Zinc deficiency and photoreceptor dysfunction in chronic liver disease


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Summary

1. In nine patients with chronic liver disease photoreceptor function was tested, by measurement of the B-wave amplitude of dark adaptation by electroretinography, and the leucocyte content and plasma concentration of zinc were determined.

2. Four of the patients were leucocyte zinc-depleted and had impaired photoreceptor function, but this was normal in the five with normal leucocyte zinc content.

Key words: alcoholic liver cirrhosis, dark adaptation, hepatitis, zinc.

Introduction

Abnormalities of dark adaptation that respond to vitamin A supplementation have been reported in patients with chronic liver disease [1–4]. These reports included patients who were judged to be zinc deficient, on the basis of low plasma zinc concentrations, and whose dark adaptation improved with zinc supplementation. This suggested that zinc deficiency has a role in the visual abnormalities of these patients. Recent work, however, has shown that the total plasma zinc concentration bears little numerical relationship to indices of tissue zinc stores, such as the zinc content of liver or muscle [5, 6], whereas the zinc content of leucocytes is well correlated with that of muscle, which contains the largest soft-tissue zinc pool in man [6].

In the present study, therefore, we have sought a relationship between photoreceptor dysfunction, nucleated tissue zinc deficiency and chronic liver disease. In contrast to previous studies we have measured both plasma and leucocyte zinc and have assessed photoreceptor function with the objective technique of electroretinography [7].

Patients and methods

The nine patients in this study were aged 24–64 years and had histologically proven chronic liver disease (alcoholic cirrhosis, six; active chronic hepatitis, three). None of the patients was decompensated with hepatic encephalopathy or ascites, although two patients with alcoholic cirrhosis (both with normal leucocyte zinc content) were taking diuretics. Furthermore, none of the patients had any clinical evidence of malnutrition, namely wasting, or vitamin deficiency, nor had any abused alcohol for at least 72 h before this study. Blood tests of liver function were similar in the two groups. All patients had an ophthalmic history taken and a full ocular examination, including Goldman perimetry and colour testing with Ishihara plates. Electroretinograms were recorded by techniques described previously [7] and the progression of B-wave amplitude during dark adaptation was measured. The function relating B-wave amplitude to time in the dark was analysed by least-square linear regression analysis.

Plasma concentration and leucocyte content of zinc were measured by atomic absorption spectrophotometry (Instrumentation Laboratories, model 257). The methods used and the coefficient of variation and recovery of leucocyte and plasma zinc have been described...
TABLE 1. Plasma zinc levels and photoreceptor function in patients with liver disease with or without leucocyte zinc depletion

Normal ranges: leucocyte zinc content, 63–90 ng/mg dry wt. (0.06–0.09 μmol/mg dry wt.); plasma zinc concentration, 0.6–1.2 μg/ml. AC, Alcoholic cirrhosis; ACH, active chronic hepatitis.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Disease</th>
<th>Leucocyte zinc content (ng/mg dry wt.)</th>
<th>Plasma zinc concn. (μg/ml)</th>
<th>B-wave slope (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AC</td>
<td>97.6</td>
<td>0.44</td>
<td>0.021</td>
</tr>
<tr>
<td>2</td>
<td>AC</td>
<td>85.4</td>
<td>0.81</td>
<td>0.035</td>
</tr>
<tr>
<td>3</td>
<td>AC</td>
<td>74.9</td>
<td>0.86</td>
<td>0.029</td>
</tr>
<tr>
<td>4</td>
<td>AC</td>
<td>73.6</td>
<td>0.70</td>
<td>0.019</td>
</tr>
<tr>
<td>5</td>
<td>ACH</td>
<td>73.4</td>
<td>0.60</td>
<td>0.020</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>81.0 ± 10.5</td>
<td>0.68 ± 0.16</td>
<td>0.025 ± 0.007</td>
</tr>
<tr>
<td>6</td>
<td>AC</td>
<td>61.2</td>
<td>0.63</td>
<td>0.007</td>
</tr>
<tr>
<td>7</td>
<td>AC</td>
<td>56.3</td>
<td>0.63</td>
<td>0.005</td>
</tr>
<tr>
<td>8</td>
<td>ACH</td>
<td>55.5</td>
<td>1.14</td>
<td>0.009</td>
</tr>
<tr>
<td>9</td>
<td>ACH</td>
<td>52.9</td>
<td>0.73</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>56.5 ± 3.5</td>
<td>0.78 ± 0.24</td>
<td>0.009 ± 0.004</td>
</tr>
<tr>
<td>Wilcoxon’s rank sum</td>
<td>—</td>
<td>N.S.</td>
<td></td>
<td><em>P &lt; 0.05</em></td>
</tr>
</tbody>
</table>

