Zinc-containing denture adhesive: a potential source of excess zinc resulting in copper deficiency myelopathy

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IN BRIEF

- Hyperzincaemia has been identified as a cause of copper deficiency which can result in anaemia and irreversible myelopathy.
- There are now a number of case reports of copper deficiency myelopathy secondary to overuse of zinc-containing denture adhesive.
- Even with copper supplementation, neurological damage due to copper deficiency may be permanent and so early detection and patient education is vital.

PRACTICE

VERIFIABLE CPD PAPER

Copper deficiency in humans can result in both anaemia and neurological symptoms affecting walking and balance. Recently zinc excess due to overuse of zinc-containing denture adhesive has been recognised as a potential cause of copper deficiency. Recovery from neurological symptoms with replacement therapy appears to be limited and so emphasis falls on education and early detection. Dentists are well placed to educate patients on use of denture adhesives and to detect early signs of copper deficiency in patients who may be using zinc-containing denture adhesive to excess. A case of a 58-year-old man diagnosed with copper deficiency myelopathy possibly due to zinc-containing denture cream overuse is presented.

INTRODUCTION

Overuse of zinc-containing denture adhesive has recently been associated with a combination of anaemia and spinal cord damage, resulting in severe neurological impairment.[1,2] As this condition is preventable but largely untreatable, dentists are well placed to detect denture adhesive overuse in patients with neurological symptoms and anaemia, and prompt further investigation.

CASE REPORT

A 58-year-old man presented to his general practitioner (GP) in May 2008 with a four-month history of progressive difficulty with balance and walking. At presentation he was able to walk with the aid of a stick and support from his wife. His GP referred him to hospital for investigation but he discharged himself almost immediately, later admitting a dislike for hospitals and doctors.

Blood taken by his GP showed a macrocytic anaemia (haemoglobin 9.3 g/dL, mean cell volume 110 fL) and leucopenia (white blood count 2.5 × 10^9/L), specifically a severe neutropenia (0.32 × 10^9/L). Further blood tests showed low folate and high ferritin levels. Vitamin B12 was normal. The patient admitted drinking alcohol to excess since retiring in 2001 and as chronic alcoholic liver damage is known to increase the release of vitamin B12-binding protein, it was suspected that this was masking a vitamin B12 deficiency.

Vitamin B12 is necessary for cell replication and is involved in myelin synthesis[3] and so a deficiency would explain the patient's anaemia as well as his neurological symptoms. Liver function tests were normal; however, bone marrow microscopy showed changes in keeping with a metabolic cause, hence vitamin B12 and folate supplementation were commenced in August 2008. At this stage the patient was wheelchair-bound.

Initially, the patient did report a subsequent improvement in his symptoms; however, he suddenly deteriorated a month later when he developed a urinary tract infection (*Escherichia coli*) with severe complications, followed by pneumonia (*Streptococcus pneumoniae*). At the peak of his illness he was bed-bound, unable to move his arms or legs, and had paraesthesia over his hands and feet. He was extensively investigated primarily for underlying malignancy but all investigations were normal. He gradually began to improve on antibiotic therapy.

By mid-November he had improved significantly and was able to stand with the help of two physiotherapists. Neurological examination found normal cognition and normal cranial nerve examination. However, brisk reflexes were elicited in the arms and at the knee, as well as bilateral extensor planter responses, and power in the lower limbs was greatly reduced. There was also sensory impairment, namely reduced vibration sensation and proprioception in his hands and legs. On magnetic resonance imaging (MRI), his spinal cord showed no abnormal changes. While undergoing neurological rehabilitation, the patient developed methicillin-resistant *Staphylococcus aureus* (MRSA) infection with liver and paracolic abscesses and septicaemia. As a result, he was too ill to attend several neurology outpatient appointments and was only reviewed in the neurology clinic eight months later.

At this point his neurological signs had progressed. He was wheelchair-bound and had a spastic paraplegia with loss of all sensory modalities up to the T10 dermatome. In other words he had features of spinal cord damage (myelopathy). He was on folate and iron supplementation, paracetamol and a sleeping tablet. Vitamin B12 had been discontinued during his stay in the rehabilitation ward. He reported significantly reducing his alcohol intake since his admission in 2008 and he had

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no notable family or past medical history. The patient denied any history of anaemia or neurological symptoms. In fact before May 2008 the patient reported having never visited his doctor and described a very good pre-morbid fitness.

