Copper Deficiency Myelopathy (Human Swayback)

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The hematologic manifestations of copper deficiency are well known and include anemia and neutropenia. In the past few years, the neurological manifestations of acquired copper deficiency in humans has been recognized, the most common being a myelopathy presenting with a spastic gait and prominent sensory ataxia. The known causes of acquired copper deficiency include prior gastric surgery, excessive zinc ingestion, and malabsorption; however, often the cause is unclear. Hyperzincemia may be present even in the absence of exogenous zinc ingestion. The clinical features and neuroimaging findings are similar to the subacute combined degeneration seen in patients with vitamin B_{12} deficiency. Copper and vitamin B_{12} deficiency may coexist. The neurological syndrome may be present without the hematologic manifestations. Copper supplementation resolves the anemia and neutropenia promptly and completely and may prevent the neurological deterioration. Improvement, when it occurs, is often subjective and preferentially involves sensory symptoms. This article describes patients with copper deficiency myelopathy seen at the Mayo Clinic in Rochester, Minn, and reviews the literature on neurological manifestations of acquired copper deficiency in humans.

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CNS = central nervous system; MRI = magnetic resonance imaging

The hematologic manifestations of acquired copper deficiency are well known and include anemia, neutropenia, and a left shift in granulocytic and erythroid maturation with vacuolated precursors and ringed sideroblasts in the bone marrow.[1-4] Only in recent years have the neurological manifestations of acquired copper deficiency in humans been recognized.[5-23] The most common manifestation is that of a myelopathy presenting with a spastic gait and prominent sensory ataxia.[6,9-21,23] Clinical or electrophysiological evidence of an associated peripheral neuropathy is common. Isolated peripheral neuropathy,[4,7] central nervous system (CNS) demyelination,[5,8] myopathy,[14] and optic neuritis[7] have also been described in association with copper deficiency, but these associations are less well established. Often, the cause of the copper deficiency is unclear. The most common abnormality on the spinal magnetic resonance image (MRI) is increased signal on T2-weighted images that involve the dorsal column in the cervical cord.[20] Somatosensory evoked potential and nerve conduction studies suggest impaired central conduction and varying degrees of peripheral neuropathy.[22] Response of the anemia and neutropenia to copper supplementation is prompt and complete.[4,7,12,15] With copper supplementation, the neurological deterioration may be prevented, and improvement is slight and often subjective.[4,8,12,15] In this article, I describe patients with copper deficiency myelopathy and review the literature on neurological manifestations of acquired copper deficiency in humans.

PATIENTS AND METHODS

The case records of 25 patients with copper deficiency myelopathy seen at the Mayo Clinic in Rochester, Minn, were reviewed. These 25 patients include 13 patients described earlier as a series.[15] Our experience with the 25 patients described herein has been previously published in abstract form[18,22]; details regarding the neuroimaging findings in this cohort have been previously published,[20] as have the clinical details of some cases.[9,11,13,14,16,21]

All 25 patients were evaluated as part of routine clinical practice within the Department of Neurology. Only 2 patients (patients 13 and 14) were identified retrospectively. Of the 25 patients, 23 were evaluated within a 24-month period. Demographic information, clinical presentation, laboratory and neurophysiological findings, neuroimaging, and response to therapy were studied. Additional investigations were performed in each patient to rule out other causes of a noncompressive myelopathy. Wilson disease as a cause of low serum copper levels was excluded in all patients by 24-hour urinary copper excretion and/or slit lamp examination for Kayser-Fleischer rings.

Available MRI studies were reviewed by a neuroradiologist. Cervical and thoracic spine MRIs were available in all patients except patient 13, in whom only a cervical spine MRI was available. Contrast imaging was performed in 14 of the 25 patients (patients 4-10, 16-19, 21, 22, and 24). A brain MRI was available in all except patients 4, 11, 20, and 25. The images were acquired using a 1.5-T strength magnet.

Electrophysiological tests included nerve conduction studies, needle electromyography, and somatosensory and visual evoked potentials. The electrophysiological studies were performed using standard techniques for our laboratory. Nerve conduction studies were available in all pa-

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TABLE 1. **Demographics, Symptom Duration, Serum Copper and Zinc Levels at the Time of Diagnosis, and Likely Cause of Copper Deficiency in 25 Patients With Copper Deficiency Myelopathy**

Patient No./ sex/age (y)	Symptom duration (y)	Serum copper (μg/mL)*	Serum zinc (μg/mL)†	Possible cause of copper deficiency	Reference(s)
1/M/65	5.0	0.45	1.51	Zinc ingestion	9, 15
2/F/46	0.5	0.24	0.43	Iron ingestion	13, 15
3/F/78	10.0	0.00	1.09	Peptic ulcer surgery	11, 15
4/M/72	0.75	0.18	1.36	Peptic ulcer surgery	13, 15
5/M/52	1.50	0.19	0.91	Peptic ulcer surgery	15
6/F/58	2.0	0.35	0.77	Peptic ulcer surgery	
7/F/71	1.0	0.16	0.96	Peptic ulcer surgery	16
8/F/59	2.5	0.00	1.92	Peptic ulcer surgery	
9/F/53	2.0	0.00	0.66	Peptic ulcer surgery	
10/F/49	5.0	0.17	0.64	Bariatric surgery	11, 15
11/F/64	0.75	0.11	0.97	Bariatric surgery	16
12/F/36	3.5	0.00	1.13	Bariatric surgery	
13/F/45	5.0	0.09	0.93	Malabsorption	14, 15
14/F/55	0.17	0.05	1.46	Malabsorption	15
15/F/55	1.5	0.24	0.57	Malabsorption	
16/F/57	2.0	0.12	0.52	Malabsorption	
17/F/48	0.75	0.11	1.47	Unknown	13, 15, 16
18/F/51	3.0	0.22	1.61	Unknown	15
19/F/45	2.75	0.05	Not available	Unknown	15
20/F/59	0.5	0.00	1.95	Unknown	21
21/M/52	5.0	0.00	1.60	Unknown	
22/M/47	2.0	0.00	1.29	Unknown	
23/F/70	0.83	0.31	0.99	Unknown	15, 16
24/F/55	2.0	0.00	Not available	Unknown	15
25/F/54	3.0	0.32	1.55	Unknown	

*Reference range, 0.75 to 1.45 μg/mL.
†Reference range, 0.66 to 1.10 μg/mL.

tients except patient 16. Somatosensory evoked potential studies were available in 20 patients (all except patients 3, 10, 14, 16, and 19). Of these 20, both tibial and median somatosensory evoked potential studies were performed in 17, tibial only in 1 (patient 11), and median only in 2 (patients 13 and 21). Eight patients had visual evoked potential studies performed (patients 6, 16, 17, 18, 19, 21, 22, and 24). In 1 patient (patient 16), it was the only electrophysiological testing done.

