Role of trace elements in hepatic encephalopathy: zinc and manganese

K CHETRI, G CHOUDHURI

Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow

Apart from increased blood ammonia, alterations in various other substances have been implicated in the pathogenesis of hepatic encephalopathy (HE). The role of trace elements like zinc and manganese has been described recently. Zinc is an essential trace element and functions as an antioxidant. Low zinc concentrations have been reported in patients with cirrhosis of the liver, particularly those with HE. Patients with fulminating hepatic failure and subacute hepatic failure have also been shown to have low serum zinc levels. In animal experiments, zinc supplementation leads to a reduction in blood ammonia. Zinc deficiency also leads to alteration of neurotransmitters like gamma aminobutyric acid and norepinephrine. Zinc supplementation has been tried in HE. It may have a role in mild chronic HE, though further trials are necessary. Increased serum manganese levels have been shown in acute and chronic hepatitis, cirrhosis and congenital disorders like Alagille's syndrome. High manganese content has been reported in the globus pallidus in animals as well as brain tissues of patients dying of HE. Miners with chronic manganese exposure have encephalopathy and extra-pyramidal features similar to HE. It has been postulated that manganese impairs neuronal oxidative metabolism. The role of manganese in the pathogenesis of HE and the possibility of its chelation as treatment need further study. [Indian J Gastroenterol 2003;22(Suppl 2):S28-S30]

Key words: Cirrhosis of liver

Hepatic encephalopathy (HE) occurs when higher mental functions are affected either due to impairment of hepatocellular function or presence of spontaneous or surgical portosystemic shunts. The exact pathogenetic mechanism underlying HE is not known. Various factors like elevated ammonia level, alteration of glutaminergic transmission, increased gamma aminobutyric acid (GABA) receptor-mediated neurotransmission and alterations of 5-hydroxytryptamine levels have been implicated. Recently, trace elements have been investigated in chronic liver disease (CLD) and HE. The role of zinc and manganese in HE have been summarized.

Zinc and HE

Zinc is an essential trace element involved in several metabolic processes. It functions as an anti-oxidant and prevents hepatocellular injury. The total body content of zinc is about 2 to 3 g and its daily requirement in an adult is around 10 mg. Jejunum is the main site for zinc absorption, but enterohepatic circulation occurs from the distal small bowel.

Zinc deficiency is common in patients with CLD, especially of alcohol etiology, with or without HE. The exact biochemical basis of zinc deficiency in CLD is not known. Various factors like poor dietary intake, impaired intestinal absorption, and excessive urinary loss have been postulated.

Loomba et al reported low serum zinc level in patients with fulminating hepatic failure, subacute hepatic failure, and CLD with HE, as compared to healthy controls. Experimental studies in humans have shown an inverse relationship of zinc status with ammonia concentration. HE has been shown to worsen with zinc deficiency and improve with supplementation.

Various mechanisms have been postulated for the role of zinc deficiency in HE. In rats, zinc supplementation has been shown to increase the activity of the urea cycle enzyme ornithine transcarbamylase and decrease blood ammonia levels. An increase in urea concentration was also noted. In animal models of HE, decreased zinc content of brain is associated with altered GABAergic neurotransmitters and decreased brain norepinephrine. These studies suggest that zinc deficiency may have a causal role in HE.

Available literature suggests that zinc supplementation or correction of deficiency should improve HE in cirrhotics. There are however only a few controlled trials evaluating the role of zinc in the treatment of HE (Table). The preparations used were zinc acetate or zinc sulfate in a daily dose of 200 mg to 600 mg. Of the two short-term studies, one showed improvement in trail-making test. Two of the three studies looking at long-term efficacy showed improvement of psychometric tests. Only one study showed improvement in Child-Pugh score. This suggests that zinc could be a reasonable addition to the standard anti-coma treatment in patients with subclinical or mild HE.

Manganese and HE

Manganese is an essential component of enzymes involved in intermediary metabolism, free-radical scavenger system, and various transport proteins. It is ab-
Table: Studies of zinc in hepatic encephalopathy

<table>
<thead>
<tr>
<th>Study design</th>
<th>Therapy</th>
<th>HE grade</th>
<th>Duration</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB</td>
<td>Zinc (10), placebo (12)</td>
<td>Chronic HE/Gr 1</td>
<td>7 days</td>
<td>Response</td>
<td>14</td>
</tr>
<tr>
<td>DBCO</td>
<td>Zinc (15), placebo (15)</td>
<td>Chronic HE</td>
<td>10 days</td>
<td>No response</td>
<td>6</td>
</tr>
<tr>
<td>DB</td>
<td>Zinc (12), zinc and histidine (12), placebo (11)</td>
<td>Zinc deficiency, subclinical HE</td>
<td>3 mo</td>
<td>Response</td>
<td>15</td>
</tr>
<tr>
<td>DB</td>
<td>Zinc and standard (45), standard (45)</td>
<td>Recurrent HE</td>
<td>6 mo</td>
<td>No response</td>
<td>16</td>
</tr>
<tr>
<td>PCCS</td>
<td>Zinc (8), no other treatment (8)</td>
<td>Chronic HE, subclinical HE</td>
<td>3 mo</td>
<td>Response</td>
<td>17</td>
</tr>
</tbody>
</table>

Numbers in parenthesis indicate number of patients in each arm; HE, hepatic encephalopathy; DB, double-blind; DBCO, double-blind cross-over; PCCS, prospective case-control study done by sorbed from the duodenum and is mainly excreted through the liver in bile.18

Serum manganese levels are elevated in a wide spectrum of liver disease, including acute and chronic hepatitis, posthepatic cirrhosis,19 and Alagille’s syndrome.20 In a study on cirrhotic rat brain, manganese content was found to be higher than in controls; further, para-caval shunted rats had higher globus pallidus (GP) Mn content.21 In patients dying of hepatic coma, the brain manganese content was reported to be high,22,23 the manganese content of the GP was reported to be 10-fold higher than in non-cirrhotic individuals.24 This accumulation of manganese results from portal-systemic shunting and impaired hepatobiliary elimination.21

Hyperintensity of the GP in T1-weighted magnetic resonance (MR) images, described in patients with CLD, is believed to be due to accumulation of manganese.25 In rhesus monkeys, manganese intoxication has been shown to cause extrapyramidal syndrome and hyperintensity of GP in T1-weighted MR images.26 This MR finding may revert to normal after the liver disease is treated. In a patient with Alagille’s syndrome, increased serum Mn level and hyperintensity of GP reverted to normal after liver transplantation.27 Similar findings have been described in patients with subclinical as well as overt encephalopathy,28,29 though these did not correlate with the severity of HE.29

Miners chronically exposed to manganese dust have been reported to develop mental changes and extrapyramidal symptoms similar to those of HE.30,31 Though the exact mechanism of nerve damage by manganese is not known, it may increase calcium influx into the nerve cells and impair oxidative metabolism, leading to inadequate replenishment of adenosine triphosphate. This energy depletion leads to neuro-degeneration in the presence of glutamate. As the GP is the output station for glutamate in the basal ganglia, it is vulnerable to manganese toxicity.26,32

**Conclusion**

Zinc may have a role in the mild form of chronic HE. The role of manganese in the pathogenesis of HE and the possible use of its chelation as treatment need further study before any recommendations can be made.

**References**


Correspondence to: Dr Choudhuri, Professor and Head. E-mail: gc@sppgl.ac.in