HIGH AST/ALT RATIO MAY INDICATE ADVANCED ALCOHOLIC LIVER DISEASE RATHER THAN HEAVY DRINKING

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Abstract — Aims: To assess the place of AST/ALT ratio (the ratio of serum aspartate aminotransferase to serum alanine aminotransferase) as a diagnostic marker in medical populations. Methods: Laboratory tests were viewed retrospectively in three groups of patients: 313 patients with alcohol dependence, consecutively admitted to an alcohol and drug treatment unit for treatment of withdrawal (W) symptoms, 78 patients with alcohol abuse or dependence consecutively admitted to surgical or medical wards with various primary somatic (S) diagnoses (e.g. respiratory, gastrointestinal and metabolic), and 48 consecutive patients with alcohol abuse or dependence admitted to surgical or medical wards for treatment of alcohol-related liver cirrhosis and its complications (C). Comparison between groups was made of the pattern of patients’ AST/ALT ratios using, for Groups S and C, laboratory data from patients’ first admission for their condition. Results: There was a significant rise in the AST/ALT ratio from the W to the S patients, and from the S to the C patients. In the W group, the ratio was ≤ 1.0 in 64% of the patients, and only exceptionally ≤ 2. In the C group, 69% had a ratio ≥ 2, and 8% a ratio ≥ 1.0. The mean ratio was midway in the S group. In the C group, there was a progressive decline in aspartate (AST/ALT) ratios after admission. Conclusions: Most patients with high alcohol consumption but without severe liver disease do not have an AST/ALT ratio above 1. High AST/ALT ratio suggests advanced alcoholic liver disease.

INTRODUCTION

High alcohol consumption is one of the most common causes of liver disease. However, high alcohol consumption as a cause for abnormal liver test results is often not evident and may even be denied. A readily obtainable blood test to reveal whether alcohol is the likely cause would be valuable.

Several markers for high alcohol consumption per se have been studied e.g. carbohydrate deficient transferrin (CDT), gamma glutamyl transferase (GGT) and aspartate aminotransferase (AST). Most have fairly low sensitivities and specificities (Conigrave et al., 2002). The use of test combinations significantly improves the information received with single serum enzyme determinations. An elevated serum AST in relation to serum ALT (alanine aminotransferase) has been proposed as an indicator that alcohol has induced organ damage. Thus, when AST/ALT ratio is > 1.5, this is considered as highly suggestive that alcohol is the cause of the patient’s liver injury (Correia et al., 1981; Salaspuro, 1987).

However, many patients who doubtless consume high amounts of alcohol and indeed are alcohol-dependent and display elevated serum aminotransferase levels do not show a high AST/ALT ratio. This suggests that additional factors lead to the high AST/ALT ratio seen in some patients. One such factor may be the severity of the liver disease. To test this hypothesis we compared the AST/ALT ratio in three groups of patients with high alcohol consumption: patients hospitalized for treatment of alcohol withdrawal syndromes, patients hospitalized in somatic (medical or surgical) wards for non-liver related causes, (both of which may have contained patients with a mild degree of liver damage) and patients hospitalized with complications from alcoholic liver cirrhosis.

METHODS

This study was performed on records of 439 patients with high alcohol consumption in whom liver tests data had been collected on admission to hospital.

Group W consisted of 313 patients (254 men and 59 women), mean age 46 years (range 19–81 years), consecutively admitted to an alcohol and drug treatment unit at a psychiatric department of the University Hospital for management of alcohol withdrawal (W). All these patients fulfilled DSM-IV criteria for alcohol dependence (American Psychiatric Association, 1994) and showed withdrawal symptoms of such a degree of severity that in-patient treatment was considered necessary. Patients who had severe somatic complications also due to their alcohol dependence, necessitating treatment in medical wards, were excluded. The W patients were considered to represent severe alcohol dependence with a need for repeated in-patient treatment for alcohol withdrawal. They had consumed high amounts of alcohol for a comparatively short period, or somewhat smaller amounts for prolonged periods. Most of the patients in this group had been consuming alcohol until the day of admission. Data on their alcohol consumption were obtained by interview.