In 2 patients with hypocupremic myelopathy and no evident cause of copper deficiency, colonic copper was measured to determine whether an absorptive defect similar to that seen in Menkes syndrome may have been responsible for the hypocupremia (patients 17 and 23). In 1 of these 2 patients (patient 17), mutations in the *ATP7A* gene were sought to determine whether a mutation similar to that seen in Menkes syndrome could have been responsible for the hypocupremia and increased colonic mucosal copper content.

RESULTS

Demographics and Clinical Features

The demographics of this cohort, duration of neurological symptoms before diagnosis, and likely cause of copper deficiency are summarized in Table 1. Also shown in Table 1 and Figure 1 are serum copper and zinc levels at presentation. The duration of neurological symptoms before the diagnosis of copper deficiency myelopathy ranged from 2 months to 10 years. The age range at the time of diagnosis was 36 to 78 years (mean age, 56 years). Twenty of the 25 patients were women. The serum copper level ranged from being undetectable in 8 to 0.45 μg/mL in 1 (reference range, 0.75-1.45 μg/mL). The mean serum copper level at presentation in this cohort was 0.13 μg/mL. A high or high-normal serum zinc level was seen in 17 of the 23 patients for whom this information was available.

The presenting complaint was gait difficulty, and all patients reported lower limb paresthesias. The gait difficulty was primarily due to severe sensory ataxia secondary to dorsal column dysfunction. In some patients, the gait also had a mild spastic component with associated corticospinal signs. Symptoms suggestive of an upper motor neuron bladder were present in 9 patients, a Lhermitte sign was present in 3 patients, and upper limb signs or symptoms were present in all except 2 patients (Table 2). A brisk knee jerk was seen in all except 4 patients. The ankle jerk was depressed in 15

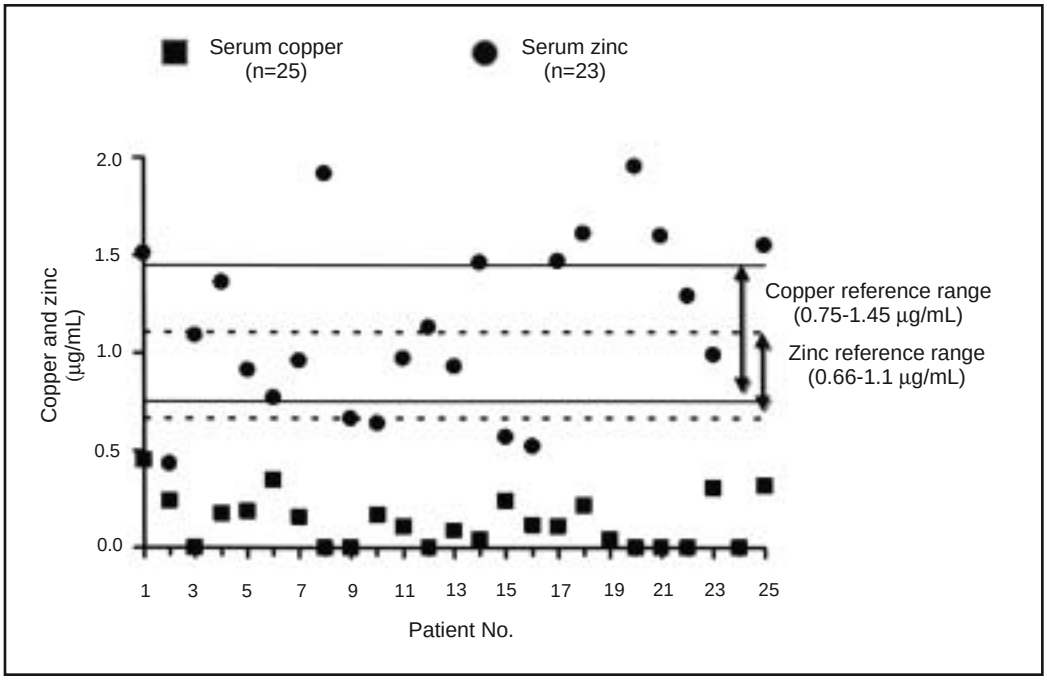

FIGURE 1. Serum copper and zinc levels in the cohort. Serum zinc levels were not available in patients 19 and 24. The dotted lines indicate the reference range for serum zinc, and the solid lines indicate the reference range for serum copper.

patients, and an extensor plantar response was seen in 12 patients.

Possible Cause of Hypocupremia

In one patient, copper deficiency was secondary to consumption of excessive amounts of zinc (patient 1) and in another possibly due to large doses of iron (patient 2). In 10 patients, the hypocupremia was attributed to a history of gastric surgery (patients 3-12), and in 4 it was due to malabsorption (patients 13-16). In the remaining 9 patients, the origin of the hypocupremia was unclear. The colonic copper level in patients 17 and 23 was increased to 39 μg/g and 57 μg/g of dry weight, respectively (reference range, 6-13 μg/g of dry weight). DNA sequence analysis of the *ATP7A* gene in patient 17 did not demonstrate any abnormalities.[24] All 22 coding exons and flanking introns were sequenced.

Laboratory Investigations

Anemia or leukopenia at presentation or in the past was seen in all except 5 patients (patients 1, 5, 15, 21, and 24) (Table 2). A history of vitamin B_{12} deficiency was present in 9 patients. Of these, 7 had a prior history of gastric surgery. All patients had a normal vitamin B_{12} level at presentation. The methylmalonic acid level was available in 14 patients (patients 2-7, 10, 12, 14, 16-19, and 21) and was elevated in 3 (patients 6, 10, and 21). Serum homocysteine measurements were within the reference range in the 14 patients for whom this information was available (patients 3-7, 12, 14, 16-19, 21, 23, and 24). Patients with a history of vitamin B_{12} deficiency showed neurological progression despite periodic vitamin B_{12} administration and repeatedly normal vitamin B_{12} levels.