Further investigations – MRI brain scan, urea and electrolytes, liver function tests, lactate dehydrogenase, protein electrophoresis, thyroid function tests and magnesium, calcium and phosphate levels – showed no abnormalities. Several tests for a range of infections, auto-antibodies and genetic disorders known to cause myelopathy were negative. Cerebrospinal fluid analysis yielded a protein level twice the upper range of normal (caused by spinal cord degeneration) but no abnormal cells and normal cytology. Plasma viscosity and vitamin B12 levels were raised, together with a mild anaemia. Finally, his serum copper level was markedly reduced at 2.0 µmol/L (normal: 10-22 µmol/L). As extensive investigation had excluded both compressive and inflammatory causes of myelopathy and the patient did not have vitamin B12 deficiency, he was therefore diagnosed with copper deficiency myelopathy.

THE ROLE OF COPPER IN HUMANS

We do not require a high serum copper level for it to carry out its physiological role. The tolerable upper intake level (ULa) is only 10 mg per day.[4] Hence copper is most often associated with toxicity due to copper in the environment, or due to a genetic impairment of copper metabolism in Wilson's disease. However, there have been a number of recent reports of copper deficiency myelopathy and anaemia.[1,5,6] These have highlighted the critical role of copper in a wide range of physiological processes from ATP production and cell maintenance to erythropoeisis and myelin synthesis.[1,3,4,7] Neutropenia, anaemia and neurological symptoms seem to be the most common manifestations of copper deficiency[1,8,9] and perhaps reflect the higher metabolic activity of the nervous system and bone marrow.

Typically copper deficiency occurs following gastric bypass or in malabsorption syndromes.[5,6,9] Malnourishment and glomerulonephritis causing overexcretion of copper in the urine have also been noted to cause copper deficiency.[1,7,8] Menkes syndrome or 'kinky hair syndrome' is an X-linked recessive inherited disorder which prevents copper being taken up by cells, however this presents in very early childhood.[10]

Our patient had no history of malabsorption nor gastrointestinal surgery, and he had a normal diet. However, his serum zinc level was 33.2 µmol/l (normal: 12-18 µmol/l). Zinc excess is recognised as a cause of copper deficiency.

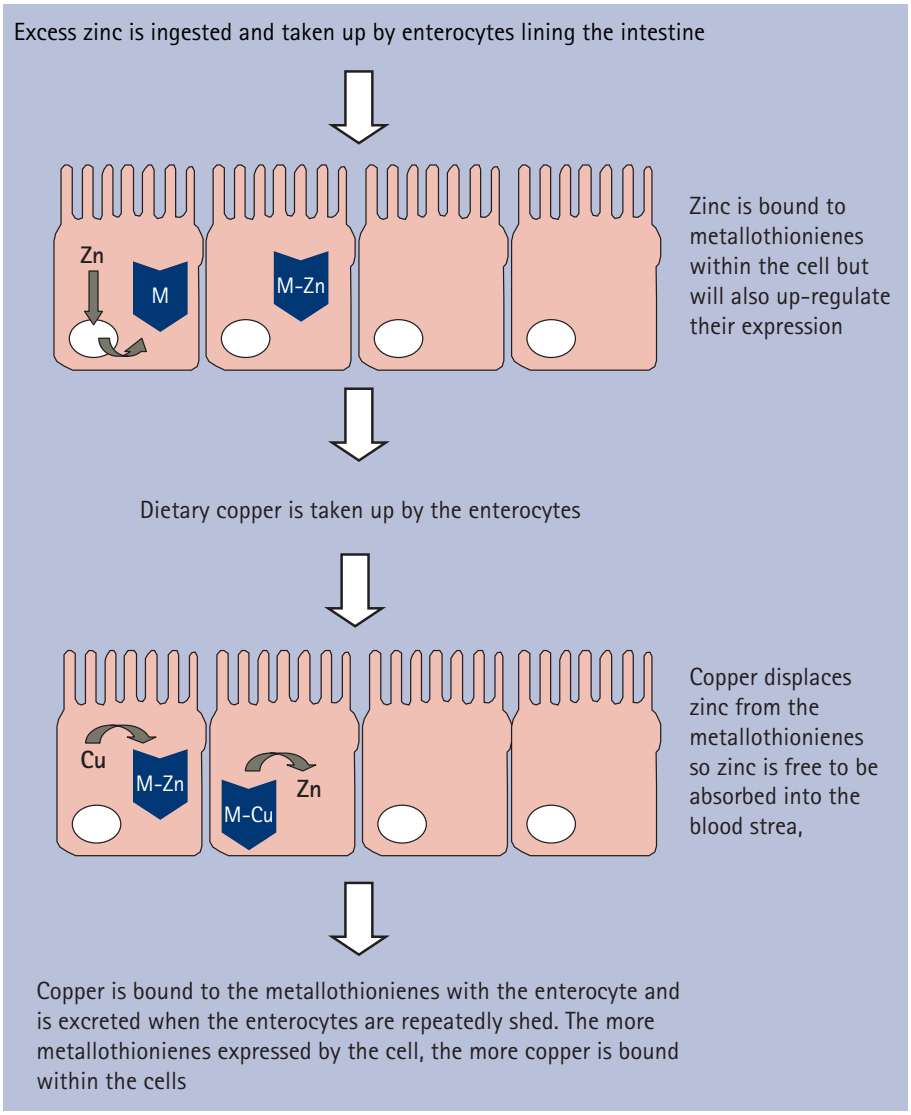

Fig. 1 The process by which zinc excess can result in copper deficiency

How does zinc excess result in copper deficiency?

