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Zinc containing dental fixative causing copper deficiency myelopathy

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Summary

A 62 year old male, previously well, was referred to the neurology clinic following 6-months history of worsening lower limbs instability, parasthesia, pain and weakness rendering him housebound. Examination revealed upper motor neuron pattern of weakness of the lower limbs and loss of proprioception. Serum analysis revealed reduced caeruloplasmin and copper levels with raised zinc. Spinal imaging revealed subtle dorsal column intensity changes in from C2-C7, confirmed with 3T MRI. A copper deficiency myeloneuropathy was diagnosed secondary to chronic use of a zinc-containing dental fixative paste. The paste was discontinued and a copper supplementation was started. Resolution of symptoms was not achieved with intensive physiotherapy. The patient remains wheelchair bound though progression of symptoms has halted. Prompt recognition and treatment of hyperzincaemia induced hypocupraemia earlier in the disease course may have prevented any irreversible neurological deficit.

Background

Copper deficiency myelopathy (CDM) is a progressive myelopathy where prompt recognition and treatment is the only intervention to prevent often irreversible neurological deficit (1-4). Hypocupraemia is associated with a myelopathy similar clinically and radiologically to B12 deficiency. (1) The condition causes progressive lower limb spasticity and also proprioceptive and fine-touch sensory loss corresponding to a myelopathy of the dorsal spinal cord. Diagnosis is confirmed with demonstration of low serum copper and T2-weighted MRI of the spinal cord showing dorsal column hyperintensity (5, 6). Previous reports highlighted the association between CDM and hyperzincaemia (6-8). The condition is managed by removal of the excess zinc and copper supplementation. Importantly, irreversible neurological symptoms may occur if diagnosis is delayed. Clinicians suspecting a dorsal column syndrome, should also consider testing for hypocupraemia.

Case Presentation

A 62-year old male reported sensory loss, imbalance and weakness affecting his lower limbs. Over 6-months period, he had progressed from walking independently to using one walking stick and now being housebound. He also reported mild tingling sensation in his hands but with normal power. He is a lifelong smoker of 10-20 cigarettes per day, with minimal alcohol use. He previously worked as a mechanic, which he stopped 14-months prior to the clinic. He has medical history of peripheral arterial disease and recent treatment for folate deficiency anaemia. Regular medications were

aspirin, ramipril, simvastatin and also folic acid, which had been taken at 5mg once-daily for 1-month. Over the counter medications included Fixodent® regular dental fixative for over 15-years with irregular use of 1-4 tubes per week and admitted to ill-fitting dentures. He has a family history of cardiovascular disease. On systematic review, he reported recent weight loss (approx. 6kg) without change in appetite. No other symptoms reported.

Examination revealed lower limb clonus (5 beats) that was equal bilaterally and a loss of full-power against resistance in all areas of both lower limbs, and in the upper limbs at right elbow flexion and extension. Reflexes were reduced in the upper-limbs but markedly increased in the lower limbs with upgoing plantar reflexes bilaterally. Vibration and joint-position sense were lost to the hip on the right and the knee on the left. The patient was unable to mobilise or to perform heel-shin movement. He was noted to have dentures, and regularly used dental fixative paste.

Investigations

1.5T MRI of the cervicothoracic spine showed multi-level mild degenerative changes without cord compression. There were subtle, linear, hyperintensity T2 signals along the dorsal column between C3-C7 (Figure 1). Routine serum result showed a mild normocytic anaemia (Hb 113 g/L). The following serum results were normal: random glucose, HbA1c, ESR, thyroid function tests, lipid, vitamin A, protein electrophoresis, ferritin, B12 and folate. His serum was also negative for HIV, Hepatitis B and C, and syphilis. Serum copper was found to be reduced at 6.4 µmol/L (10-22 µmol/L), caeruloplasmin was also low at 0.14 g/L (0.16-0.47g/dl) and vitamin E was also reduced at 12 µmol/L (15-45µmol/L), with zinc levels raised at 20.3 µmol/L (11-18µmol/L). Furthermore, a 24-hour urinary collection showed raised zinc at 30.3 µmol/24-hours (3.0 - 19.0 umol/24h), though urinary copper levels in this time period were normal.

Differential Diagnosis

In the absence of multiple aetiologies, progressive upper motor neuron signs with a sensory ataxia localises the pathology to the dorsal spinal cord where the gracile and cuneate fasciculi and lateral corticospinal tract lie. Vitamin B12 deficiency, cervical myelopathy and infective causes (syphilis, HIV, Hepatitis C) should all be considered but have been ruled out in this case (9). Serum B12 deficiency as measured in clinical practice may not reflect true cellular B12 concentrations and polymorphisms affecting cellular transport proteins may cause variations in cellular B12 levels (10), though the physiological relevance of this remains questionable. Hypocupraemia has been associated with hypercholesterolaemia and cardiac arrhythmia (11), however the lack of these features in our case, the temporal onset of symptoms and MRI findings make a vascular cause unlikely.

