Reflexes were 2+ in the upper extremities, 4+ at the knees, and 1+ at the ankles, with mute toes. Rydel-Seiffer tuning fork was 0 at the toes and ankles and was minimally reduced to 7 at the fingers. Ankle proprioception was intact only to large-amplitude foot movements. There was no sharp or dull discrimination in the lower extremities up to the mid-calf, sensation was reduced to pin over the hands and forearms, and a sensory level was present at T4-5. Fine-finger movements were diminished. She required assistance to stand and walked with bilateral support, a wide-based gait, and slow shuffling steps.

Laboratory testing showed that the following results were within the normal range: white blood cell count(2500/μL [to convert white blood cell count to $\times 10^9$/L, multiply by 0.001]), hemoglobin level (9.2 g/dL [to convert hemoglobin to grams per liter, multiply by 10.0]), and platelet count (342 000/μL [to convert platelet count to $\times 10^9$/L, multiply by 1.0]). Vitamin $B_{12}$, homocysteine, and methylmalonic acid levels were also normal. Her serum copper level was 15 μg/dL (reference range, 70-155 μg/dL [to convert serum copper level to micromoles per liter, multiply by 0.157]). Her serum zinc level was low normal at 72 μg/dL (normal range, 70-150 μg/dL [to convert serumzinc level to micromoles per liter, multiply by 0.153]), and iron deficiency was confirmed by an elevated soluble transferrin receptor level of 52.5 nmol/L (reference range, 8.7-28.1 nmol/L). Her neuromyelitis optica IgG status was negative. Serum immunofixation and neuromuscular antibody panels were normal, including GM1, histone H3, GalNAc-GD1a, asialo-GM1, GD1b, GQ1b, sulfatide, MAP, TS-HDS, tubulin, and decorin. Pattern visual evoked potentials were unobtainable because of the patient's inability to fixate. Flash visual evoked potentials were abnormal bilaterally (the left side had no response, and the right side had a P120 of 167 milliseconds and a negative N180 of 210 milliseconds). The results of cerebrospinal fluid analysis were normal, with no oligoclonal bands and a normal angiotensin-converting enzyme level. Brain and orbit magnetic resonance imaging 4 months after onset of vision loss showed nonspecific changes in the white matter and normal orbital views. Spine magnetic resonance imaging performed 10 months after onset was normal. Magnetic resonance diffusion tensor imaging of the optic nerves 9 months after onset

confirmed that disease was localized to the optic nerves, with a 40% increase in mean diffusivity and a greater than 15% decrease in fractional anisotropy bilaterally.[1]

Nerve conduction studies showed small compound muscle action potentials and sensory nerve action potential amplitudes in the lower extremities. Denervation with irritability and reduced recruitment was observed on electromyogram of distal muscles in the lower extremities. A nerve and muscle biopsy specimen was obtained to exclude vasculitic or inflammatory neuropathy. The sural nerve showed small fascicles with moderate loss of small and large myelinated axons, without evidence of vasculitis or amyloid. The gastrocnemius muscle displayed prominent grouped atrophy with angular muscle fibers, indicative of denervation.

The patient received intravenous and then oral replacement of copper starting 5 months after vision loss. Blood cell counts and copper level normalized. Follow-up neurologic examinations over 1 year demonstrated no changes. Thickness of the retinal nerve fiber layer as measured on optical coherence tomography at 18 months confirmed significant degenerative injury to the optic nerve. The retinal nerve fiber layer thickness was less than the fifth percentile in both eyes (79.3 μm OD and 75.0 μm OS), with the thickness of the temporal quadrants measuring less than the first percentile.

## COMMENT

This case illustrates a devastating onset of acute bilateral optic neuropathy in the setting of chronic progressive myeloneuropathy, macrocytic anemia, and leukopenia. Acquired copper deficiency is an important consideration in the differential diagnosis because early recognition and repletion may prevent further deterioration. The patient had been diagnosed years previously as having unspecified neuropathy, but myelopathy was unappreciated until examination findings revealed increased reflexes and sensory level. Although a causal relationship may be conferred by a dramatic response to copper repletion, the neurologic syndrome described herein with markedly low copper levels following gastric bypass surgery strongly implicates acquired copper deficiency. Findings from an extensive workup to exclude other causes of myelo-optic neuropathy, including demyelinating, infectious, inflammatory, and vasculitic origins, showed no abnormalities.

Treatment with copper infusion improved the patient's hematologic parameters for white blood cell count (nadir of 1200/μL before treatment and 7000/μL after treatment), hemoglobin level (nadir of 9.2 g/dL before treatment and 11.0 g/dL after treatment), and mean corpuscular volume (nadir of 106 fL before treatment and 101 fL after treatment). Although visual acuity remained unchanged during the follow-up period, her myeloneuropathy seemed to stabilize from the previous annual deterioration. Copper supplementation before the onset of visual symptoms might have prevented subsequent development of blindness.

