RAPID COMMUNICATION

VITAMIN B12 AND HEPATIC ENZYME SERUM LEVELS CORRELATE IN MALE ALCOHOL-DEPENDENT PATIENTS

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Abstract — Vitamin B12 serum levels and markers for alcohol consumption were determined in 80 male alcohol-dependent patients. Spearman correlation coefficients ($r_s$) were calculated. Significant positive correlations between vitamin B12 and hepatic enzyme values were found (gamma-glutamyltransferase: $r_s = 0.58$; alanine aminotransferase: $r_s = 0.43$; aspartate aminotransferase: $r_s = 0.47$; glutamate dehydrogenase: $r_s = 0.43$; all $P < 0.001$). Therefore, for a proper interpretation of vitamin B12 levels, it may be clinically relevant to take markers of hepatocellular damage into account.

INTRODUCTION

It has frequently been reported that liver disease leads to elevated vitamin B12 levels in serum (Rachmilewitz et al., 1956; Baker et al., 1987; Djalali et al., 1988; Zhou et al., 1992; Lambert et al., 1997) and a lowered liver tissue total vitamin B12 concentration (Baker, 1998).

Serum vitamin B12 levels, plasma cobalamin, total corrinoids and their analogues were found to be elevated in patients suffering from alcoholic cirrhosis (Airoldi et al., 1987). Lambert et al. (1997) found that the concentration of vitamin B12 bound to transcobalamins I and III was positively correlated with plasma aspartate aminotransferase (ASAT; $r_s = 0.53$; $P = 0.02$) in alcoholic cirrhotic patients. In patients with alcoholic liver disease, vitamin B12 levels were found to range within normal limits, except for a group of cirrhotic patients where vitamin B12 levels were raised, so biochemical changes in blood vitamin B12 status may precede clinical manifestations of a cirrhotic process and may have prognostic value (Majumdar et al., 1982). However, sex differences in the serum vitamin B12 levels have been described: in a study by Goldman et al. (1979), high vitamin B12 levels were as accurate an indicator of alcoholism in female patients as elevated alanine aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT) and mean corpuscular volume (MCV) values. In contrast, for males the vitamin B12 serum levels of alcoholics were not significantly different from non-alcoholics.

The markers GGT, MCV and carbohydrate-deficient transferrin (CDT) are clinically established markers of recent alcohol abuse (Sillanaukee, 1996). In this article, we report data of a sample of 80 male alcohol-dependent actively drinking patients consecutively admitted for detoxification at our department, where we investigated a possible relationship between vitamin B12 levels and CDT, MCV, as well as the the hepatic enzymes GGT, aspartate aminotransferase (ASAT), ALAT, and glutamate dehydrogenase (GLDH).

METHODS

The report is based on chart reviews of 80 male actively drinking patients with alcohol dependence (DSM-IV) (American Psychiatric Association, 1994), consecutively admitted for detoxification to our department. Serum vitamin B12, CDT, GGT, ASAT, ALAT, GLDH and MCV were determined within 24 h after hospitalization according to clinical routine procedures. Females were excluded because of previously described gender differences.

All parameters were measured using established routine techniques at the University’s central laboratory. GGT, ASAT and ALAT levels were measured according to the International Federation of Clinical Chemistry (IFCC) methods for measurement of enzymes (Shaw et al., 1983; Bergmeyer et al., 1986a,b), GLDH according to the ‘Optimierte Standard-Methode’ (Deutsche Gesellschaft für Klinische Chemie, 1974). An automatic blood count including the determination of MCV was performed according to Weber (1992). CDT levels were determined using the CDTect™ method from Pharmacia, Sweden (Stibler et al., 1991). Vitamin B12 levels were determined using the Chiron Diagnostics ACS:180™ assay (National Committee for Clinical Laboratory Standards, 1990).

For every parameter, descriptive statistics (mean, SD, minimum and maximum) were calculated. For the analysis of the correlations between the parameters, Spearman’s rank correlation coefficients ($r_s$) were calculated using the SPSS statistical software package. This publication consists of anonymous data derived from the chart review, therefore it is in full accordance with the German regulatory laws (Landesgesetz für psychisch kranke Personen; PsychKG, from November 17, 1995; § 5 Abs. 1).

