Copper deficiency-associated myelopathy in cryptogenic hyperzincemia: a case report

Carlotta Mutti1,3, Veronica Bazzurri3, Elena Tsantes2, Erica Curti2, Liborio Parrino1,3, Franco Granella2,3
1Sleep Disorders Center, Department of General Medicine, University Hospital of Parma, Parma, Italy; 2Neurosciences Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; 3Neurology Unit, Department of General Medicine, University Hospital of Parma, Parma, Italy

Abstract
Copper deficiency syndrome is an underestimated cause of posterior myelitis. We describe the case of a 41-year-old woman, who developed a subacute ataxic paraparesis associated with low back pain. Her 3T spine MRI showed a thin hyperintense FS-Echo T2 longitudinally extensive lesion involving the posterior columns of the cervical cord (from C2 to C6). An extensive diagnostic work-up excluded other causes of myelopathy and blood tests pointed out hypocupremia and mild hyperzincemia. Patients affected by this rare form of oligoelement deficiency typically develop progressive posterior column dysfunction with sensory ataxia and spasticity, sometimes associated with sensori-motor polyneuropathy. Clinical and radiological characteristics of posterior myelopathy due to copper deficiency are briefly reviewed. Physicians should be aware of this condition since a prompt introduction of copper supplementation can avoid progression of the neurological damage. (www.actabiomedica.it)

Keywords: posterior myelopathy, copper, zinc, spine MRI

Background and Aim of The Work

Copper deficiency syndrome is an underestimated cause of posterior myelitis that may closely mimic vitamin B12 deficiency, being associated with both hematological abnormalities and neurological symptoms and presenting identical neuroradiological features. Physicians should be aware of this condition since a prompt introduction of copper supplementation can avoid progression of the neurological damage. We report the case of a young patient who developed longitudinally extensive transverse myelitis involving the posterior column of the cervical cord due to mild hyperzincemia and hypocupremia of unknown origin. We briefly reviewed clinical and radiological characteristics of this metabolic syndrome.

Clinical Vignette

A 41-year-old woman, without significant past medical history, was admitted to our hospital for a subacute ataxic paraparesis associated with low back pain. At neurological examination she presented mild bilateral proximal lower limb hyposthenia, hyperreflexia and severe distal hypopallesthesia. Spinal cord 3.0 T-MRI showed a thin hyperintense FS-Echo T2 longitudinally extensive lesion involving the posterior columns of the cervical cord (from C2 to C6), without contrast enhancement. Upper limb somatosensory evoked potential amplitude was markedly reduced on the left side, while no cortical potential could be detected on the right side.
She underwent a complete diagnostic work-up comprehensive of: routine laboratory examination, thyroid function tests, serum electrophoresis, serum cobalamin and folate and urinary metylmalonate levels, CSF analysis (including cell counts, protein, glucose and oligoclonal bands), serum antibodies against aquaporin 4 and myelin oligodendrocyte glycoprotein (MOG), rheumatological screening tests (including ANA reflex, c-ANCA, p-ANCA, cryoglobulin, rheumatoid factor, LAC test, anti beta2glycoprotein, anti cardiolipin, complementaemia, celiac antibodies, thyroid antibodies), serology for neutrotropic viruses (including HSV1-2, CMV, EBV, HBV, HCV, HIV, HTLV1-2), serology for Borrelia Burgdorferi and Treponema Pallidum and brain MRI. All the listed examinations were normal.

Serum copper level was under normal limits (26 µg/mL, nv 65-165), ceruloplasmin was normal and serum zinc concentration mildly exceeded the reference range (1093 ug/L, nv 600-1080). The patient denied any history of zinc abuse. Treatment with oral copper supplementation produced a partial clinical improvement: she recovered from low back pain and ataxia albeit moderate hypopallesthesia persisted. At regular follow-up controls (6 months-1 year-2 years) her neurological condition was substantially unchanged and spine MRI excluded progression of the disease.

Discussion

Copper is a trace mineral that plays an essential role in multiple enzymatic processes in the human body. Due to its wide distribution among food its deficiency is rare. In Western countries a normal diet fulfills the daily requirement. Copper bioavailability may differ due to the presence of amminoacids as cysteine or metals as molybdenum and zinc\(^1\). Furthermore an indiscriminate use of multivitamins over-the-counter, rich in zinc amount, could indirectly cause hypocupremia (1).