Gastric bypass surgery is often implicated in copper deficiency, as absorption occurs in the stomach and proximal duodenum.[2,3] Cobalamin requires the secretion of intrinsic factor within the duodenum for absorption in the ileum, making vitamin $B_{12}$ deficiency a common codeficiency. However, cobalamin had been continually supplemented in our patient, with normal serum and metabolite values. Acquired copper deficiency also occurs in adults with malabsorption syndromes, toxic levels of zinc, prolonged total parenteral nutrition, and medications that act as chelators (eg, ethambutol hydrochloride).

Although there are some case reports of optic neuropathy after gastric bypass surgery, 3 other case reports suggest an origin due to copper deficiency.[4-6] Optic neuropathy associated with gastric bypass surgery was noted to be typically unilateral, occurring within the first few years, and more indolent than in the present case. Copper deficiency in rats leads to pathologic features consistent with demyelination in the optic nerves.[7] The use of clioquinol, an antimicrobial

agent that chelates copper, has been associated with more than 10 000 cases of subacute myelo-optic neuropathy in Japan.[8] The pathologic finding of subacute myelo-optic neuropathy has been described as symmetric demyelination of lateral and posterior columns in the spinal cord, optic nerve, and peripheral nerves.[8]

Optic neuropathy seems to be an uncommon manifestation of acquired copper deficiency. A case series[9] of 25 patients found documentation of visual system involvement in 2 patients by visual evoked potentials. Notable observations in the present case include (1) an interval of longer than 20 years since the time of gastric bypass surgery, (2) the delay between the onset of myeloneuropathy and that of optic neuropathy, (3) and the rapidity of optic nerve involvement. Dysfunction in mitochondrial metabolism and oxidative stress may contribute to variability in the disease time course and neurologic systems involved among central nervous system functions served by copper. Neurologic manifestations may require more than 1 environmental exposure or increased individual susceptibility due to gene-environment interactions.

Copper deficiency should be in the differential diagnosis for optic neuropathy (whether acute, subacute, or chronic) and should be considered in any neurologic condition after gastric bypass surgery. Although no improvement was noted after repletion of copper in the patient described herein, her vision complications may have been avoidable had copper levels been monitored serially after gastric bypass surgery. Because neurologic effects associated with copper deficiency can be devastating, intravenous supplementation in the setting of acute neurologic dysfunction should be considered. Although only a mild response may be possible with acute repletion, even a 1-line or 2-line recovery in visual acuity could improve the patient's level of function and independence.

## Acknowledgments

**Funding/Support:** This publication was made possible by grant UL1 RR024992 from the National Center for Research Resources (NCRR), a component of the NIH and NIH Roadmap for Medical Research. Other NIH funding included grants K23NS052430-01A1 and K12RR02324902 (Dr Naismith), K08AG026271-01 (Dr Weihl), and K24 RR017100 and CA1012 (Dr Cross). Dr Cross was supported in part by the Manny and Rosalyn Rosenthal–Dr John L. Trotter Chair in Neuroimmunology.

**Role of the Sponsors:** National Institutes of Health had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

## REFERENCES

1. Naismith RT, Xu J, Tutlam NT, et al. Disability in optic neuritis correlates with diffusion tensor-derived directional diffusivities. Neurology 2009;72(7):589–594. [PubMed: 19073948]
2. Kumar N, Ahlskog JE, Gross JB Jr. Acquired hypocupremia after gastric surgery. Clin Gastroenterol Hepatol 2004;2(12):1074–1079. [PubMed: 15625652]
3. Juhasz-Pocsine K, Rudnicki SA, Archer RL, Harik SI. Neurologic complications of gastric bypass surgery for morbid obesity. Neurology 2007;68(21):1843–1850. [PubMed: 17515548]
4. Spinazzi M, De Lazzari F, Tavolato B, Angelini C, Manara R, Armani M. Myelo-optico-neuropathy in copper deficiency occurring after partial gastrectomy: do small bowel bacterial overgrowth syndrome and occult zinc ingestion tip the balance? J Neurol 2007;254(8):1012–1017. [PubMed: 17415508]
5. Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodys-plastic syndrome. Blood 2002;100(4):1493–1495. [PubMed: 12149237]
6. Prodan CI, Holland NR, Wisdom PJ, Burstein SA, Bottomley SS. CNS demyelination associated with copper deficiency and hyperzincemia. Neurology 2002;59(9):1453–1456. [PubMed: 12427906]
7. Dake Y, Amemiya T. Electron microscopic study of the optic nerve in copper deficient rats. Exp Eye Res 1991;52(3):277–281. [PubMed: 2015857]

8. Tateishi J. Subacute myelo-optico-neuropathy: clioquinol intoxication in humans and animals. Neuropathology 2000;20(20)(suppl):S20–S24. [PubMed: 11037182]

9. Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc 2006;81(10):1371–1384. [PubMed: 17036563]