Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin II. The denture cream is a primary source of excessive zinc

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ABSTRACT

Neurodegeneration of the central and peripheral nervous system associated with hypocupremia and hyperzincinemia has been widely recognized but the origin of high zinc remained unknown. Denture cream has been recently suggested as one possible source of zinc, but the frequency with which denture fixative alone accounts for this syndrome is unknown. We analyzed the origin of excessive zinc in eleven patients with a progressive myelopolyneuropathy and unexplained hypocupremia with hyperzincemia. These patients had a detailed clinical assessment, determination of zinc and copper levels, and analyzed use of denture cream with the estimates of daily zinc exposure. We identified denture cream as a source of excessive zinc in 100% patients in our cohort. They all had a history of ill-fitting dentures requiring large amounts of denture cream, resulting in significant zinc exposure. Their copper and zinc normalized after stopping denture cream, further confirming that this is the source of high zinc. Inappropriate use of denture cream appears to be the sole source of excessive zinc in these patients.

1. Methods

Plasma and urine copper and zinc levels were obtained through the clinical laboratories used for the clinical care. We estimated the
amount of daily zinc exposure by asking the patient the approximate amount of cream needed per day for a typical application and the most commonly used brand of denture cream. We used the zinc concentration values reported by Nations et al. (Nations et al., 2008). If patients used both major brands (Poli-Grip and Fixodent), we used the brand with lower zinc concentration (Fixodent) for conservative estimates of daily zinc exposures. We then multiplied the reported intake (in estimated grams) times the zinc concentration to determine the daily zinc intake. Patients were also screened for other possible causes, including plasma vitamin B12 and vitamin E levels, plasma protein electrophoresis, and serologic testing for Lyme disease, HTLV1 and HIV.

2. Results

We identified eleven patients with previously unexplained hyperzincinemia and copper deficiency. Demographic and clinical data is summarized in the Table 1; subject #9 was previously reported (Hedera et al., 2003). Clinical features were quite uniform. Every patient reported numbness and paresthesia affecting the lower extremities as the initial symptom with a rapid progression to the upper extremities, and loss of balance. Neurologic examination showed deficits involving motor-sensory polyneuropathy and myelopathy (corticospinal tract and dorsal columns). Bone marrow suppression was evident in all subjects (pancytopenia in 9 subjects; isolated normocytic anemia in 2 subjects). Neuroimaging studies encompassing the whole neuroaxis were unremarkable with the exception of two patients. Patient #1 had abnormal signal on T2-weighted images confined to the region of dorsal columns in the cervical segments C1 through C5 with normal brain MRI; and patient #5 who had signs of centrum semiovale demyelination; his cerebrospinal fluid analysis did not show any signs of inflammation or intrathecal production of immunoglobulins. Copper oral supplementation with a typical dose of 6 mg of copper/day (range 2–8 mg/day) resulted in improved copper levels in compliant patients. Only patient #4 required subcutaneous supplementation with 2 mg copper/day. All hematologic abnormalities resolved after copper supplementation, even though hyperzincinemia persisted. The degree of neurological improvement varied and is summarized in the Table 1.

We did not identify any obvious source of zinc at the time of initial diagnosis and previously known causes of hyperzincinemia, such as coin swallowing or an excessive intake of zinc supplements were ruled out. These individuals also did not have any relevant history of malabsorption or gastric surgeries with the exception of patient #8 who had a partial gastrectomy as a teenager. However, his copper and zinc abnormalities followed the same pattern as seen in other patients, arguing against the causative role of his gastric surgery. The same individual had also a 5-year history of taking zinc supplements containing approximately 230% of the US recommended daily allowances dose of zinc; this supplement also contained 1 mg of copper.

After the report of high zinc content in commonly used denture creams (Nations et al., 2008), we contacted all individuals and every patient reported a long-term use of dentures. Each subject described their dentures as poorly fitting and reported applying large amounts of the denture creams and often reported using dentures overnight. Estimated daily exposures and duration of the denture use are summarized in the Table 1. The patients were instructed to stop using denture cream and their copper and zinc values normalized. The shortest interval before the repeated laboratory evaluation was three weeks.

Additionally, marked reduction in hyperzincinemia was associated with patient-initiated reduction in the use of denture fixative. Patient #7 had a 5-year history of progressive sensory ataxia, lower extremity hyperreflexia, and painful dysesthesia and persistent hyperzincinemia, hypocupremia, and low serum ceruloplasmin. In the fall of 2008 she received a new pair of dentures which fit better and required much less use of denture adhesive. Urine zinc excretion prior to use of these new dentures (August 2008) measured 5032 μg/24 h and was markedly reduced (1295 μg/24 h, November 2008) after wearing new dentures and using less denture adhesive. Serum copper did not substantially change during this interval.