Group S comprised 78 patients (67 men and 11 women with mean age of 53 years, range 23–85 years) with alcohol abuse or dependence, admitted to surgical or medical wards, with a wide range of different somatic (S) diseases (e.g. respiratory, gastrointestinal and metabolic) as main diagnoses. These diagnoses are by themselves not expected to give increased serum aminotransferase levels. As to the diagnosis of alcohol abuse or dependence, we had to rely upon the diagnosis made by the treating physician, in view of the retrospective character of this study.

Group C comprised 48 patients (35 men and 13 women with mean age 58 years, range 40–81) admitted to surgical or medical wards for treatment of complications of alcohol-related liver cirrhosis (C). Included were only those patients in...
whom the diagnosis of cirrhosis was based on liver biopsy or the presence of oesophageal varices or ascites.

In Groups S and C, we were not able to obtain information regarding the consumed amounts of alcohol, in view of the retrospective nature of this study.

In Group W, blood samples for determination of liver function were collected in the morning, the day after admission and before start of medication for withdrawal symptoms.

Data on patients in Groups S and C were collected consecutively from the cohort of patients hospitalized during 1998–1999. The first time treatment in this period was chosen. Included were only those patients in whom AST and ALT and bilirubin were studied not only at admission but AST/ALT also on days 4–6 and 7–10 of hospitalization, when present.

The laboratory tests as well as the questioning of the patients about alcohol consumption were part of the routine clinical assessment of the patients. Thus, this study was considered as a clinical quality control study. Since the data were put into data files in an unidentified status, no ethical permission was considered necessary.

Standard laboratory methods were used for the laboratory analyses. AST: BM/Hitachi Laboratory Accreditation Compliance Sheet: BM-GPT IFCC, cat. no. 1730576; ALT: BM/Hitachi Laboratory Accreditation Compliance Sheet: BM-GoT IFCC, cat. no. 1552481; bilirubin BM/Hitachi cat. no. 1730452; GGT: Enzymat; CDT: FPLC (Jeppsson et al., 1993).

ANOVA was used to test differences between groups (level of significance 5%).

RESULTS

As is evident from Table 1, the C and S patients had higher AST, but not ALT, than the W patients. There was a progressive rise in the AST/ALT ratio from the W to the S, and from the S to the C patients. In the W group, the ratio was ≤1.0 in 64% of the patients, and only exceptionally ≥2 (Fig. 1). The reverse was true for the C group, where a majority had a ratio ≥2, and a minority ≤1.0. The ratio was midway between in the S group.

In 17 of the C patients, we retrieved aminotransferase values from 4–6 and 7–10 days after admission. There was a progressive decline in AST/ALT ratios from mean 2.7 (±0.4 SD) through 2.2 (±0.3) to 1.7 (±0.2) at 4–6 and 7–10 days, respectively, after admission.

The C group patients had higher serum bilirubin values than the other patient groups. A significant positive correlation ($P < 0.001$) between the AST/ALT ratio and bilirubin level in serum was found in the S group. No similar correlation was found in the two other groups of patients. In the W group, we also had admission values for GGT (mean 3.0 μkat/l, SD 4.5; reference values for men <1.3 and for women <0.8) and CDT (mean 4.6%, SD 3.6, reference values <1.7). There were weak but significant correlations between the AST/ALT ratio and the serum GGT ($P < 0.001$, $r^2 = 0.05$) and the serum CDT ($P < 0.006$, $r^2 = 0.02$). GGT and CDT were not regularly analysed in the S and C groups. In the W group, but not in the S or C groups, patients were asked to estimate the

### Table 1. Values of serum aminotransferases and bilirubin in Group W (patients with withdrawal symptoms), Group S (patients with somatic diagnoses in addition to a diagnosis of alcohol abuse or dependence) and Group C (patients with alcoholic cirrhosis)