RESULTS

Mean ($\pm$ SD) age of the patients was $44.6 \pm 9.7$ years, range: 22–65. The descriptive measures of the parameters are shown in Table 1. Only six patients exhibited vitamin B12 levels >1100 pg/ml (normal range: 240–1100 pg/ml).

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We found highly significant positive correlations between vitamin B12 and GGT (r_S = 0.58; P < 0.001), GLDH (r_S = 0.43; P < 0.001), ASAT (r_S = 0.47; P < 0.001) and ALAT (r_S = 0.43; P < 0.001). A scatterplot of GGT and vitamin B12 values is shown in Fig. 1. The correlation of vitamin B12 with GGT was superior compared with the correlation of vitamin B12 with other liver enzymes, but this difference in correlation coefficients did not reach statistical significance.

As expected, significant correlations between the hepatocellular markers GGT, ASAT, ALAT and GLDH were observed, also between MCV and the hepatic enzymes GGT and GLDH.

Between CDT and vitamin B12, or between MCV and vitamin B12, no statistically significant correlation was found. The correlation coefficients are shown in Table 2.

DISCUSSION

We found highly significant positive correlations between vitamin B12 and the hepatocellular enzymes GGT, GLDH, ASAT and ALAT. These findings are in accordance with Lambert et al. (1997), who found that the serum concentration of vitamin B12 was positively correlated with plasma ASAT levels, but who did not investigate the relation of vitamin B12 to GGT, GLDH and ALAT. In our sample, the highly significant correlation was found despite the fact that most vitamin B12 values ranged within normal limits. In male alcohol-dependent patients, values within normal ranges have previously been described by Goldman et al. (1979), but no correlation coefficients were calculated. Their report may have led to the assumption that vitamin B12 levels are not substantially affected in these patients. Our results demonstrate a substantial positive relationship between vitamin B12 and hepatic enzyme serum levels. This correlation may be interpreted as meaning that, with increasing hepatocellular damage, as indicated by elevated hepatic enzymes, serum vitamin B12 also tends to be higher. Possible explanations for this phenomenon may be the failure of the damaged liver to take up cobalamin and analogues from the serum (Green, 1983; Kanazawa and Herbert, 1985). Another plausible explanation may lie in the finding that, in hepatic damage, liver tissue vitamin B12 binding and storage of transcobalamin is disrupted and causes vitamin B12 to leak out of the liver into the circulation (Baker et al., 1998). The latter may have relevant clinical implications: in a malnourished patient with primarily decreased peripheral vitamin B12 levels, the deficiency of vitamin B12 in the periphery may be temporarily masked by vitamin B12 leaking out of hepatic cells affected by acute alcohol consumption. A single measurement of vitamin B12 levels might therefore be misleading in some patients.

Table 1. Descriptive statistics for laboratory parameters of alcohol-dependent patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>80</td>
<td>265.0</td>
<td>1527.0</td>
<td>602.3</td>
<td>294.8</td>
<td>240–1100</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>80</td>
<td>10.0</td>
<td>1294.0</td>
<td>168.7</td>
<td>233.5</td>
<td>&lt;48</td>
</tr>
<tr>
<td>GLDH (U/l)</td>
<td>78</td>
<td>0.5</td>
<td>159.0</td>
<td>17.9</td>
<td>27.3</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>80</td>
<td>5.0</td>
<td>238.0</td>
<td>45.7</td>
<td>45.7</td>
<td>&lt;18</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>80</td>
<td>7.0</td>
<td>188.0</td>
<td>38.6</td>
<td>34.4</td>
<td>&lt;17</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>79</td>
<td>84.7</td>
<td>113.0</td>
<td>96.2</td>
<td>5.8</td>
<td>80–100</td>
</tr>
<tr>
<td>CDT (U/l)</td>
<td>63</td>
<td>5.6</td>
<td>119.0</td>
<td>36.2</td>
<td>23.1</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

\(n\), number; Min, minimum; Max, maximum; GGT, gamma-glutamyltransferase; GLDH, glutamate dehydrogenase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; MCV, mean corpuscular volume; CDT, carbohydrate-deficient transferrin.

