COMPARISON OF CAGE AND MAST WITH THE ALCOHOL MARKERS CDT, \( \gamma \)-GT, ALAT, ASAT AND MCV

TILMAN WETTERLING*, ROLF-DIETER KANITZ, HANS-JÜRGEN RUMPF, ULFERT HAPKE and DOROTHEA FISCHER

Department of Psychiatry, University Medical School of Lübeck, Lübeck, Germany

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Abstract — Many alcoholics deny abuse. To screen greater samples for alcohol dependence, short questionnaires, e.g. the CAGE or MAST are often applied. Frequently laboratory parameters [i.e. 'alcohol markers', such as carbohydrate-deficient transferrin (CDT), \( \gamma \)-glutamyl transferase or mean corpuscular volume of erythrocytes] are used to support the diagnosis of long-standing heavy alcohol consumption. In this study, the self-ratings (CAGE and MAST) were compared with the above laboratory parameters in an unselected sample of 204 patients admitted to a general hospital. The sensitivities, specificities, and positive (PPV) as well as negative predictive values of the CAGE, the MAST, and the alcohol markers were calculated along with the reported alcohol consumption or the ICD-10 diagnosis as standard. According to recent harmful alcohol consumption levels (women >225 g/week; men >350 g/week), the sensitivities and the PPVs were rather low in all tests (sensitivity <60%; PPV <50%). With the ICD-10 diagnosis as standard, the CAGE and MAST showed a rather high specificity (>95%) and PPV (about 90%). CDT revealed the best PPV of all alcohol markers (60%). However, the sensitivity of the CAGE, MAST, and the alcohol markers for the ICD-10 diagnosis was rather poor (<60%). This low sensitivity impedes the usefulness of these questionnaires and alcohol markers as screening tests for alcoholism in general hospitals.

INTRODUCTION

Many alcoholics deny excessive alcohol consumption and patients consulting a physician for the treatment of somatic complaints frequently do not report their alcohol abuse. Thus, in cases with somatic diseases or trauma, an underlying harmful alcohol consumption is under-diagnosed (Umbricht-Schneider et al., 1991; Nielsen et al., 1994). Furthermore, alcohol abuse may cause complications, particularly a severe withdrawal syndrome (Foy et al., 1988). Often short questionnaires (Allen et al., 1995), such as the CAGE (Mayfield et al., 1974) or MAST (Selzer, 1971) are used to screen for alcohol abuse. But these self-ratings do not give any information on recent alcohol consumption. However, the clinician is less interested in the diagnosis of alcohol dependency rather than in the question of whether the present symptomatology may be caused by prior heavy alcohol drinking or whether s/he should be aware of a severe alcohol-withdrawal syndrome. To ascertain current alcohol abuse, laboratory parameters (alcohol markers) such as \( \gamma \)-glutamyl transferase (\( \gamma \)-GT) are often used (Conigrave et al., 1995). More recently, carbohydrate-deficient transferrin (CDT) has been reported to be a good indicator of elevated long-term alcohol consumption (Stibler, 1991). The available alcohol markers, such as \( \gamma \)-GT, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), mean corpuscular volume of erythrocytes (MCV), and CDT have different time spans, in which they can indicate increased alcohol consumption. However, as long as relatively little is known about the neurobiological causes of alcoholism, these frequently used markers only refer to superficial phenomena and do not permit conclusions to be drawn about the underlying pathological process, i.e. elevated serum levels of liver enzymes indicating organ damage (liver disease), which is very common in alcoholism. Since these changes are not specific, the finding of

*Author to whom correspondence should be addressed at. Department of Psychiatry and Psychotherapy I. Johann Wolfgang Goethe University, Heinrich Hoffmann Str 10, 60528 Frankfurt/Main, Germany.
pathological laboratory parameters, like elevated $\gamma$-GT, ALAT, ASAT or MCV, do not always indicate alcohol abuse.

Up until now only a few studies have compared the sensitivity and specificity of alcohol-markers, like $\gamma$-GT, MCV or CDT, with scores of self-rating questionnaires, such as the CAGE or MAST (Nystrom et al., 1992; Bisson and Milford-Ward, 1994; Girela et al., 1994; La Grange et al., 1994; Lof et al., 1994; Gronbaek et al., 1995) and only a weak correlation ($r < 0.4$) between CAGE and CDT values has been observed (Nystrom et al., 1992; La Grange et al., 1994; Lof et al., 1994).

Therefore, the aim of this study was to compare the diagnostic value of laboratory parameters (the so-called alcohol-markers) with those of the CAGE and MAST in an unselected sample of consecutively admitted patients to a general hospital.