Electrophysiological Studies

Clinical findings and nerve conduction studies suggested varying degrees of peripheral neuropathy (Table 3). An axonal peripheral neuropathy was detected in 21 of 24 patients. Eleven were mixed sensory motor, 5 were pure motor, 2 pure sensory, 2 predominantly motor, and 1 predominantly sensory. The neuropathy was mild in 10, moderately severe in 3, and severe in 8. In 3 patients, severe, bilateral, posterior interosseous neuropathies were superimposed on the generalized neuropathy. Myopathic changes were noted on the electromyogram in 4 patients (patients 6, 13, 23, and 24). Somatosensory evoked potential studies were abnormal in all 20 patients in whom these data were available, although in patient 13 the abnormality was only peripheral. Nineteen patients had neurophysiological evidence of impaired conduction in the central pathways. This correlated with the clinical presentation that suggested myelopathy. Visual evoked poten-

TABLE 2. **Clinical Features and Laboratory Findings in 25 Patients With Copper Deficiency Myelopathy***

Patient No.	Urinary symptoms	Lhermitte sign	UL	KJ	AJ	Plantars	History of decreased Hb	Hb (g/dL)†	History of decreased WBC	WBC ($\times 10^9$/L)‡	History of B_{12} deficiency	B_{12} (ng/L)§	Reference(s)
1	Yes	No	No	↑	↓	↑	No	14.8	No	7.3	No	565	9, 15
2	Yes	No	Yes	↑	↓	?	Yes	12.6	No	9.5	Yes	404	13, 15
3	No	No	No	↑	↓	↑	Yes	9.4	Yes	3.0	Yes	631	11, 15
4	No	No	Yes	↑	↑	↑	Yes	12.5	No	4.3	Yes	2000	13, 15
5	Yes	No	Yes	↑	↑	↑	No	16.0	No	4.5	Yes	307	15
6	Yes	No	Yes	↑	↓	?	Yes	11.4	Yes	5.6	Yes	287	
7	No	No	Yes	↑	↓	↓	Yes	12.4	No	3.7	Yes	507	16
8	No	No	Yes	↑	N	↑	Yes	10.7	Yes	1.0	Yes	317	
9	No	No	Yes	↑	↓	↓	Yes	11.4	No	12.4	No	419	
10	Yes	No	Yes	↑	↑	↑	No	11.9	No	5.8	Yes	228	11, 15
11	No	No	Yes	↑	N	↓	Yes	10.6	No	3.3	No	1108	16
12	No	No	Yes	↓	↓	↓	Yes	9.4	Yes	1.3	No	459	
13	No	No	Yes	↓	↓	↑	Yes	10.6	Yes	3.1	No	297	14, 15
14	No	No	Yes	↑	↓	↓	Yes	10.0	Yes	1.5	Yes	905	15
15	Yes	Yes	Yes	↑	↑	↓	No	14.2	No	6.8	No	≥2000	
16	Yes	Yes	Yes	↑	↑	↑	No	12.1	No	2.4	No	419	
17	No	No	Yes	↑	↑	↑	Yes	14.0	No	8.9	No	388	13, 15, 16
18	Yes	No	Yes	↑	↓	↑	No	11.4	No	5.9	No	342	15
19	No	Yes	Yes	↑	↓	↑	Yes	7.9	Yes	1.8	No	315	15
20	No	No	Yes	↑	↓	↓	Yes	8.3	Yes	1.5	No	388	21
21	No	No	Yes	↑	↓	?	No	13.6	No	4.2	No	265	
22	No	No	Yes	↑	↑	↓	Yes	10.4	Yes	2.2	No	1493	
23	No	No	Yes	N	↓	↓	Yes	13.2	Yes	3.4	No	1055	15, 16
24	Yes	No	Yes	↑	↑	↑	No	12.3	No	3.7	No	1196	15
25	No	No	Yes	↓	↓	–	Yes	10.5	No	4.2	No	371	

*AJ = ankle jerk; Hb = hemoglobin; KJ = knee jerk; N = normal; UL = upper limb signs or symptoms; WBC = white blood cell count; ↑ = increased; ↓ = decreased;? = equivocal; – = absent.
†Reference range, 13.5 to 17.5 g/dL for men and 12.0 to 15.5 g/dL for women.
‡Reference range, 3.5 to 10.5 $\times 10^9$/L.
§Reference range, 200 to 650 ng/L.

tials were abnormal in 2 of 8 patients in whom these data were available.

Neuroimaging

A signal change in the spinal cord on MRI has been the most consistent neuroimaging finding and was seen in 11 of the 25 patients in this series (patients 3-9, 17, 21, 22, and 24) (Table 3). The cervical cord was involved in 10 (patients 3-9, 17, 22, and 24), thoracic cord in 6 (patients 4-8 and 21), and both in 5 (patients 4-8). Of the 6 patients with thoracic cord involvement, the involvement was contiguous with the cervical involvement in 2 (patients 5 and 6). The involvement was most often in the paramedian dorsal cord that involved the dorsal columns (Figure 2, A and B), although in 2 patients (patients 9 and 21) the central cord was involved. It is difficult to be certain that this did not represent a small central syrinx. Slight cord atrophy of the thoracolumbar cord was seen in 3 patients (patients 3, 21, and 24). Of the 11 patients with signal change in the spinal cord, contrast was given in all except 1 (patient 3). None of these 10 had any evidence of contrast enhancement. Often the involvement was subtle and in 2 patients (patients 3 and 24) had been missed before a neuroradiologist's review. Foci of increased T2 signal on the brain MRI were seen in 15 patients (patients 1, 3, 5-7, 9, 10, 15, 16, 18, 19, 21, and 22-24), and in some (patients 1, 6, 7, 19, 22, and 24) the appearance and distribution of the lesions suggested lacunar disease. The importance of this finding is uncertain.

Response to Therapy and Follow-up

Inadequate follow-up data were available for patients 7, 9, 12, 16, and 25. With oral or parenteral copper replacement, normal serum copper levels were achieved in 18 of the remaining 20 patients (Table 4). Hematologic manifestations when present were promptly and completely reversed. Residual neurological deficits were present in all 20. In all 20 patients except patient 5, further deterioration was prevented. A few months after diagnosis, patient 21 died after a massive stroke. Neurological improvement when present was often more subjective than objective. The cervical dorsal column signal change noted on the T2-

TABLE 3. **Neurophysiological and Neuroimaging Findings in 25 Patients With Copper Deficiency Myelopathy***