Table 2. Spearman’s rho correlation coefficients between laboratory parameters

<table>
<thead>
<tr>
<th></th>
<th>B12</th>
<th>GGT</th>
<th>GLDH</th>
<th>ASAT</th>
<th>ALAT</th>
<th>MCV</th>
<th>CDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12</td>
<td>1.00</td>
<td>0.58**</td>
<td>0.43**</td>
<td>0.47**</td>
<td>0.43**</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>GGT</td>
<td>0.58**</td>
<td>1.00</td>
<td>0.75**</td>
<td>0.76**</td>
<td>0.71**</td>
<td>0.38**</td>
<td>0.01</td>
</tr>
<tr>
<td>GLDH</td>
<td>0.43**</td>
<td>0.75**</td>
<td>1.00</td>
<td>0.82**</td>
<td>0.76**</td>
<td>0.30**</td>
<td>0.14</td>
</tr>
<tr>
<td>ASAT</td>
<td>0.47**</td>
<td>0.76**</td>
<td>0.82**</td>
<td>1.00</td>
<td>0.87**</td>
<td>0.27*</td>
<td>0.16</td>
</tr>
<tr>
<td>ALAT</td>
<td>0.43**</td>
<td>0.71**</td>
<td>0.76**</td>
<td>0.87**</td>
<td>1.00</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>MCV</td>
<td>0.20</td>
<td>0.38**</td>
<td>0.30**</td>
<td>0.27*</td>
<td>0.09</td>
<td>1.00</td>
<td>0.04</td>
</tr>
<tr>
<td>CDT</td>
<td>0.05</td>
<td>0.01</td>
<td>0.14</td>
<td>0.16</td>
<td>0.04</td>
<td>0.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Correlations: \(*P < 0.05\) (2-tailed); \(**P < 0.01\) (2-tailed).

For abbreviations, see Table 1.
a proper interpretation of vitamin B12 serum levels in alcohol-dependent patients, it may be clinically relevant to take values of GGT, ASAT, ALAT and GLDH as markers of hepatocellular damage into account, because, in alcohol-dependent patients, a serum cobalamin test may not reflect the true amount of available vitamin B12, nor the extent of hepatic damage. Baker and colleagues, who investigated vitamin B12 changes in plasma and liver tissue in alcoholics with liver disease, concluded that eventually liver disease could produce enough severe tissue B12 deficits to cause metabolic dysfunction despite elevated plasma total vitamin B12 (Baker et al., 1998). So if a patient with alcohol dependence shows normal or elevated vitamin B12 levels, the clinician has to pay attention to the hepatic enzyme levels. If those are elevated, the patient could suffer from a deficit of vitamin B12, although he exhibits normal or elevated vitamin B12 levels.

We would recommend determination of the elevation of methylmalonic acid and homocysteine as metabolites of vitamin B12 in urine or serum for diagnosis and confirmation of vitamin B12 deficiency. For the cobalamin-deficient patients, measuring serum metabolite concentrations has proved to be a highly sensitive test of deficiency and normal levels of both methylmalonic acid and total homocysteine are thought to rule out clinically significant cobalamin deficiency with virtual certainty (Savage et al., 1994).

Vitamin B12 values did not correlate with CDT, but did so with GGT. This may be due to the following. CDT and GGT reflect different patterns of drinking. For men, CDT levels appear to respond primarily to frequency of drinking, whereas GGT is influenced primarily by drinking intensity (Anton et al., 1998). Also CDT, as a more specific marker of alcoholism, is less influenced than GGT by associated liver disease (Rubio et al., 1997). The mechanism of GGT and vitamin B12 elevation is assumed to be hepatocellular damage. In contrast, CDT elevation in alcohol-dependent patients is supposed to be due to decrease in hepatic sialyltransferase and increase in sialidase activities (Xin et al., 1995).

REFERENCES


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