

# Hypocupremia: An Under Recognized Cause of Subacute Combined Degeneration

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## SUMMARY

It is increasingly evident that a multitude of etiologies can give rise to signal abnormality in the dorsal and lateral columns of the spinal cord, apart from pernicious anemia. We report a case of dorsal and lateral columns signal abnormality related to hypocupremia resulting in progressive sensory ataxia and weakness in the lower and upper limbs, compounded by a recent diagnosis of Sjögren's syndrome.

## INTRODUCTION

Menkes kinky hair disease is a well recognized inherited copper deficiency resulting in neurodegenerative disorder. Neurological manifestation of acquired copper deficiency is less well known and may be under diagnosed given its similarity in clinical presentation and imaging findings to several other types of sensory ataxic neuropathy, which includes pernicious anemia and Sjögren's syndrome.

## CASE REPORT

A 71-year-old man presented with six months history of sensory disturbance in upper and lower limbs, described like limbs being "encased in sand". Peripheral neuropathy was initially suspected. Apart from emphysema, he was otherwise well. Magnetic resonance imaging (MRI) brain demonstrated non-specific cerebral white matter hyperintensities. Initial MRI spine showed high signal in the dorsal columns of both cervical and upper thoracic cord, and high signal in the lateral columns in the thoracic cord (Figure 1). Given the imaging findings, the diagnosis of vitamin B<sub>12</sub> deficiency was suspected. No initial vitamin B<sub>12</sub> level was acquired prior to starting the patient on high dose vitamin B<sub>12</sub> replacement. Despite normal levels of vitamin B<sub>12</sub> on follow up, the patient's condition deteriorated.

He was referred to a tertiary hospital for further investigation. By this time, he had also developed urinary incontinence and urgency. On examination, he had normal muscle tone and power. There was absent ankle jerk and proprioception was diminished from his hips to toes and in his metacarpophalangeal joints. There was diminished light touch and pinprick sensation to his knees. Profound sensory ataxia was exhibited. The patient was also found to have a very dry tongue. The diagnosis of exclusion was peripheral neuropathy secondary to paraneoplastic syndrome given the history of weight loss and prior history of heavy smoking.

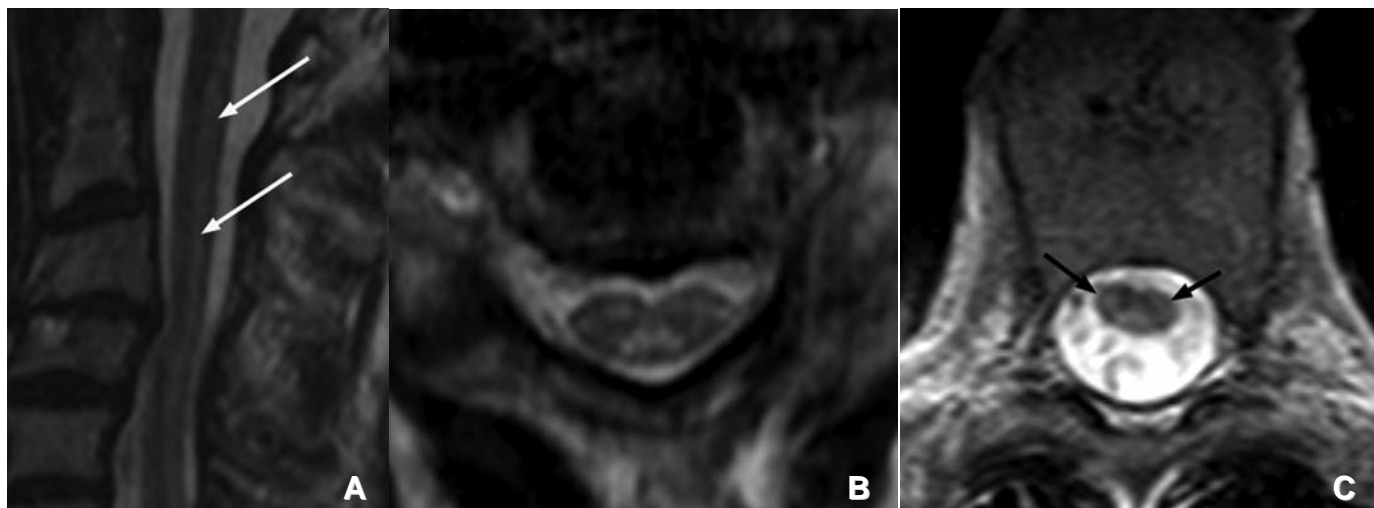
Paraneoplastic work up, which included computed tomogram (CT) Thorax and Abdomen, did not revealed any malignant process. Paraneoplastic antibodies including anti-Hu and anti-Yo