Etiology of copper deficiency is heterogeneous and includes: prolonged parenteral nutrition, malabsorption in celiac disease, cystic fibrosis, prolonged diarrhea, post-gastrectomy and jejuno-ileal bypass surgery, increased zinc intake (zinc supplements, denture adhesives), excessive loss of ceruloplasmin-bound copper in nephrotic syndrome (2). There are also genetic causes of copper deficiency such as Menkes disease (3) and MEDNIK syndrome (4).

Our patient had no personal history of malnourishment or causes of malabsorption and denied usage of dental adhesive or over-the-counter supplements. Despite the extensive diagnostic work-up no cause was found for copper deficiency and hyperzinemia.

The clinical and radiological features of adult-onset copper deficiency syndrome closely resemble those seen in vitamin B12 (cobalamin) deficiency and occasionally these two etiologies can even co-exist in the same patient (5). Besides neurological manifestations, hematological abnormalities, such as anemia and leukopenia, can be associated with copper deficiency, closely resembling a myelodysplastic syndrome (2). While hematological abnormalities are reversible with treatment, residual neurological abnormalities may persist in a significant number of patients affected by copper deficiency (6). Moreover the neurological features of copper deficiency may be seen without the hematologic manifestations and vice versa (7). In the present case our patient lacked any blood examination abnormality. Were normal.

The typical neurological picture of copper deficiency is an ataxic myelopathy: unsteady gait with mixed features of sensory ataxia and spasticity produced by posterior and lateral column dysfunction, respectively (3). Sporadic case reports of copper deficiencies describe association with cerebral demyelination, optic neuropathy, isolated peripheral neuropathy, late cortical cerebellar atrophy and myopathy (7-9).

Our patient presented a posterior cervical myelopathy with high T2-signal intensity longitudinally extended across more than three vertebral segments on sagittal spinal cord MRI scan, known as longitudinally extensive transverse myelitis (LETM). Towards LETM a broad differential diagnosis must be ruled out: inflammatory disease (neuromyelitis optica, MOG ab disease, Sjogren’s syndrome, SLE, Behcet’s disease, sarcoidosis, primary CNS angiitis/ vasculitis, multiple sclerosis), metabolic disease (Vitamin B12 deficiency, Vitamin E deficiency), infectious disease (HIV, HTLV I-II, neurosyphilis, CMV, HSV, VZV, Arbovirus and parasitic infections). vascular disease
In conclusion, hypocupremia is an underestimated mimic of a subacute combined degeneration of the spinal cord due to cobalamin deficiency and sometimes the two condition can even co-exist. Clinicians must be aware of this treatable disorder and we suggest that copper dosage should be included in the diagnostic investigation of LETM of unknown origin, particularly when the posterior column of the spinal cord is involved.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Table 1. Posterior myelopathy radiological differential diagnosis

| Inflammatory diseases                                      | Neuromyelitis Optica                     |
|------------------------------------------------------------|------------------------------------------|
| Anti-MOG antibodies disease                                |                                          |
| Sjogren Disease                                            |                                          |
| Systemic Lupus Eritematosus                                |                                          |
| Behcet’s Disease                                           |                                          |
| Sarcoïdosis                                                |                                          |
| Primary central nervous system angitis                     |                                          |
| Multiple sclerosis                                         |                                          |
| Metabolic diseases                                         | Vitamin B12 deficiency                   |
| Vitamin E deficiency                                       |                                          |
| Infectious diseases                                       | HIV                                      |
| Neurosyphylis                                              |                                          |
| CMV                                                       |                                          |
| HSV                                                       |                                          |
| VZV                                                       |                                          |
| Arboviral infections                                       |                                          |
| Parasitic infections                                       |                                          |
| Vascular diseases                                          | Dural atero-venous fistula               |
| Spinal cord infarction                                     |                                          |
| Intramedullary spinal neoplasms                           | Astrocytoma                              |
| Ependymoma                                                 |                                          |
| Radiation myelopathy                                       |                                          |

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Correspondence:
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Dr. Carlotta Mutti, Neurology Unit/Sleep Disorders Center, Department of General Medicine, University Hospital of Parma, University Hospital of Parma, Via Gramsci 14, 43126 Parma, Italy, Tel. +39-0521-704107, email: carlotta.mutti88@gmail.com