Patient No.	NCS	SEP	Spine MRI	Brain MRI	Reference(s)
1	Severe, SM, axonal	Abnormal	Incidental disk disease	Lacunar infarcts (left thalamus, right pons, cerebellum)	9, 15
2	Mild, sensory, axonal	Abnormal	Incidental disk disease	Negative	13, 15
3	Mild, SM, axonal	NA	Incidental disk disease, osteoporosis, slightly atrophic thoracolumbar cord, probable multiple patchy T2 hyperintensities from C2 to C6	Minimal cerebellar atrophy, lacunes	11, 15
4	Mild, SM, axonal	Abnormal	Increased T2 signal in posterior column from C1 to C7 and in mid and lower thoracic region, incidental disk disease	NA	13, 15
5	Mild, SM, axonal, ulnar elbow, median wrist	Abnormal	Diffuse posterior cord signal abnormality from cervicomedullary junction to lower thoracic level, incidental disk disease, status postlaminectomy (C4 through C6)	Single focus of increased T2 signal in left frontal lobe	15
6	Moderate, SM, axonal, myopathy	Abnormal	T2 hyperintensity in dorsal midline cervical cord from C2 to T6, patchy focal T2 hyperintensity in dorsal cord at T8, multiple nerve root sheath cysts, incidental disk disease	Multiple periventricular and pontine T2 hyperintensities, minimal biparietal atrophy, inferior right frontal cavernoma	
7	Mild, SM, axonal	Abnormal	Abnormal T2 signal in posterior cord from medulla to C7, patches of abnormal signal in mid and lower thoracic cord, incidental disk disease	Multiple periventricular and pontine foci of T2 hyperintensity	16
8	Severe, M(S), axonal	Abnormal	Subtle T2 signal change in posterior paramedian cord at the cervical level and T10/11 level, incidental disk disease, prominent pial vasculature	Normal	
9	Old right C7 radiculopathy	Abnormal	Central cord signal change at C5/6, subtle central cord signal change at C4, moderately severe multilevel cervical stenosis, incidental hemangiomas	Nonspecific T2 hyperintensity in right frontal and parietal lobes	
10	Mild, SM, axonal	NA	Incidental disk disease	Nonspecific foci of increased T2 signal in frontal lobes	11, 15
11	N	Abnormal (tibial only)	Incidental disk disease	NA	16
12	Mild, sensory, axonal	Abnormal	Incidental disk disease	Normal	
13	Severe, SM, axonal, myopathy	Abnormal (median only: peripheral)	Normal	Normal	14, 15
14	Severe, S(M), axonal	NA	Normal	Minimal generalized atrophy	15
15	N	Abnormal	Incidental disk disease	Nonspecific foci of T2 hyperintensity	
16	NA	NA	Normal	Hyperintense T2 foci in subcortical white matter	
17	Moderate, SM, axonal	Abnormal	Increased T2 signal in paramedian dorsal cervical cord from C2 through C7, incidental disk disease	Chiari I malformation, partially empty sella	13, 15, 16
18	Mild, motor, axonal	Abnormal	Thin central syrinx from T7 to T10, incidental disk disease	Several punctate foci of white matter hyperintensity	15
19	Severe, M(S), axonal, posterior interosseous	NA	Incidental disk disease	Foci of T2 hyperintensity (right cerebellum, right temporal, left frontal)	15
20	Severe, multifocal, motor, axonal, carpal tunnel, posterior interosseous	Abnormal	Incidental disk disease	NA	21
21	Severe, axonal, SM posterior interosseous	Abnormal (median only)	Central T2 hyperintensity from T7 to T9, possible focus of T2 hyperintensity at T4, incidental disk disease, lower thoracic cord atrophy	Periventricular T2 hyperintensity, moderate biparietal atrophy, minimal cerebellar atrophy	
22	Moderate, axonal, SM	Abnormal	Possible patchy T2 hyperintensity from C3 through C5, incidental disk disease	Punctate T2 hyperintensities (periventricular, right basal ganglia, right frontal, left parietal)	
23	Mild, motor, axonal, myopathy	Abnormal	Incidental disk disease	Increased T1 signal in basal ganglia, foci of increased T2 signal in white matter	15,16
24	Mild, motor, axonal, myopathy	Abnormal	Subtle T2 signal change in dorsal column of spinal cord at C2 and C6, small caliber of thoracic spinal cord, incidental disk disease	Focal and confluent areas of increased T2 signal in periventricular white matter, internal and external capsule, and corona radiata; increased T2 signal in middle cerebellar peduncles, midbrain and thalami. Small incidental right temporal meningioma	15
25	Severe, motor, axonal	Abnormal	Compression fracture T12	NA	

*On nerve conduction studies (NCS) and electromyography (EMG), mild involvement was defined as minimal NCS and EMG changes with no absent NCS responses and no signs of active denervation on EMG. Moderate involvement was defined as absent or low amplitude motor and/or sensory responses on NCS and signs of denervation by EMG. Predominantly absent NCS responses and prominent signs of denervation indicated severe peripheral involvement. MRI = magnetic resonance imaging; M(S) = predominantly motor; N = normal; NA = not available; SEP = somatosensory evoked potentials; SM = sensory motor; S(M) = predominantly sensory.

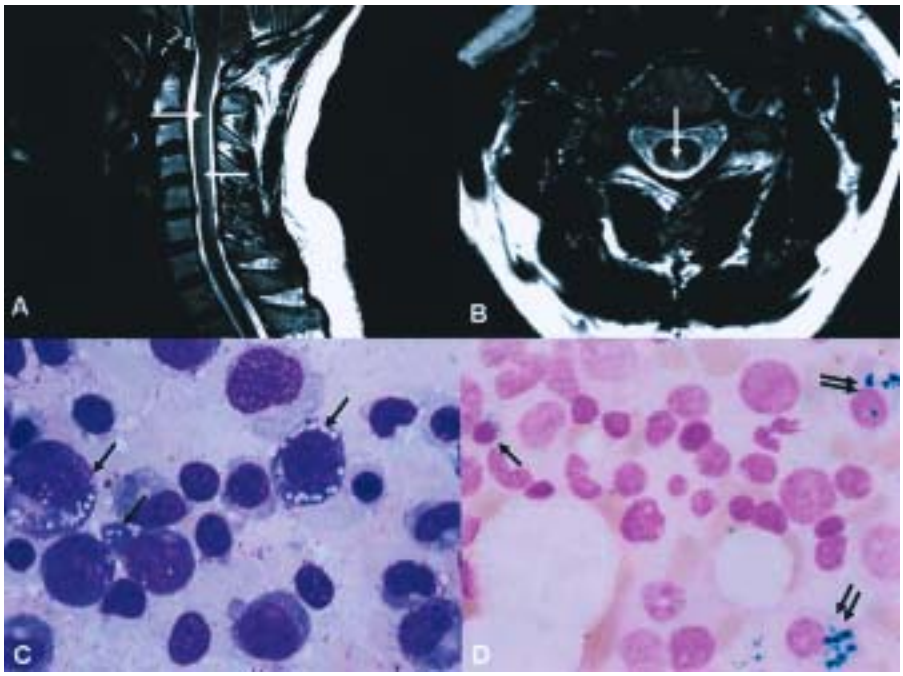

FIGURE 2. Magnetic resonance images and bone marrow study. Sagittal (A) and axial (B) T2-weighted magnetic resonance images of patient 17 show increased signal in the paramedian aspect of the dorsal cervical cord (single arrow). C, Bone marrow study in patient 14 shows vacuolated myeloid precursors (single arrow). D, Iron staining in patient 20 shows a ringed sideroblast (single arrow) and iron-containing plasma cells (double arrows). A and B from *Neuroradiology*,[20] with permission from Springer Science and Business Media.

weighted MRI in patient 17 showed nearly complete resolution with normalization of serum copper.