The significance of differences between the normal and low leucocyte zinc groups was assessed by Wilcoxon’s rank-sum test, since the results were not normally distributed. Correlation between leucocyte zinc and the slope of the B-wave amplitude was tested by the Spearman rank-correlation coefficient test.

The study was approved by St Thomas’ Hospital Ethical Committee and informed written consent obtained from all subjects.

Results

In four patients the leucocyte zinc content was below our normal range of 63–90 ng of zinc/mg dry weight (n = 100). (Table 1). The plasma zinc concentrations were normal in eight of the nine patients (normal range 0.6–1.2 μg of zinc/ml, n = 100) (Table 1). During dark adaptation the mean slope of the rise in B-wave amplitude as a function of time was significantly different in the group with low leucocyte zinc compared with the mean of the group with normal leucocyte zinc content (P < 0.05) (Fig. 1). The Figure shows that the B-wave amplitude at each measurement (2–10 min) during dark adaptation was significantly depressed in the low leucocyte zinc group (P < 0.05–< 0.01). The slope of B-wave amplitude during dark adaptation was correlated with the results of leucocyte zinc in all nine patients (P < 0.05), but there was no relationship between the electroretinogram slope and the plasma zinc concentration. Each group contained patients with and without alcoholic liver disease.

Discussion

Some patients with alcoholic cirrhosis or other chronic liver disease have low plasma concentrations of zinc [8] and these have been considered to be indicators of low total zinc stores. This assumption, however, may not be valid. Plasma zinc content constitutes less than 1% of total body stores, drops rapidly in response to acute stress and depends heavily on the concentration of plasma proteins, which may themselves be decreased in chronic liver disease [9]. Furthermore, recent work from this laboratory has failed to demonstrate any correlation between total plasma zinc concentration...
and the zinc content of muscle [6], which contains the largest soft-tissue store of zinc in man. More recently, however, leucocyte zinc content has been demonstrated to be an excellent indicator of nucleated tissue zinc status [5, 6].

All the subjects who were leucocyte zinc-deficient had abnormal photoreceptor function from the electroretinographic studies, whereas no patient with normal leucocyte zinc had abnormal electroretinographic findings. There was also a significant correlation between the results of leucocyte zinc determination and the increasing scotopic B-wave amplitude in the nine patients, suggesting a relationship between tissue zinc content and photoreceptor function. The numbers of patients were small because each test required the co-operation of the subject for at least 4 h.

Our results suggest that nucleated tissue zinc deficiency is associated with photoreceptor dysfunction in both alcoholic and non-alcoholic liver disease. The most likely site of action of zinc in the retina is the enzyme retinol dehydrogenase, which in the rat is sensitive to zinc deficiency [10, 11]. Thus dark-adapted electroretinography may be a sensitive test of true deficiency, rather than biochemical depletion.

Serum vitamin A depletion has been reported [1–3] to be associated with similar changes in dark adaptation in patients with alcoholic liver disease. However, like zinc, it is unlikely that a single measurement of vitamin A in serum will predict intracellular vitamin A depletion, but until assessments of intracellular vitamin A are made it could be argued that intracellular zinc depletion is a marker of vitamin A deficiency.

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References