Once hypocupraemia has been identified and corresponding imaging changes found, the known causes are limited to gastric resection, malabsorption and hyperzincaemia (2) of which the latter is the most plausible explanation in our case. A supportive feature for this diagnosis is unexplained anaemia, which is a recognised consequence of hypocupraemia (4, 6). Other reported manifestations of hypocupraemia such as dyslipidaemia, impaired glucose tolerance, iron deficiency and optic atrophy were not present though formal visual field testing and optical coherence

tomography were not undertaken given the lack of visual symptoms (12). Rarely, hypocupraemia can present with motor neurone disease or peripheral neuropathy in the absence of myelopathy (7), though given evidence of myelopathy on MRI we did not perform electrophysiological studies. We recognise a low vitamin E concentration in our case, which is known to have adverse effects when severely low from genetic defects or malabsorption syndromes and can present with ataxia and peripheral neuropathy (13, 14), however mild vitamin E deficiency is common in adulthood and unlikely to be relevant to our current presentation.

Treatment, Outcome and Follow-up

Withholding the zinc containing dental fixative and short-term copper replacement resulted in prompt normalisation of zinc and copper levels and haemoglobin concentration. The patient reported a gradual reduction in the sensation of tingling and numbness. He also reported subjective improvement of joint-position sense. Intensive goal-directed therapy to enable the patient to walk with aids has been performed with progression to independent transfers, though the gentleman remains largely wheelchair bound. Physiotherapy is to continue, with occupational therapy input and neurology follow-up as an outpatient.

Discussion

Copper is a trace element that is absorbed in the upper gastrointestinal tract. It is essential for several enzymes maintaining the structure and function of the bone marrow and nervous system (4, 6). Low copper has been associated with multiple neurological presentations including motor neuron disease, cerebral demyelination, cognitive dysfunction, optic neuropathy, myopathy and peripheral neuropathy (4). Primary deficiency is rare but secondary deficiency has long been recognised to be a result of malabsorption (e.g. coeliac disease) or as the consequence of upper gastrointestinal surgery, where it is known to cause anaemia and other cytopenias (4, 6). Patients with CDM typically present with gait difficulties from a sensory ataxia and spasticity, with examination showing a spastic paraparesis or tetraparesis (1, 4). The clinical syndrome of CDM is similar to that seen in B12 deficiency. The diagnosis of CDM is confirmed with low serum copper and caeruloplasmin levels, and characteristic high signal T2-weighted changes in the dorsal columns of the spinal cord, typically at cervicothoracic levels (4-6). However, it should be noted that not all individuals show typical or any neuroimaging appearances (5).

Gastrointestinal malabsorption is a common cause of CDM. Other cause includes hypocupraemia induced CDM secondary to excess serum zinc (3, 4, 6-8, 15). The prevalence of patients with CDM, of whom have high serum zinc level, varies from 16% to 75% (2, 4, 6). Zinc upregulates the enzymes in enterocytes that have a high-affinity for copper, resulting in copper deposition and excretion. This resulted in serum copper deficiency (4, 16). Sources for excess zinc may include diet, over the counter multi-vitamins and diasylates.

Hypocupraemia is managed with copper supplementation (4, 6). Prevention of long periods of hypocupraemia may be achieved by screening those at risk, such those who have undergone bariatric surgery, those on enteral feeds or with Menkes syndrome (a rare, X-linked disorder of

copper metabolism) (2, 4, 6). Where possible, as in our case, removal of the cause for excess zinc with the substitution of dental fixative and supplementation of dietary copper results in normalisation of serum zinc and copper levels (4, 6, 7, 17). In the present case we suspect an increasing use of dental fixative to accommodate ill-fitting dentures, which were replaced following diagnosis of hypocupraemia. The gentleman had used a brand of dental fixative containing ~17mg/g zinc (Nations et al, 2008) with product instructions contained within each packet to not exceed once-daily application of 1.25g per day, advice that each tube should last ~4-weeks, advice not to use excess product for poorly fitting dentures and to consult a doctor if using other zinc containing products. With use of the adhesive 2-4 times a day resulting in consumption of 1-2 tubes per week the patient had exceeded recommended use by ~4-8 times. Currently in the UK both zinc-containing and zinc-free dental fixative is available.

Patients with treated CDM showed variable rates of neurological recovery, with the most common outcome being the cessation of progression (4, 6, 7). The degree of neurological improvement is uncertain (2, 3, 6, 7, 18). Given the high morbidity of CDM, prompt recognition and management of patients affected by the condition seems the best recourse. Clinicians should be mindful of risk-factors for copper deficiency, e.g. potential malabsorption or routine use of zinc containing products. In patients with progressive sensory ataxia and spasticity, investigations should include appropriate MRI imaging of the spinal cord and serum copper studies, in the absence of a clear alternative diagnosis. The presence of anaemia or cytopenia may point towards hypocupraemia.

Learning Points

- (1) Hypocupraemia should be considered in patients at-risk of malabsorption and those at risk of excess zinc intake, especially in the presence of anaemia or cytopenia.
- (2) When assessing a patient with suspected dorsal column dysfunction, i.e. when testing vitamin B12 levels, consideration should be given to serum copper and zinc testing.
- (3) Prompt recognition and treatment of copper deficiency myelopathy prevents progressive and likely irreversible neurological dysfunction.

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