



# Two cases of polyneuropathy, microcytic anemia and copper deficiency after prolonged allopurinol treatment

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**ABSTRACT** – Copper is a cofactor for numerous coenzymes and metalloproteins essential for normal neurologic function. The most common neurological presentations of copper deficiency are myelopathy, polyneuropathy and optic neuropathy. Here we present two cases of sensorimotor polyneuropathy, copper deficiency and microcytic anemia in conjunction with allopurinol management for gout. These two patients presented with a clinical description similar to that of chronic idiopathic axonal polyneuropathy. It would be advisable to determine the levels of trace elements in patients with polyneuropathy of unknown cause. We believe that further studies are necessary in order to gain better understanding of the role of copper serum levels in the development of sensorimotor polyneuropathy.

**Key words:** allopurinol, copper deficiency, polyneuropathy.

## INTRODUCTION

Copper is a trace element essential for proper functioning of all living organisms. Common etiologies of copper deficiency include dietary inadequacy, Menkes disease, previous upper gastrointestinal surgery, zinc overload from denture cream or zinc supplements, malabsorption, and drug-induced deficiency (1). The most common neurological presentations are myelopathy, neuropathy and optic neuropathy (2). Allopurinol, considered to be the prototypical xanthine oxidase inhibitor, continues to be the basis of the clinical management of

hyperuricemia. Although there are a few articles describing allopurinol-induced neuropathy (3-5), there have been no studies published on copper deficiency and microcytic anemia in the presence of allopurinol-induced neuropathy.

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## CASE REPORTS

Two patients were admitted to the Department of Neurology with almost identical symptoms and laboratory results. Patient 1, a 57-year-old male, was admitted due to chronic paresthesia and numbness in his feet that he described as a 'pins-and-needles' sensation. Patient 2, a 68-year-old female, was admitted due to gait disturbance and paresthesia in her extremities. Upon clinical neurological examination, disturbance in touch, vibration, pain, and temperature sensation was observed in both patients. While patient 2 had absent triceps reflexes and attenuated quadriceps reflexes (1+), patient 1 had bilaterally attenuated triceps reflexes.

Nerve conduction studies (NCS) showed significantly decreased compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) amplitudes in all nerves with mild reduction in conduction velocity of sensory and motor fibers of nerves in the legs. Motor unit recruitment in electromyography (EMG) indicated distal symmetrical neurogenic pathology with no spontaneous activity. Quantitative sensory testing (QST) showed moderate and significant elevations of the threshold for pain, cold, heat and vibration as a possible sign of C, A delta and A beta fiber affection. According to EMG, NCS and QST, the diagnosis of sensorimotor polyneuropathy with predominant axonal damage was established in both patients.

Routine laboratory tests showed microcytic anemia with normal iron and serum ferritin levels, but with a decrease in copper levels (2  $\mu\text{mol/L}$  in patient 1 and 4  $\mu\text{mol/L}$  in patient 2; NV: 12-25). The mean corpuscular volume (MCV) was decreased in both patients (72 fL in patient 1 and 75 fL in patient 2; NV: 86-98 fL), hemoglobin value (Hb) was 107 g/L in patient 1 and 110 g/L in patient 2 (NV: women 120-155 g/L, NV: men 135-165 g/L). All laboratory results important for polyneuropathy evaluation were normal in both patients: HbA1c, homocysteine, vitamin B12, folic acid, vitamin E, iron, lead, zinc, anti Hu, Yo, Ri antibodies, paraneoplastic markers, antiganglioside antibodies, erythrocyte sedimentation rate, lipids, immunological parameters, urine and serum proteins analyses. Molecular genetic analysis of PMP 22 (peripheral myelin protein) deletion and mutation was negative. Serologic analyses for cytomegalovirus, herpes viruses, Epstein-Barr virus, varicella zoster virus, hepatitis B and C viruses showed no signs of recent infection. Serologic analyses for *Borrelia burgdorferi* were negative. Our patients

did not have any phenotypic markers of Menkes disease, while ceruloplasmin plasma levels and electrophoresis of hemoglobin were normal. The findings of cerebrospinal fluid (CSF) analyses were normal. CSF analysis was performed in order to exclude sensorimotor type of chronic inflammatory demyelinating polyneuropathy (CIDP). Magnetic resonance imaging of the brain and cervical and thoracic medulla showed no alterations.

Both patients were continuously monitored for gout. Patient 1 had a 10-year history of the disease and was maintained on a regimen of allopurinol (600 mg daily). Patient 2 was monitored for 6 years on a 400 mg daily dose of allopurinol. Patient 1 had a five-year history of neuropathy signs and patient 2 had a two-year history of neuropathy. Signs of neuropathy were present in both patients after the introduction of allopurinol.

Following the diagnosis of copper deficiency, both patients were further treated over a period of two and four years, respectively, and mild gradual improvement of neurological symptoms (paresthesia, numbness, and gait disturbance) was noted after continuous copper administration (2 mg *per day*). Copper levels were checked in both patients every three months. In patient 1, the level of copper normalized after 3 months and in patient 2 after 6 months of supplementation therapy. Follow up EMG and NCS were performed but no significant improvement was detected. It is not expected to find impressive improvement in electroneurographic parameters in axonal polyneuropathies because the reduction of CMAP and SNAP amplitude is usually the consequence of irreversible axonal damage. In both patients, we found moderate improvement in QST, especially in vibration sense, as a possible indicator of A beta fiber functional improvement. The dose of allopurinol was not changed during the period of copper supplementation and uric acid levels were normal. MCV and Hb values normalized in both patients during copper supplementation.