<table>
<thead>
<tr>
<th></th>
<th>W ($n = 313$)</th>
<th>S ($n = 78$)</th>
<th>C ($n = 48$)</th>
<th>Significance of differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (ULN = 0.7 μkat/l)</td>
<td>1.2 ± 1.4* (0.1–12.0)</td>
<td>4.0 ± 13.9* (0.2–120)</td>
<td>3.4 ± 6.0* (0.21–42)</td>
<td>$P &lt; 0.001$ for W vs S, $P = 0.02$ for W vs C</td>
</tr>
<tr>
<td>ALT (ULN = 0.7 μkat/l)</td>
<td>1.2 ± 1.7 (0.2–20.0)</td>
<td>1.7 ± 2.5 (0.18–18.5)</td>
<td>1.8 ± 2.9 (0.23–15)</td>
<td>NS</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>1.0 ± 0.6* (0.3–6.7)</td>
<td>1.7 ± 1.0* (0.4–6.5)</td>
<td>2.6 ± 1.9* (0.03–12.1)</td>
<td>$P &lt; 0.0001$ for W vs S, W vs C and S vs C</td>
</tr>
<tr>
<td>Bilirubin (ULN = 21 μmol/l)</td>
<td>16.2 ± 11.0* (3–117)</td>
<td>18.1 ± 14.7* (1.8–79)</td>
<td>95.9 ± 133* (2.8–710)</td>
<td>$P &lt; 0.0001$ for W vs C and S vs C</td>
</tr>
</tbody>
</table>

Mean ± SD. ULN = upper limit of normal.
duration and amount of alcohol consumed before admission. The AST/ALT ratio in the W group was not significantly related to the total duration of high alcohol consumption [16 ± 9 (SD) years], the amount of alcohol consumed during the last period before admission (median 250 g/day, range 40–2273 g/day), or the duration of the last drinking period (median 449, range 1–3500 days).

**DISCUSSION**

We have presented data suggesting that the well-recognised high AST/ALT ratio in alcoholic liver disease is, in fact, predominantly found in patients whose disease is advanced. In patients with increased serum aminotransferase activity, the predominance of AST over ALT in alcoholic liver disease was first reported by Harinasuta et al. in 1967. However, it became more widely recognized only after the paper by Cohen and Kaplan in 1979. The diagnostic significance of a high AST/ALT ratio for alcoholic liver disease was recently underscored in the Practical Guidelines for Alcoholic Liver Disease published by the American College of Gastroenterology in 1998 (McCullough and O’Connor, 1998). Different, to some extent possibly interrelated, reasons have been reported for the high AST/ALT ratio in alcoholic liver disease: i) a decreased hepatic ALT activity (Matloff et al., 1980); ii) pyridoxal 5’-phosphate depletion in the livers of alcoholics (Diehl et al., 1984); and iii) mitochondrial damage leading to an increase in serum activity of mitochondrial aspartate in patients with high alcohol consumption (Nalpas et al., 1984).

An increased AST/ALT ratio in patients with increased serum aminotransferase activity has also been associated with the development of cirrhosis in Nonalcoholic Steatohepatitis (Sorbi et al., 1999), even though a still higher AST/ALT ratio was observed in a group of non-biopsied patients with alcoholic liver disease. Furthermore, a high AST/ALT ratio in patients with increased serum aminotransferases has been reported in chronic viral hepatitis (Williams and Hoofnagle, 1988; Cadiot et al., 1989; Reedy et al., 1998; Sheth et al., 1998; Anderson et al., 2000; Assy and Minuk, 2000; Park et al., 2000; Giannini et al., 2001, 2003; Pohl et al., 2001) even though reports on relatively low positive predictive values have been published (Imperial et al., 2000).