were also negative. Electromyography (EMG) and nerve conduction studies were normal. Evoked potentials performed showed abnormalities in both upper and lower limb somatosensory evoked potentials. Cerebrospinal fluid (CSF) was normal with negative cell count, protein and oligoclonal bands. Patient has a low Hb level, 103 g/L, with microcytic hypochromic anemia. There was no evidence of leucopenia. Vitamin B<sub>12</sub> level was normal (216 µmol/L – normal range 110-630 µmol/L). Toxicology panel was negative. Patient had a elevated erythrocyte sedimentation rate 131mm/Hr (normal range 0-9mm/Hr) and C-reactive protein 62 mg/L (normal range 0-5 mg/L). Inflammatory antibody panel that was performed was positive for anti-SSA(Ro) antibody -196 EU/ml (positive >25 EU/ml) and anti-SSB (La) antibody -73 EU/ml (positive >25 EU/ml). Schirmer's test and minor salivary gland biopsy confirmed the diagnosis of Sjögren's syndrome. The patient was diagnosed with Sjögren's sensory ataxia and was started on methyl-prednisolone and IV immunoglobulin. Unfortunately, there was no clinical improvement despite therapy. Repeat spinal MRI demonstrated no change to the signal abnormality within the spinal cord.

At this time, seven months after initial presentation, we discovered a history of gastric resection about 45 years ago. Further blood panel performed found low levels of ceruloplasmin at 0.14g/L (normal range 0.22-0.58 g/L). His serum copper level was very low at 4.3mol/L (normal range 11-22mol/L). Serum zinc level was not performed. He was treated with IV copper replacement initially, given the prior gastric surgery and this was followed by oral copper replacement. Follow-up MRI two months later, demonstrated improvement in the dorsal column signal abnormality in the cervical cord with minimal residual signal abnormality (Figure 2). Unfortunately, no interval change was found in the dorsal and lateral columns signal abnormality of thoracic cord. Instead, thoracic cord atrophy was evident on the follow-up study. Despite improvement in the cervical cord signal abnormality, the patient's condition worsened.

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**Figure 1:** Presentation Spinal MRI. A & B: Sagittal and axial T2-weighted MR imaging were performed on Philips 1.5T (Philips Medical Systems, Best, the Netherlands) (TR/TE 3000/120ms; FOV, 22 x 22cm; Matrix, 304x285; ST, 3mm with 0.1 gap) of the cervical cord demonstrates signal abnormality in the dorsal columns bilaterally. Axial image is acquired at C4 level. C: Axial T2-weighted MR imaging of the thoracic cord reveals signal abnormality in the corticospinal tracts (lateral columns) and dorsal columns bilaterally at T7 level.

## DISCUSSION

Copper is a heavy metal and a component of numerous metalloenzymes and proteins that have a key role in maintaining the structure and function of the nervous system<sup>1</sup>. When it is incorporated into specific enzymes, it can alternate between two oxidation states, thereby facilitating electron transfer reactions<sup>2</sup>. It is a constituent of cytochrome oxidase (oxidative phosphorylation), superoxide dismutase (antioxidant defense), ceruloplasmin (iron metabolism), tyrosinase (melanin synthesis), and dopamine-monoxygenase (catecholamine synthesis)<sup>1,2</sup>.