A written informed consent was obtained from the patients for publication of this case report.

## DISCUSSION

Here we present for the first time two cases of sensorimotor polyneuropathy, copper deficiency and microcytic anemia in conjunction with allopurinol management for gout. These two patients presented with a clinical description similar to that of chronic idiopathic axonal polyneuropathy (CIAP)

(6). CIAP typically manifests in the sixth decade of life and is characterized by a normally symmetrical and insidious onset of mainly sensorimotor (or purely sensory) dysfunction in the legs (7). CIAP tends to progress slowly and will never lead to severe disability.

Several studies have attempted to demonstrate an association between dyslipidemia and impaired glucose tolerance with the signs and symptoms of CIAP. Other factors (alcohol, autoantibodies to axonal antigens, and family history) have also been found to potentially contribute to the development of neuropathy (6). However, all of these potential contributors were absent in our patients. A decreased concentration of serum copper was documented. Furthermore, both patients were on allopurinol treatment for their gout.

Copper is a cofactor for numerous coenzymes and metalloproteins essential for normal neurologic function. Copper levels normalize with replacement therapy but neurologic recovery may be incomplete or absent if treatment is delayed (8). Copper deficiency is an under-recognized cause of reversible leukopenia and refractory anemia that is unresponsive to iron therapy, sometimes found with hypoferrremia, and often misdiagnosed as myelodysplastic syndrome (9). Copper acts as a ligand to ferroxidase II, which oxidizes iron, allowing it to be mobilized and transported from hepatic stores to the bone marrow for use in erythropoiesis.

Experimental studies have demonstrated that oxidative stress induces damage to the peripheral nervous system (10). Singer *et al.* have proposed a connection between elevated levels of reactive oxygen species (ROS) and the underwhelming response of cellular antioxidant systems, suggesting that increased ROS damages peripheral nerves while interfering with injury repair (11). Indeed, we can conclude that low levels of Cu and Zn-SOD contribute to the lack of proper antioxidant response in copper deficiency states.

Allopurinol directly decreases the production of uric acid by inhibiting the enzyme xanthine oxidase, and is thus very effective in the prophylactic treatment of gout. Further benefits are the reduction of superoxide anions and other ROS (12).

Only one study attempting to explain the possible connection between the administration of allopurinol and copper deficiency or CIAP has been published. Fields *et al.* fed rats a high-fructose diet inducing hyperuricemia and hyperuricosuria. An overload of uric acid causes an increase in the activity of xanthine oxidase, which catalyzes the oxida-

tion of hypoxanthine and xanthine to uric acid and, in the process, generates ROS (13). Hyperuricemia causes a reduction in the activity of GSH-Px (glutathione peroxidase) and, combined with copper deficiency, causes greater reduction in GSH-Px (14). However, these effects are meant to be ameliorated with the administration of allopurinol, thus allowing us to conclude either that allopurinol has no contributive effect on the symptoms displayed by our patients, or that the gout was not fully controlled. Our patients' polyneuropathic symptoms improved upon the administration of copper. Additional studies are needed to understand the pathophysiology of CIAP in relation to copper deficiency and increased oxidative stress. We could not say with any degree of certainty whether the neuropathy cases presented are the result of long-term allopurinol treatment or consequent copper deficiency.

## CONCLUSION

This case report illustrates the importance of comorbidity of other chronic diseases in patients with diagnosed CIAP. Before making the diagnosis of CIAP, it is important to analyze the possible pathophysiological mechanisms shared with other chronic diseases but also the possible influence of various drugs and therapeutic procedures which may have negative influence on peripheral nerves. The pathophysiology of copper deficiency (or a deficiency of other trace elements) has an important role in the processes of neurodegeneration. It would be advisable to determine the levels of trace elements in patients with polyneuropathy of unknown cause. We believe that further studies are necessary in order to gain better understanding of the role of copper serum levels in the development of sensorimotor polyneuropathy.

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## Dva slučaja polineuropatije, mikrocitne anemije i nedostatka bakra nakon produljene terapije alopurinolom

**SAŽETAK** - Bakar je dodatni faktor za brojne koenzime i metaloproteine koji su bitni za neurološku funkciju. Najčešće neurološke slike pomanjkanja bakra su mijelopatija, polineuropatija, manjak bakra i mikrocitna anemija povezano s liječenjem alopurinolom zbog gušavosti. Ova dva bolesnika su se očitovale kliničkom slikom sličnom onoj kronične idiopatske aksonalne polineuropatije. Bolesnicima s polineuropatijom nepoznatog uzroka trebalo bi savjetovati određivanje razina elemenata u tragovima. Smatramo da su potrebna daljnja istraživanja u cilju boljeg razumijevanja uloge razina serumskog bakra u razvoju senzomotorne polineuropatije.

**Ključne riječi:** alopurinol, nedostatak bakra, polineuropatija