In order to further study the influence of the diagnosis of cirrhosis per se on the AST/ALT ratio, we have also analysed the AST/ALT ratio in 42 patients with primary biliary cirrhosis (PBC) from this centre. This patient group participated in a study of the effect of ursodeoxycholic acid in this disease (Erikssen et al., 1997). In spite of the name cirrhosis, the diagnosis of PBC also includes early disease, i.e. patients who have not yet developed cirrhosis. However, the AST/ALT ratio in eight PBC patients who had developed cirrhosis did not differ from that in 34 PBC patients without cirrhosis [1.13 ± 0.35 (SD) vs 0.97 ± 0.35] arguing against the development of cirrhosis as the sole determinant for a high AST/ALT ratio. Furthermore, in contrast to the high ratio observed in our alcohol cirrhotic patients, the magnitude of the reported mean AST/ALT ratio in the patients with chronic viral hepatitis and cirrhosis is generally only slightly above 1 (Williams and Hoofnagle, 1988; Cadiot et al., 1989; Sheth et al., 1998; Park et al., 2000; Anderson et al., 2000; Assy and Minuk, 2000; Giannini et al., 2001; Pohl et al., 2001). The mean and maximum ratio in our PBC patients was 1.0 and 2.0, respectively. This should be compared with the 2.6 and 12.1 in our patients with alcohol-related cirrhosis. A further argument against the development of cirrhosis as the sole determinant for the AST/ALT ratio is the rapid decrease in this ratio after admission in the C group patients. This would suggest the contribution of a direct toxic effect of alcohol on the AST/ALT ratio. We did not find support for a direct dose-related effect of alcohol on the AST/ALT ratio in the W patients, where we observed no relationship between the AST/ALT ratio and the magnitude or duration of alcohol consumption. Admittedly, the self-reported data on alcohol consumption in our W patients might not be highly reliable. However, the alcohol effect on the AST/ALT ratio may depend on factors other than dose.

Our observation that the AST/ALT ratio decreased rapidly after admission in the C patients raises the question of whether the difference in AST/ALT ratio between the groups could be explained by a longer period of abstinence before blood sampling in the W and S groups of patients. This explanation is contradicted by the fact that the patients in the W group usually had stopped their high alcohol consumption immediately before admission. We do not have exact data on the drinking before admission in the C group of patients, but according to what was reported in the medical records, many of the patients in the C group had stopped or reduced drinking some time before admission.

Our findings of a high AST/ALT ratio in advanced alcoholic liver disease are somewhat at variance with those reported by Hourigan and Bowling (2001) in a clinical series in an Australian private practice. These authors found that, in 190 patients with alcoholic liver disease subjected to liver biopsy, only two-thirds of patients with cirrhosis exhibited an AST/ALT ratio greater than unity, i.e. clearly less than the 91% observed in the present investigation. There are at least two possible explanations for these discrepant findings. One is selection bias in the study by Hourigan and Bowling, for they excluded from biopsy patients with more advanced liver disease and patients in which ‘cirrhosis was clearly present on clinical grounds ... with portal hypertension or ascites’. In contrast, 38 of our 48 cirrhotics had ascites, and 28 had diagnosed oesophageal varices. It is of interest that the Australian authors mention that ‘there was a trend towards higher rates in more advanced disease’. Another contributing explanation could be that the AST/ALT data were recorded in connection with the biopsies and that the biopsies were performed after a period of abstinence, when the AST/ALT ratio might have already declined.

The only test of liver function that was regularly analysed in all the patients was serum bilirubin. The ranges of serum bilirubin shown in Table 1 indicate that there were some patients with liver damage in each group. A correlation between the AST/ALT ratio and serum bilirubin was found in the S group but not in the C group. A hypothetical explanation for this difference between the groups might be that alcohol-induced liver disease sometimes induces significant cholestasis without corresponding cytolytic changes in the hepatocytes, reflected in the serum aminotransferases.

To conclude, most patients with high alcohol consumption do not have an AST/ALT ratio above 1. A high AST/ALT ratio is suggestive of advanced alcoholic liver disease.
REFERENCES