Effects of copper deficiency in ruminants are well known and often result in progressive ataxic myelopathy (“swayback”)<sup>3-5</sup>. Wallerian degeneration and demyelination with microcavitation of the white matter in the spinal cord and brainstem<sup>6</sup> have been found in sheep, which also classically have brittle hair. Like the “swayback” ruminant, in humans, a similar congenital condition was first described in 1962, by Menkes et al, termed Menkes kinky hair disease. It is a neurodegenerative disorder, where the underlying abnormality is failure to mobilize absorbed copper in the mucosal cells<sup>7,8</sup>.

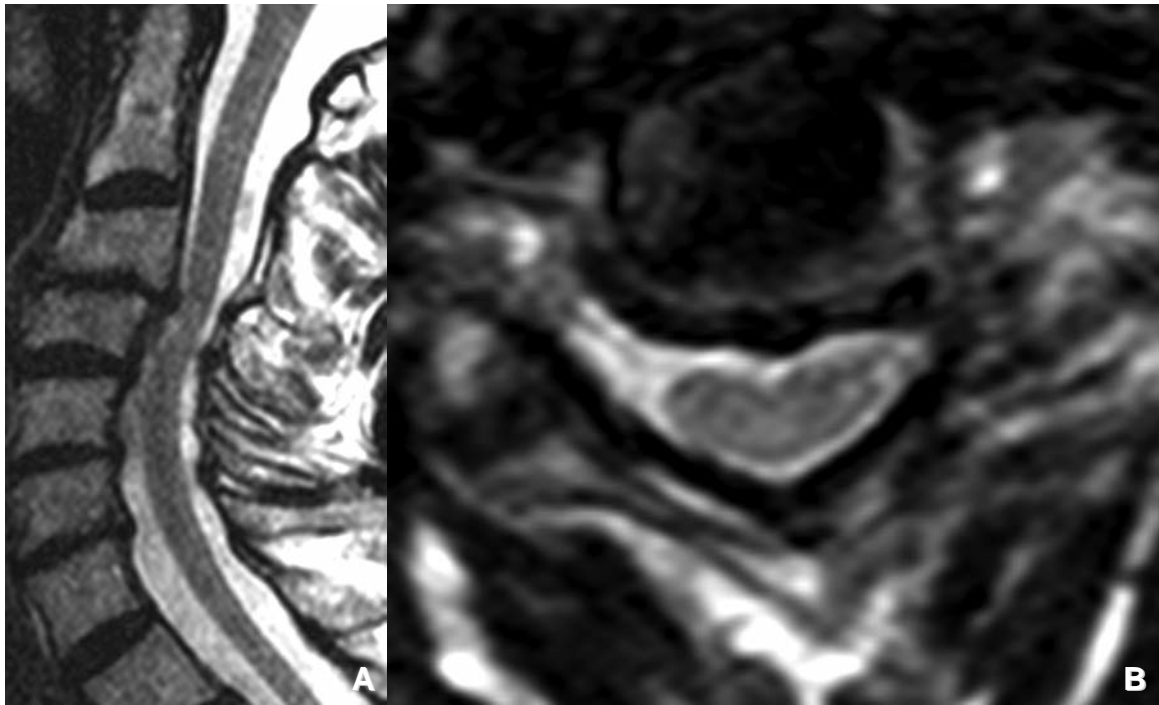
Acquired copper deficiency in human is less well recognized, given its similarity in clinical presentation to vitamin B<sub>12</sub> deficiency. Although the hematological effects, which include anemia and leucopenia, have been well described, its effect on neural structures are less well known. Only a handful of case reports and small series<sup>9-12</sup> have been published in the medical literature since it was first described by Schleper et al in the year 2001<sup>13</sup>. Patients classically present with unsteady gait with mixed features of sensory and spasticity produced by dorsal and lateral column dysfunction. It is often accompanied by varying degrees of superimposed peripheral neuropathy. Impaired pin-prick sensation in a stocking distribution and marked

proprioceptive dysfunction has also been described<sup>14</sup>. Our patient exhibited most of these features, including bladder dysfunction, which had also been described.

