The clinical course was suggestive of a copper deficiency, with anemia, elevated ceruloplasmin levels, and hypoprolactinemia. The patient was diagnosed with a copper deficiency anemia, and was started on oral copper supplementation. The anemia improved gradually, and the patient's symptoms resolved over the following months.

The patient was 60-year-old woman with a history of mild gastrointestinal symptoms and anemia. She had undergone a hysterectomy due to menorrhagia. Despite treatment with iron supplements, her anemia persisted. She was found to have an elevated serum ceruloplasmin level and a decreased copper level. A diagnosis of copper deficiency anemia was made, and the patient was started on copper supplementation.

After several weeks of treatment, the patient's anemia improved, and her serum copper levels normalized. The patient's symptoms improved, and she no longer required iron supplements.

The patient was advised to continue copper supplementation and to avoid foods high in phytates, which can decrease copper absorption. The patient was referred to a dietitian for dietary counseling.
Figure 1  Left: cervical MRI scan, sagittal plane, T2-weighted sequence. Hyperintensity in the spinal cord. Right: brain MRI scan, axial plane, T2-weighted sequence. Multiple round hyperintense lesions in the cerebellum.

completely restored; the patient was left with decreased tactile sensitivity in the right arm (up to the elbow) and decreased vibration sense in the legs and right hand. Follow-up blood tests revealed that anaemia had resolved and copper levels were within the normal range. Neuroimaging revealed small, nearly imperceptible, foci of myelopathy in the cervical spinal cord, with slight contrast uptake and focal atrophy, in addition to small, non-specific hyperintensities in the cerebellum on T2-weighted sequences, with no associated contrast uptake or oedema.6

Determining the aetiology of LETM requires a combination of several tests. Although the presence and characteristics of certain radiological findings may guide diagnosis (multiple small spinal cord lesions are indicative of systemic lupus erythematosus or multiple sclerosis, whereas extensive lesions at multiple levels suggest vasculitis), no specific characteristics for each condition have been defined. Likewise, the aetiology cannot be determined based on the symptoms. Differential diagnosis therefore requires a thorough analysis including a biochemical study, a complete blood count, serological tests, autoimmunity tests (ANA, ANCA, TPO antibodies, complement, ENA, NMO-IgG), and a nutritional study (copper, vitamin B12, folic acid). Tumour screening tests and an FDG-PET scan should be performed when there is suspicion of a paraneoplastic origin.6,7–9

Although the exact role of copper deficiency in acute myelopathy is yet to be determined, copper is known to be essential to the proper functioning of the nervous system. The mineral is present throughout the brain, particularly in the basal ganglia, hippocampus, and cerebellum. The central nervous system contains several copper-dependent enzymes: tyrosinase, peptidylglycine alpha-amidating monoxygenase, copper/zinc superoxide dismutase, ceruloplasmine, hephaestin, dopamine beta-hydroxylase, and cytochrome c oxidase.5,10 Copper deficiency has an estimated prevalence of 23%11 and is associated with haematological alterations in 78% of cases (68% present anaemia and 50% leukopaenia), brain and spinal cord MRI alterations in 47% of cases, and neurological alterations in 48%12; these neurological alterations include myelopathy associated with symptoms of subacute combined degeneration. Although the literature includes some cases of patients with similar CSF results to our own (pleocytosis and presence of oligoclonal bands), most patients show normal CSF results (copper deficiency of paraneoplastic origin may be associated with elevated protein levels and mild pleocytosis). The inflammation secondary to neurodegeneration (with demyelination probably secondary to copper deficiency) that occurs during this condition may be responsible for these alterations. Up to 47% of the patients have a history of gastrointestinal surgery, whereas the cause is unknown in 20% of cases.13 Other more prevalent conditions, such as myelopathy secondary to vitamin B12 deficiency or to varicella-zoster virus infection, may present with similar symptoms, which adds to the complexity of diagnosing this condition (Table 1).

We may conclude that LETM due to copper deficiency is a rare entity whose clinical and radiological features make it indistinguishable from other more prevalent conditions, such as combined spinal cord degeneration secondary to vitamin B12 deficiency. The co-occurrence of these 2 conditions, especially in patients with no history of gastrectomy and in whom malabsorption syndrome is not suspected, delays the onset of copper replacement therapy, resulting in potentially irreversible neurological sequelae.
### Table 1: Differential diagnosis of acquired, non-compressive myelopathies and the diagnostic process followed.

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Tests</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Nutritional aetiology:</strong> Inhalation of nitrous oxide Copper deficiency Vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency</td>
<td>Biochemical study and complete blood count Serological tests Autoimmune tests (TPO antibodies, NMO-IgG, ANA, ANCA, ENA, complement)</td>
<td>Blood test: Nornocytic normochromic anaemia (haemoglobin: 8.1 g/dL) Total copper 46.9 μg/dL, ceruloplasmin 15.10 mg/dL, normal 24-h urine copper No signs of infection or tumour. Negative results from serological tests Normal levels of vitamin B&lt;sub&gt;12&lt;/sub&gt;, folic acid, zinc, and vitamins A, D, and E ANA 1:80, speckled; ANCA 1:20; TPO antibodies 79 IU/mL. Results for the remaining antibodies were normal</td>
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<tr>
<td><strong>Infectious aetiology:</strong> Brucella, syphilis, Lyme disease, HIV, HBV, HCV, Epstein-Barr virus, HTLV-1, herpes simplex virus, varicella-zoster virus, etc.</td>
<td>Lumbar puncture</td>
<td>CSF analysis: 17 cells/mm&lt;sup&gt;3&lt;/sup&gt;; glucose level 40 g/dL; protein level 60 g/L; presence of oligoclonal bands. Culture: negative. Cytology: moderate lymphocytosis</td>
</tr>
<tr>
<td><strong>Immunological/inflammatory aetiology:</strong> Sarcoidosis Demyelinating diseases: multiple sclerosis, transverse myelitis, acute disseminated encephalomyelitis, neuromyelitis optica Sjögren syndrome Behçet disease Vasculitis</td>
<td>Brain and spinal cord MRI</td>
<td>Brain and spinal cord MRI: diffuse involvement of the spinal cord (predominantly cervical segment), both cerebellar hemispheres, the right middle cerebellar peduncle, and the white matter in the periaqueductal area and globus pallidus bilaterally No significant alterations</td>
</tr>
<tr>
<td><strong>Vascular aetiology:</strong> Venous hypertensive myelopathy Dural arteriovenous fistula</td>
<td>Gastroscopy Chest CT EMG Doppler ultrasound (transcranial, supra-aortic trunks)</td>
<td>Abnormal findings are shown in bold. Taken from Kitley et al.&lt;sup&gt;1&lt;/sup&gt; and Eckstein et al.&lt;sup&gt;2&lt;/sup&gt;</td>
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</table>

ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; CSF: cerebrospinal fluid; CT: computed tomography; EMG: electromyography; ENA: extractable nuclear antigens; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HTLV-1: human T-lymphotropic virus type 1; MRI: magnetic resonance imaging; NMO-IgG: aquaporin-4 antibodies; TPO: thyroperoxidase antibodies.

References


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