DISCUSSION

Neurological Manifestations in Copper-Deficient Animals

Copper deficiency–associated myelopathy has been well described in various animal species.[25-29] Often seen in ruminants, it has been referred to as swayback or enzootic ataxia. The typical distribution of lesions in the spinal cord is greater involvement of the cervical cord with less severe changes in the thoracic and lumbar segments.[29] Wallerian degeneration and demyelination with microcavitation of the white matter of the spinal cord and brainstem are seen.[26] Menkes syndrome is the well-known copper deficiency–related disease in humans and is due to congenital copper deficiency.[30,31] Comparative neuropathological studies have shown similarity between Menkes syndrome and swayback.[28] Both are characterized by defects in mitochondrial oxidative metabolism due to a decrease in a copper metalloenzyme, cytochrome oxidase.[32,33] Abnormalities of CNS myelination are seen in copper-deficient rats.[34,35] Zinc-induced copper deficiency has been known to cause ataxia in kittens who were exposed to zinc from the galvanized iron bar doors of their cages.[36] Wallerian degeneration in the spinal cord was present at necropsy.

Role of Copper in Maintaining the Structure and Function of the Nervous System

Copper functions as a prosthetic group, permitting electron transfer in key enzymatic pathways. It is a component of key metalloenzymes that have a critical role in the structure and function of the nervous system. These include cytochrome-*c* oxidase for electron transport and oxidative phosphorylation in the mitochondrial respiratory chain, copper-zinc superoxide dismutase for antioxidant defense, tyrosinase for melanin synthesis, dopamine β-hydroxylase for catecholamine biosynthesis, lysyl oxidase for crosslinking of collagen and elastin, peptidylglycine α-amidating monooxygenase for neuropeptide and peptide hormone processing, and ceruloplasmin for brain iron homeostasis. Reduction in cytochrome oxidase activity may be the likely basis for neurological dysfunction associated with the copper deficient state.

Causes of Copper Deficiency

In the study patients, the most common association with copper deficiency was a remote history of gastric surgery.

TABLE 4. **Route of Copper Supplementation and Response to Therapy in 25 Patients With Copper Deficiency Myelopathy***

Patient No.	Route of copper supplementation	Normal copper levels achieved	Residual deficits	Further deterioration prevented	Reference(s)
1	PO	Yes	Yes	Yes	9, 15
2	IV, PO	Yes	Yes	Yes	13, 15
3	IV, PO	No	Yes	Yes	11, 15
4	PO	Yes	Yes	Yes	13, 15
5	PO	No	Yes	No	15
6	PO	Yes	Yes	Yes	
7	PO	?	?	?	16
8	IV, PO	Yes	Yes	Yes	
9	PO	?	?	?	
10	IV, PO	Yes	Yes	Yes	11, 15
11	PO	Yes	Yes	Yes	16
12	PO	?	?	?	
13	PO	Yes	Yes	Yes	14, 15
14	PO	Yes	Yes	Yes	15
15	IV, PO	Yes	Yes	Yes	
16	PO	?	?	?	
17	IV, PO	Yes	Yes	Yes	13, 15, 16
18	PO	Yes	Yes	Yes	15
19	PO	Yes	Yes	Yes	15
20	PO	Yes	Yes	Yes	21
21	PO	Yes	Yes	Yes	
22	PO	Yes	Yes	Yes	
23	PO, IV	Yes	Yes	Yes	15, 16
24	PO	Yes	Yes	Yes	15
25	PO	?	?	?	

*Hematologic manifestations when present showed a prompt and complete response to therapy. Neurological improvement when present was often more subjective than objective. IV = intravenous; PO = oral; ? = inadequate follow-up data.

Copper absorption in humans most likely occurs in the stomach and proximal duodenum.[37] Prompt appearance of copper 64 in the blood after oral administration suggests that most copper absorption occurs from the proximal gut.[38] Although no data are available on the incidence or prevalence of hypocupremia after gastric surgery, copper deficiency after gastric surgery (for peptic ulcer disease or bariatric surgery) is being increasingly recognized.[6,7,11,13,15,16,18,23,39] Neurological complications after gastrectomy for ulcer disease or bariatric surgery have been well recognized, but frequently the cause has not been determined.[40-46]

Excessive zinc ingestion, although seen in only 1 of the study patients (patient 1), is a well-recognized cause of copper deficiency (Figure 3, A).[2-4,9,19,48-58] In addition to the common use of zinc in the prevention or treatment of common colds and sinusitis, zinc therapy has been used for conditions such as acrodermatitis enteropathica, decubitus ulcers, sickle cell disease, celiac disease, memory impairment, and acne. Unusual sources of excess zinc have included a patient who consumed an entire tube of a denture cream that contained zinc daily for 5 years[4] and patients swallowing coins containing zinc.[53,55-57] Zinc causes an upregulation of metallothionein production in the enterocytes.[59] Metallothionein is an intracellular ligand, and copper has a higher affinity for metallothionein than zinc. Copper displaces zinc from metallothionein, binds preferentially to the metallothionein, remains in the enterocytes, and is lost in the feces as the intestinal cells are sloughed off (Figure 3, A). In patient 2, excess iron consumption may have contributed to the hypocupremia. In animals, excess iron has been associated with copper deficiency.[60-62] If the diagnosis of copper deficiency is not suspected, iron supplementation may be administered for presumed iron deficiency anemia, which may further exacerbate the copper deficiency.[13,63,64] The extent to which oral iron interferes with copper absorption in humans is unknown. Tetrathiomolybdate may have a role in inhibiting tumor angiogenesis, and chemotherapy regimens using tetrathiomolybdate can also result in copper deficiency.[65,66]

Copper deficiency since birth is seen in Menkes syndrome.[30] In this syndrome, copper absorption from the gut is impaired,[31] and high levels of copper are seen in duodenal mucosal cells.[67] A defect in enterocyte transport of