It has been postulated that zinc upregulates metallothionein expression in the enterocytes lining the intestines. These metallothioneins are intracellular ligands which bind to a range of metals and prevent their absorption into the bloodstream. This protects us from metal toxicity. They have a greater affinity to copper than zinc and so copper will displace and replace zinc bound to the metallothioneins in the enterocytes. Zinc excess will increase the number of metallothioneins available and hence increase the amount of copper bound within the enterocytes. The copper cannot be absorbed into the bloodstream but is shed and excreted with the enterocytes and copper deficiency results (Fig. 1).[1,11]

Zinc excess can occur with parenteral feeding,[1] use of supplements[6,11] and accidental ingestion of zinc-containing denture adhesive.[1,2] Our patient reported using dentures for the past seven to eight years and in the past four years had noticed a deterioration in the fit of the dentures. He admitted to using three 40 g tubes of zinc-containing denture adhesives per week, a selection of which were found to contain 17-34 mg of zinc per gram.[2] Although the patient did admit to swallowing some of

the denture adhesive, the exact amount of zinc ingested could not be calculated nor could the amount of zinc absorbed in the small intestine as this can vary with zinc status.[4] However, in a week the patient was exposing himself to 2,040-4,080 mg of zinc. It is therefore feasible to propose that the patient could have been ingesting more than the 11 mg daily zinc allowance recommended by the National Institutes of Health (8 mg for women)[12] and perhaps even exceeding the tolerable upper intake level (ULa) of 40 mg per day.[4] Questioning on possible occupational exposure or use of vitamin supplements yielded no other possible source of the zinc.

He was advised to immediately change to a zinc-free denture adhesive and was started on copper supplementation. On review in November 2009 his symptoms, particularly sensory symptoms, had improved slightly, but he was still wheelchair-bound and catheterised and had very little power in his legs. In January 2011 the patient was still using a wheelchair and required a hoist at home. However, he reported an improvement in his weight and well-being and he had not suffered any new complication, specifically no new infection, since commencement of copper therapy.

SUMMARY

Our patient presented with copper deficiency myelopathy probably caused by excessive use of zinc-containing denture adhesive. Copper deficiency myelopathy has been recognised in animals as 'swayback' for many years,[6] but has only recently been recognised in humans, and even more recently the role of zinc containing adhesives has been described in several case reports.[1,2] While evidence remains at case report level and without being able to exactly determine the amount of ingested denture adhesive/absorbed zinc, the relationship between copper deficient myelopathy and zinc-containing denture adhesive remains a hypothesis. However, our patient's zinc levels improved on cessation of zinc-containing denture cream and extensive investigation ruled out other possible sources.

Considering the widespread use of denture cream across the world, the development of severe myelopathy does appear to be a rare occurrence. It is unclear whether there are predisposing factors in some patients. Some manufacturers have halted the production of zinc-containing adhesives;[13] however, clinicians still need to be aware of the condition, particularly in patients who present with clinical features of vitamin B12 deficiency but have normal vitamin B12 levels or do not respond to therapy.

There is very limited follow-up data available regarding the efficacy of copper replacement in patients with copper deficiency myelopathy, but available data suggest that while haematological symptoms may improve, neurological recovery is limited.[1,2,8,11] Prevention is therefore essential and dentists have an important role in educating patients about denture adhesive use. Dentists are well placed to identify patients who may be using zinc-containing denture adhesives to excess and who have anaemia or neurological symptoms affecting balance and walking. These patients should be referred for further investigation for early detection of zinc excess and copper deficiency before irreversible damage occurs.

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Erratum

CPD questions (*BDJ* 2011; **210:** 382)

CPD Article 1 – The effect of disposable infection control barriers and physical damage on the power output of light curing units and light curing tips

Question 1 should have read as follows:
What proportion of LCUs were affected by the long-term adherence of composite resin/bonding agent to the light tips?

A correction notice was placed on the BDJ Eastman CPD website as soon as the incorrect wording of this question was noticed.

We apologise for any inconvenience caused.