3. Discussion

Blocked copper absorption in the presence of increased zinc intake is a well-known phenomenon, resulting in the development of a negative copper balance (Brewer et al., 1977; Prasad et al., 1978; Hoffman et al., 1988; Broun et al., 1990; Gyoryfi and Chan, 1992). This is, for example, the principle of the FDA approved use of zinc for maintenance therapy of Wilson’s disease (Brewer et al., 1998; Brewer et al., 1999; Brewer, 2005). Long-term oral zinc therapy slowly removes accumulated copper and prevents the reaccumulation of copper, thereby protecting against further liver and brain damage (Brewer et al., 1998, 1999; Brewer, 2005; Brewer et al., 1987, 1985). However, an excessive zinc intake in non-Wilson’s disease patients also leads to copper deficiency, manifesting as a combined degeneration of the spinal cord, neuropathy and bone marrow suppression (Hedera et al., 2003; Prodan et al., 2002; Kumar et al., 2004a; Greenberg and Brienm Berg, 2004; Kumar et al., 2004b; Schleper and Stuerenburg, 2001; Kumar, 2006; Kumar et al., 2003b).

The obscure source of excessive zinc in several reported patients with a copper deficiency (human swayback disease) has been a problem for the medical community, because these patients typically suffer from a devastating neurological condition with a severe functional deficit. Furthermore, many patients only partially improved neurologically on copper supplementation in spite of relatively early recognition of the problem.

Detection of high zinc content in common brands of denture creams identified a possible source of excessive zinc intake (Nations et al., 2008). However, the frequency of the use of denture cream as the basis for a copper deficiency associated with severe neurologic and hematologic abnormalities was unknown. The main finding of this follow up report is the finding that 100% (eleven of eleven) patients followed by us with the copper deficiency syndrome ingested large amounts of zinc from denture cream, suggesting that probably most patients, if not all, with otherwise idiopathic hyperzincinemia have developed this problem due to application of high amounts of denture cream. These patients previously fit the concept of an idiopathic syndrome because their hypocupremia was not explained by any gastrointestinal absorption abnormalities and the hyperzincinemia was not solely explained by an inappropriate use of zinc supplements. One of the patients (subject #8) with a 17-year history of dentures had a partial gastrectomy and for a few years also took higher than recommended zinc supplementation; however, his copper and zinc abnormalities followed the same pattern as seen in other patients using denture cream. We did not identify any other possible contributing factors to hyperzincinemia, arguing against the causative role of his gastric surgery.

One of the unresolved issues is whether these patients are more susceptible than the general population of denture users to the exposure of increased zinc content, either by increased absorption or reduced elimination of zinc (Hedera and Brewer, 2004; Spinazzi and Armami, 2009). Additional shared characteristics in every reported individual included poorly fitting dentures requiring a prolonged application of large amounts of adhesive paste, with the average use of more than two tubes per week, containing approximately 80 g of the denture cream. The shortest duration of denture use was seven years with presumed similar daily use of the denture cream. We could only estimate daily zinc exposure and
Table 1
Clinical and laboratory characteristics of studied patients.