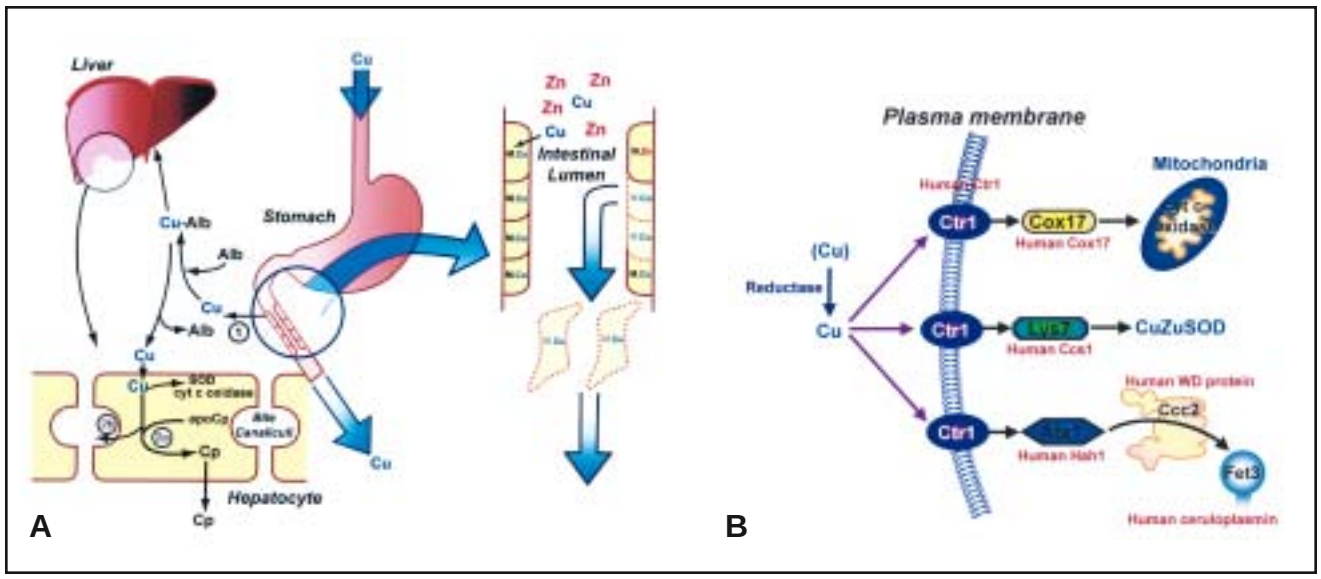

FIGURE 3. Copper (Cu) absorption and distribution. A, Excess dietary zinc (Zn) decreases Cu absorption by inducing metallothionein formation in mucosal cells. Metallothionein has a high affinity for Cu and binds it preferentially, and the bound Cu is lost as the cells slough into the intestinal lumen. By this mucosal block, Zn induces a negative Cu balance. Failure to mobilize absorbed Cu from intestinal cells forms the basis of Menkes syndrome (1). In Wilson disease, there is decreased incorporation of Cu into ceruloplasmin (2a) and impaired biliary excretion of Cu (2b).[47] B, Cu trafficking in yeast. Copper is reduced by a plasma membrane reductase and then transported across the membrane by a Cu transporter (Ctr1). Three Cu transporters or chaperones (Cox17, Lys7, and Atx1) deliver Cu to specific proteins (cytochrome-*c* [cyt c] oxidase, CuZn superoxide dismutase [SOD], and Fet3, respectively) in different cellular compartments. Human counterparts for Ctr1 and the 3 Cu chaperones are indicated in the figure. The human Wilson disease protein is homologous to yeast Ccc2, a P-type ATPase transmembrane Cu transporter. The multi-Cu oxidase Fet3 is homologous to human ceruloplasmin. Adapted from *Clin Gastroenterol Hepatol*,[16] with permission from the American Gastroenterology Association. alb = albumin; Cp = ceruloplasmin; M = metallothionein.

absorbed copper causes copper accumulation in the intestinal mucosa and resulting hypocupremia (Figure 3, A). The genetic basis is mutations in the *ATP7A* gene, which encodes a P-type adenosine triphosphatase (*MNK*) that has multiple copper binding motifs near its amino terminus.[68-70] Loss of function of this protein results in failure of copper transfer across the gastrointestinal tract, placenta, and blood-brain barrier, with resultant copper deficiency. The increased colonic copper seen in patients 17 and 23 suggests that a similar defect in copper transport may underlie idiopathic hypocupremia. Similar observations have been made in a patient with a progressive neurological disease and hypocupremia.[71] Even though an *ATP7A* mutation was not identified in patient 17, changes in the promoter or other noncoding regions and large intragenic deletions could not be ruled out.

It is known that mutations in the *ATP7A* gene are responsible for a wide spectrum of manifestations of Menkes syndrome.[72] Emerging knowledge about copper transport[73,74] may help clarify the origin of idiopathic hypocupremia. Studies in yeast have shown that reduced copper is transported across the membrane by the high-affinity copper transporter Ctr1, and 3 different proteins transport copper to cytochrome-*c* oxidase, copper-zinc superoxide dismutase, and the post-Golgi compartment for insertion into a multicopper oxidase essential for high-affinity iron uptake (Figure 3, B). The copper transporter Ctr1 is the primary avenue for copper uptake in mammalian cells and provides an essential function in mammalian embryonic development.[75]

Copper deficiency may occur in premature infants and low-birth-weight infants.[76,77] Because of copper's ubiquitous distribution and low daily requirement, acquired dietary copper deficiency is rare.[78] It may occur in malnourished infants,[63,79-81] patients with nephrotic syndrome,[82] and those with enteropathies associated with malabsorption.[14,83-86] Malabsorption without a history of gastric surgery was the second most commonly identified cause of hypocupremia in the cohort.

Copper deficiency may be a complication of prolonged total parenteral nutrition,[64,87-92] particularly so when copper supplementation in total parenteral nutrition is withheld because of cholestasis.[93,94] Enteral feeding with inadequate copper has also been known to result in copper deficiency.[95,96]

Associated Hyperzincemia

An elevated serum zinc level in the absence of exogenous zinc ingestion was commonly seen in the study patients. Hyperzincemia in association with hypocupremia has also

been reported by others.[4,8,10,12] The hyperzincemia (as assessed by increased serum zinc or urinary zinc excretion) may persist or increase despite correction of the copper deficient state.[8,10,12,15] The importance of the associated hyperzincemia seen in the absence of exogenous zinc ingestion is unclear,[97,98] as is the importance of increased urinary zinc excretion without elevation of the plasma zinc level.[11,14] Copper deficiency may result from a zinc overload syndrome.[10] A metabolic abnormality that results in increased zinc absorption or decreased intestinal excretion has been proposed. Since the syndrome of myeloneuropathy has been described with hypocupremia and normal zinc levels,[6,11,13-15,18] it is unlikely that hyperzincemia is causative. No definite reports have been published of neurological toxicity due to hyperzincemia *without* hypocupremia in animals or humans. Elevated zinc levels have been described as a heritable anomaly with no clinical manifestations.[99] High doses of oral zinc have been administered long term in patients with Wilson disease with no development of neurological complications. The hyperzincemia seen in some patients with neurological manifestations and copper deficiency is probably a secondary feature associated with the hypocupremia.