Based on studies of radioactive isotopes of copper, most of the copper is absorbed in the stomach and duodenum of the gastrointestinal tract<sup>15</sup>. The etiology of acquired hypocupremia in patients with myelopathy is unknown in approximately one-third of patients<sup>15</sup>. Similar to our patient, the majority of these patients often have a history of remote gastric surgery and malabsorption. Increased zinc levels, either via excessive consumption or idiopathic<sup>16</sup>, has also been implicated and this was explained by the competition for binding sites with zinc during the absorption process. Prolonged parenteral or enteral feeding without copper supplement and use of copper chelating agents are other well known causes.

Primary Sjögren’s syndrome, a systemic autoimmune disease, can have a wide variety of neuropathic manifestation, with peripheral neuropathy being its major neurological manifestation. The sensory ataxic form of Sjögren’s syndrome was found by Malinow et al<sup>17</sup> to have dorsal root ganglionitis with degeneration of dorsal root ganglion neurons and mononuclear cell infiltration. A large series of Sjögren’s syndrome associated neuropathy reviewed by Mori et al, demonstrated 25% of patients with ataxic sensory neuropathy and 17% of patients with painful neuropathy had T2 hyperintensities in the dorsal columns on MRI<sup>18</sup>. In our patient, nerve conduction studies did not support the presence of a sensory ganglioneuropathy. Hence in retrospect, Sjögren’s syndrome is unlikely to be the cause for patient’s symptoms.

Nitrous oxide toxicity is also another known cause of dorsal columns signal abnormality<sup>19,20</sup>. This entity had been described in cases of health care abuse of nitrous oxide and occupational



**Figure 2:** Follow-up Spinal MRI after copper replacement therapy. A & B: Near complete resolution of abnormal signal in the dorsal columns of the cervical cord. Axial image is acquired at C4 level.

exposure in others<sup>21,22</sup>. In patients with borderline vitamin B<sub>12</sub> deficiency, a recent exposure to nitrous oxide (for anesthetic purpose), have been shown to induce this phenomenon.

Imaging features in myelopathic patients secondary to hypocupremia is primarily dorsal columns and occasionally lateral columns hyperintense T2 signal abnormality on MRI without enhancement. Lateral column signal abnormality had not been described in Sjögren's syndrome, however lateral columns involvement in vitamin B<sub>12</sub> deficiency have been reported<sup>23</sup>. Lateral and dorsal columns involvement and partial resolution of signal abnormality in our patient following copper supplementation favors hypocupremia as the primary culprit. However, Sjögren's syndrome may still play a role.

Given its similarity to subacute combined degeneration secondary to vitamin B<sub>12</sub>, a number of the patients described in case reports were treated with vitamin B<sub>12</sub> supplements, even in the setting of normal vitamin B<sub>12</sub> levels<sup>10</sup>. These patients not only had a lack of response but progressive deterioration as seen in our patient. Vitamin B<sub>12</sub> and copper deficiency may also co-exist<sup>9</sup>, prolonging the time to diagnosis. Unlike vitamin B<sub>12</sub> deficiency, the myelopathic symptoms due to hypocupremia often remain stable despite treatment. Very rarely, partial clinical recovery can occur with treatment but complete recovery remains to be seen. Clinical and imaging finding reversibility is very variable. In a case where mild improvement was observed after both oral and IV supplement of copper, no cord abnormality was found on imaging<sup>24</sup>. Our case, despite near complete

recovery of cord signal abnormality in the dorsal columns, did not translate to neurological improvement. In the only other documented case of cord signal improvement, partial neurological improvement was observed<sup>25</sup>.

Dorsal and lateral columns signal abnormality accompanying myelopathic symptoms has been shown to have a wide differential diagnosis. In a few reported cases of hypocupremia, partial neurological recovery has been documented. However most of these were likely treated early prior to permanent neuronal damage. Hence, it is vital for this entity to be known and to be included in the differential diagnosis of MRI dorsal and lateral columns cord lesions to expedite diagnosis and treatment.

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