<table>
<thead>
<tr>
<th>Subject #: gender</th>
<th>#1: Male</th>
<th>#2: Male</th>
<th>#3: Male</th>
<th>#4: Female</th>
<th>#5: Male</th>
<th>#6: Female</th>
<th>#7: Male</th>
<th>#8: Male</th>
<th>#9: Male</th>
<th>#10 Male</th>
<th>#11 Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48 years</td>
<td>51 years</td>
<td>54 years</td>
<td>39 years</td>
<td>48 years</td>
<td>42 years</td>
<td>51 years</td>
<td>69 years</td>
<td>51 years</td>
<td>33 years</td>
<td>51 years</td>
</tr>
<tr>
<td>Age of symptom onset</td>
<td>45 years</td>
<td>49 years</td>
<td>53 years</td>
<td>41 years</td>
<td>40 years</td>
<td>38 years</td>
<td>41 years</td>
<td>45 years</td>
<td>46 years</td>
<td>31 years</td>
<td>44 years</td>
</tr>
<tr>
<td>Myelopathy: pyramidal tract (PS) signs</td>
<td>PS+</td>
<td>PS+</td>
<td>PS+</td>
<td>PS+</td>
<td>PS+</td>
<td>PS+</td>
<td>PS+</td>
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<td>PS+</td>
<td>PS+</td>
<td>PS+</td>
</tr>
<tr>
<td>Dorsal columns (DC) signs</td>
<td>DC+</td>
<td>DC+</td>
<td>DC+</td>
<td>DC+</td>
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<td>DC+</td>
<td>DC+</td>
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<td>DC+</td>
</tr>
<tr>
<td>Gait</td>
<td>Wheelchair</td>
<td>Wheelchair</td>
<td>Cane</td>
<td>Walker</td>
<td>Independent</td>
<td>Walker</td>
<td>Wheelchair</td>
<td>Walker</td>
<td>Cane</td>
<td>Wheelchair</td>
<td></td>
</tr>
<tr>
<td>Axonal (A), Demyelization (D)</td>
<td>A</td>
<td>D</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Hematologic manifestation</td>
<td>Pan-cytopenia</td>
<td>Pan-cytopenia</td>
<td>Anemia</td>
<td>Pan-cytopenia</td>
<td>Anemia</td>
<td>Pan-cytopenia</td>
<td>Anemia</td>
<td>Pan-cytopenia</td>
<td>Pan-cytopenia</td>
<td>Pan-cytopenia</td>
<td>Pan-cytopenia</td>
</tr>
<tr>
<td>History of dentures</td>
<td>10 years</td>
<td>20 years</td>
<td>15 years</td>
<td>7 years</td>
<td>11 years</td>
<td>10 years</td>
<td>11 years</td>
<td>17 years</td>
<td>18 years</td>
<td>15 years</td>
<td>25 years</td>
</tr>
<tr>
<td></td>
<td>600–1,360</td>
<td>500–935</td>
<td>350–1,700</td>
<td>700–1,200</td>
<td>600–1,360</td>
<td>600–1,360</td>
<td>700–1,700</td>
<td>1,000–1,700</td>
<td>400–1,200</td>
<td>600–1,200</td>
<td>700–1,200</td>
</tr>
<tr>
<td>Preferred brand</td>
<td>Poli-Grip</td>
<td>Fixodent</td>
<td>Poli-Grip</td>
<td>Fixodent</td>
<td>Poli-Grip</td>
<td>Poli-Grip</td>
<td>Poli-Grip</td>
<td>Fixodent</td>
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<tr>
<td>Copper and zinc urine levels after cessation of denture cream µg/24 h</td>
<td>N/A</td>
<td>N/A</td>
<td>Cu: 27</td>
<td>Cu: 9</td>
<td>Cu: 11</td>
<td>Cu: 16</td>
<td>Cu: 8</td>
<td>Cu: 12</td>
<td>Cu: 22</td>
<td>Cu: 75</td>
<td>Cu: 98</td>
</tr>
</tbody>
</table>

| Neurologic outcome | Remained wheelchair dependent | Improved balance, independent walking | No change, walking with support (walker) | Improved, almost complete recovery | Mild improvement, still walker dependent | No change, wheelchair dependent | Reduced pain | No change in his gait, Markedly improved sensory deficit | Mild improvement, uses cane, feels more stable | Improved, can walk with walker |
|---------------------|-------------------------------|-------------------------------------|--------------------------------|-------------------------------------|-------------------------------------|--------------------------------|---------------------------------|-----------------------------------------------|-----------------------------------------------|

- Previously reported.
- Normal plasma levels (µg/dL): Cu 75–125; Zn 75–110.
- Normal urine levels (µg/24h): Cu 20–50; Zn 200–500.
- Patient was not compliant with copper supplementation therapy.
it varied from 350–1700 mg/day, even though the bioavailability of zinc from denture cream is unknown.

Relevant to this question is the experience with the therapy in Wilson’s disease. In Wilson’s disease, 75 mg of zinc per day in two or three divided doses, if taken separate from food, consistently produced negative copper balance (Brewer et al., 1993). In the eleven patients reported here, zinc intake was 5–23 times that amount. Presumably, most of the ingested cream was between meals, which makes the zinc much more effective in blocking copper absorption. Because of the enormous zinc quantities ingested by these patients, at this time we do not have to postulate an increased susceptibility to zinc.

In summary, poorly fitting dentures requiring large amounts of denture cream to provide a sufficient seal appear to be the common characteristics of patients with idiopathic hypocupremia, hyper-zincemia, bone marrow suppression and a combination of polyneuropathy with spinal cord degeneration. Patients presenting with this constellation of neurologic and hematological signs need to be immediately screened for abnormal blood copper and zinc levels, and the use of large amounts of denture cream. It appears their disease is fully explained by denture cream use.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

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