Associated Vitamin B_{12} Deficiency

Some of the study patients had a history of vitamin B_{12} deficiency, most of whom had undergone gastric surgery. None of the patients had low vitamin B_{12} levels at the time the copper deficient state was diagnosed. The myelopathy of copper deficiency closely mimics the subacute combined degeneration of vitamin B_{12} deficiency.[15] Copper and vitamin B_{12} deficiency may coexist.[4,15] Patients may be given vitamin B_{12} despite normal serum vitamin B_{12} levels.[6] A similar spine MRI appearance can be seen in patients with vitamin B_{12} deficiency.[100]

Clinical Features, Neurophysiology, and Neuroimaging in Copper Deficiency Myelopathy

The clinical presentation of all the study patients was that of a gait difficulty primarily due to severe sensory ataxia. The sensory ataxia was primarily due to dorsal column dysfunction. At times, symptom onset was subacute. Clinical or electrophysiological evidence of a peripheral neuropathy was often present. Involvement of the peripheral nervous system was not the predominant reason for the sensory ataxia in any patient. The MRI and evoked potential studies provided additional evidence of posterior column dysfunction (Table 3, Figure 2, A and B). The most consistent finding on spine MRI is increased signal on T2-weighted images that involve the dorsal columns. The cervical cord is most commonly involved, and contrast enhancement is not present. Follow-up imaging was available in 1 patient (patient 17) and showed resolution of the dorsal column signal change with improvement in serum copper.[20] Vitamin B_{12} deficiency and copper deficiency can coexist, and the ataxic myelopathy of copper deficiency can mimic the subacute combined degeneration seen with vitamin B_{12} deficiency.[15] Clioquinol, a copper-zinc chelating antibiotic, is the likely etiologic agent in subacute myelo-opticoneuropathy,[101] and both copper deficiency myelopathy and myelo-opticoneuropathy are characterized by involvement of the dorsal column and corticospinal tracts. It is speculative whether copper deficiency could have been the proximate cause of myelo-opticoneuropathy.[102] Table 5 details the salient features in some of the other described patients with neurological manifestations due to acquired copper deficiency.

Most of the noted areas of increased T2 signal on brain MRI in the study patients were nonspecific; however, the appearance and distribution of some of these lesions suggested lacunar disease. Neuropathological studies in Menkes syndrome have shown arterial tortuosity and fragmentation of the internal elastica in large arteries.[31] Some of the pathological changes in the CNS in Menkes syndrome are likely due to vascular involvement. Experimental copper deficiency has been associated with aneurysmal dilation of large arteries and massive hemorrhage.[104] The possible role of acquired copper deficiency in cerebrovascular disease requires further study. Two described patients have had brain MRI findings that were believed to be consistent with demyelinating disease.[5,8] The importance of the brain MRI findings requires further study. Neurophysiological studies show varying degrees of axonal peripheral neuropathy, at times predominantly motor. Abnormalities in somatosensory evoked potential studies indicating central conduction delay are common. Other reported electrophysiological abnormalities noted in patients with copper deficiency and neurological manifestations include prolonged visual evoked potentials[5] and impaired central conduction on transcranial magnetic stimulation.[6]

Associated Hematologic Manifestations

A history of anemia or leukopenia or anemia or leukopenia at presentation was present in most of the study patients. It is being increasingly recognized that hematologic manifestations may not accompany the neurological syndrome.[9,15,18,105] The hematologic hallmark of copper deficiency is anemia and neutropenia.[1,51,95,96,106] The anemia may be microcytic,[49,51,54] macrocytic,[4,7] or normocytic.[4,95] Thrombocytopenia and resulting pancytopenia are relatively rare.[92-94] A prolonged copper deficient state may be necessary for the development of thrombocytopenia.[96]

Typical bone marrow findings include a left shift in granulocytic and erythroid maturation with cytoplasmic

TABLE 5. **Clinical and Imaging Characteristics of Other Reported Patients With Neurological Manifestations Due to Acquired Copper Deficiency***

Source	Age (y)/ sex	Symptom duration	Neurological manifestations	Serum copper at diagnosis (μg/dL)†	*Possible* cause of copper deficiency	Spine MRI	Brain MRI	Additional observations
Buchman et al[103]	21/M	6 y	Ataxia, peripheral neuropathy	41 (70-155)	Intestinal pseudo-obstruction and malnutrition	No information	Increased intensity in white matter on T2-weighted brain MRI	No increase in serum copper level despite parenteral copper administration
Schleper et al[6]	46/F	18 mo	Myelopathy	308 (760-1800)	Gastric surgery, segmental colonic resection	Hyperintense T2 signal involving the dorsomedial part of the cord from C1 to C7	Normal	Elevated blood manganese level, normal serum zinc level
Gregg et al[7]	44/F	Unknown	Peripheral neuropathy and optic neuritis	Undetectable	Gastric surgery	No information	No information	Myelodysplastic syndrome
Prodan et al[8] (patient 1)	45/F	2 y	Brisk reflexes, reduced vibratory sense in lower limbs, ataxic gait	5 (70-155)	Unknown, hyperzincemia present	Normal	Multiple bilateral subcortical white matter lesions, predominantly frontal, consistent with demyelination	Splenomegaly, improved sensory symptoms with copper level normalization, further increase in serum zinc level
Prodan et al[5,8] (patient 2)	45/M	4 mo	Saccadic dysmetria, decreased feet vibratory and joint position sense, hyperreflexia, truncal ataxia	Undetectable	Unknown, hyperzincemia present	No information	Demyelination involving the periventricular regions, corpus callosum, and cerebellar peduncles	Significant neurological improvement with copper supplementation, persisting hyperzincemia
Hedera et al[10]	46/M	5 mo	Myeloneuropathy	<10 (80-120)	Unknown, hyperzincemia present	Normal	3-mm area of increased T2 signal in the left centrum semiovale	Improvement with partial reversal of neurological signs
Greenberg et al[12]	52/F	2 y	Myeloneuropathy	Undetectable (>200)	Unknown, hyperzincemia present (serum and urine)	T2 hyperintensity at T6-7	Normal	History of gluten-sensitive enteropathy controlled with diet
Prodan et al[17]	45/F	Unknown	Myelopathy	"Markedly reduced"	Unknown, no hyperzincemia	No information	No information	No information
Rowin et al[19]	53/F	4 mo	Myeloneuropathy	7 (70-155)	Hyperzincemia present, exogenous ingestion	Normal	Normal	Improved gait and nerve conductions
Willis et al[4]	47/M	30 mo	Peripheral neuropathy	8 (70-145)	Hyperzincemia present, cause unknown	No information	No information	No neurological improvement
Willis et al[4]	42/M	8 mo	Peripheral neuropathy ingestion	Undetectable	Hyperzincemia, exogenous	No information	No information	No neurological improvement
Bartner et al[23]	71/F	6 mo	Ataxic gait	<100 (850-1900)	Gastric surgery and possibly urinary copper loss due to glomerulonephritis	Hyperintensity dorsal part of cervical and thoracic cord	No information	No neurological improvement

*Symptom duration refers to duration of neurological symptoms before diagnosis of copper deficiency. MRI = magnetic resonance imaging.
†Reference range is shown parenthetically.

vacuolization in erythroid and myeloid precursors (Figure 2, C) and the presence of ringed sideroblasts (Figure 2, D).[1,2,4,5] Hemosiderin-containing plasma cells (Figure 2, D) may be present.[1,7] The bone marrow findings are not pathognomic but are highly characteristic, and reports have been published of patients in whom the diagnosis of the copper deficient state was first suggested by the bone marrow findings.[4] Patients may be diagnosed as having sideroblastic anemia or myelodysplastic syndrome.[3,4,7,21,50,52,57] In one described patient with copper deficiency and hematologic abnormalities, a pretransplantation evaluation was considered, and treatment with blood transfusions, erythropoietin, and granulocyte colony-stimulating factors was given before copper deficiency was detected.[7]

Copper-containing enzymes likely play a role in cell differentiation and proliferation in the bone marrow. Impaired erythroid and myeloid maturation and reduced erythrocyte and neutrophil life spans are the likely reasons for the anemia and neutropenia.

Treatment of Copper Deficiency

No studies have addressed the most appropriate dose, duration, route, and form of copper supplementation. Little information is available on human copper stores. Serum copper may be inadequate for assessing total body copper stores, and activity of copper enzymes, such as erythrocyte superoxide dismutase and platelet or leukocyte cytochrome-*c* oxidase, may be a better indicator of metabolically active copper stores.[107-109]

In patients with zinc-induced copper deficiency, discontinuing use of the zinc may suffice, and no additional copper supplementation may be required.[4,52,54] At times, prolonged oral therapy may not result in improvement; parenteral therapy may be required, and elimination of excess zinc may be slow, and until such elimination occurs, the intestinal absorption of copper may be blocked.[51] Some investigators have used initial parenteral administration followed by oral administration.[7,19]

Despite a suspected absorption defect, oral copper supplementation is generally the preferred route of supplementation. Copper supplements may not be adequately absorbed when administered through a jejunostomy tube, necessitating parenteral therapy.[110] Studies of yeast have shown that the copper transport pathways are high-affinity pathways active in conditions of low copper concentration, and increasing the concentration of copper may result in the pathways being bypassed.[73] This may explain why in most of the current study patients normal serum copper levels were achieved by increasing the amount of copper ingested. Oral administration of 2 mg/d of elemental copper seems sufficient. A comparable dose of elemental copper may be given intravenously. Doses as high as 9 mg/d orally have been used.[7,10,23] Commonly used copper salts include copper gluconate[23] and copper chloride.[7] The oral bioavailability of copper gluconate may be limited.[111]

Currently, my colleagues and I at the Mayo Clinic give 6 mg/d of elemental copper orally for a week, 4 mg/d for the second week, and 2 mg/d thereafter. Periodic assessment of serum copper is essential to determine adequacy of replacement and the most appropriate long-term administration strategy. Because of the need for long-term replacement, parenteral therapy is not preferred and is generally not required. If required, a daily dose of 2 mg of elemental copper may be administered intravenously for 5 days periodically thereafter.

Response of the hematologic parameters (including bone marrow findings) is prompt and often complete.[3,4,7,12,49,92,95,106] Hematologic recovery may be accompanied by reticulocytosis.[12,64,95,106] Transient improvement with hematopoietic growth factors may occur even if copper deficiency is the cause of the hematologic manifestations.[7,21]

Recovery of neurological signs and symptoms seen in association with copper deficiency varies. Improvement in neurological symptoms is variable, although progression is typically halted.[4,8,12,15,18] A relapse in the copper deficient state may not be necessarily accompanied by neurological deterioration.[8] Improvement when present is often subjective and preferentially involves sensory symptoms.[6,8,11] There are some reports of definite improvement in the neurological deficits,[5,10,19] nerve conduction studies,[19] evoked potential studies,[9] and MRI T2 cord signal change[20] with normalization of serum copper.

CONCLUSION

I believe that myelopathy due to acquired copper deficiency in adults is an underrecognized syndrome. Estimation of serum copper levels should be a part of the work-up in patients with myelopathy or myeloneuropathy, particularly in those with a high risk of developing copper deficiency. Hematologic manifestations such as anemia or neutropenia are often but not always present. The presence of unexplained cytopenia in association with neurological manifestations should prompt clinicians to look for copper deficiency. The clinical picture resembles the subacute combined degeneration seen with vitamin B_{12} deficiency. The 2 conditions can coexist. Continued neurological deterioration in patients with a history of vitamin B_{12} deficiency–related myelopathy who have a normal vitamin B_{12} level while receiving vitamin B_{12} replacement therapy should be evaluated for copper deficiency. Exogenous zinc ingestion, prior gastric surgery, prematurity, malnutrition, parenteral alimentation, and

malabsorption are the commonly recognized risk factors for the copper deficient state. Often, the cause of copper deficiency is unknown. Hyperzincemia may be present even in the absence of exogenous zinc supplementation. Somatosensory evoked potential studies may show delay in central conduction. Variable degrees of peripheral neuropathy may be seen on nerve conduction studies. Spine MRI may show a dorsal paramedian cord signal hyperintensity on T2-weighted images. The hematologic manifestations reverse promptly with copper replacement. Early recognition and prompt treatment may prevent significant neurological morbidity.

It is unclear which patients may develop copper deficiency after gastric surgery and if routine screening and supplementation should be considered as is commonly done in these patients for vitamin B_{12} deficiency. Given the increasing rates of bariatric surgery, this is a particularly pertinent issue. The copper deficient state may not manifest for decades. The role of the commonly observed hyperzincemia in the absence of exogenous zinc ingestion is unclear. The association between copper deficiency and CNS demyelination, isolated peripheral neuropathy, and optic neuritis requires further study. Studies are needed to determine the best dose, route, and duration of copper therapy. Further understanding of copper transport and trafficking may provide insights into the cause of copper deficiency in those with idiopathic hypocupremia.

ADDENDUM

Three additional patients with copper deficiency myelopathy and prior gastric surgery were recently described.[112-114] Also noteworthy is a recent report of 3 patients who presented with asymmetric lower motor neuron weakness, minimal sensory manifestations, and electrodiagnostic evidence of diffuse denervation, 2 of whom had a history of gastrointestinal surgery.[115]

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