PATIENTS AND METHODS

All patients were aged under 65 years and were admitted consecutively to the internal or surgical department of a general hospital (Krankenhaus Süd in Lübeck) over a 6-month period. They were interviewed by two psychologists (H.J.R. or U.H.) in an epidemiological survey. In this study, a subsample of 204 subjects [74 women (mean age ± SD: 43.7 ± 15.1 years) and 130 men (mean age ± SD: 43.1 ± 15.1 years)], who gave informed consent to participate and for a CDT measurement to be made were included. A concise self-report of alcohol intake (frequency and average daily alcohol intake) could only be obtained from 174 cases. On the day after admission, a venous blood sample was drawn. Levels of $\gamma$-GT, ALAT, ASAT, and MCV were measured by automated routine clinical laboratory methods. CDT was determined by a commercially available RIA Kit (CDTect™) from Kabi Pharmacia (Uppsala, Sweden).

Each patient was administered the CAGE (Mayfield et al., 1974) and the MAST (Selzer, 1971) questionnaires. A history of alcohol consumption was obtained by a structured questionnaire. According to the method used in WHO studies (Bohn et al., 1995), those consuming more than 350 g (males) or 225 g (females) of alcohol/week and at least twice in a month more than 100 g (males) or 65 g (females) of alcohol/day were diagnosed as persons with alcohol problems. All available information by chart review was used to detect alcohol-related disorders. These patients and those with positive results in one of the screening questionnaires or requiring a withdrawal medication were interviewed using section 11 of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN: World Health Organization, 1992) to provide diagnoses of alcohol dependence or abuse according to ICD-10 (World Health Organization, 1992) or DSM-III-R (American Psychiatric Association, 1987). The diagnostic procedure was described in detail elsewhere (Rumpf et al., 1997, 1998). The statistical analysis of the results was performed using an SPSS program package (Chicago, IL). Results are presented as means ± SD.

RESULTS

According to the ICD-10 criteria, 50 cases were classified as alcohol-dependent and five cases as alcohol abusers. These 55 cases were of the same age as the rest of the sample (43.9 ± 13.4 years vs 43.1 ± 15.6 years). According to the commonly recommended cut-off values of the CAGE (≥2) and MAST (≥5), 30 (14.7%) or 28 (13.7%), respectively, were identified as problem drinkers.

The daily alcohol consumption during the 4 weeks before admission was estimated according to self-report (data available from 174 cases). The mean alcohol intake/day was reported as 22.6 ± 60.3 g. Men drank significantly more alcohol (33.7 ± 74.6 g/day) than women.

Table 1. Comparison of cases classified as alcohol-dependent with those diagnosed as non-alcoholics using the ICD-10 criteria

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Non-dependent</th>
<th>Dependent</th>
<th>U-test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT</td>
<td>16.3 ± 9.6</td>
<td>28.9 ± 22.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\gamma$-GT (U/l)</td>
<td>24.9 ± 26.2</td>
<td>123.4 ± 165.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>12.3 ± 11.1</td>
<td>30.2 ± 41.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>18.3 ± 41.8</td>
<td>30.5 ± 29.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>89.1 ± 5.2</td>
<td>92.9 ± 6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>g alcohol/day (n=174)</td>
<td>7.1 ± 15.7</td>
<td>56.3 ± 98.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAGE</td>
<td>0.1 ± 0.4</td>
<td>1.6 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MAST</td>
<td>0.5 ± 1.2</td>
<td>10.3 ± 13.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SD. For abbreviations, see the text.
Table 2. Biochemical parameters in cases categorized by the CAGE questionnaire

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Abstainers/light drinkers</th>
<th>Heavy drinkers</th>
<th>U-test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT (mg/l)</td>
<td>19.7 ± 15.0</td>
<td>25.9 ± 19.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>γ-GT (U/l)</td>
<td>36.1 ± 52.8</td>
<td>183.1 ± 209.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>15.4 ± 20.7</td>
<td>33.7 ± 45.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>22.9 ± 45.6</td>
<td>32.2 ± 24.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>89.7 ± 5.5</td>
<td>94.6 ± 4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>g alcohol/day (n = 174)</td>
<td>11.4 ± 19.7</td>
<td>76.9 ± 126.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SD. For abbreviations, see the text.

Table 3. Biochemical parameters in cases categorized by the MAST questionnaire

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Abstainers/light drinkers</th>
<th>Heavy drinkers</th>
<th>U-test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT (mg/l)</td>
<td>18.3 ± 13.4</td>
<td>28.4 ± 21.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>γ-GT (U/l)</td>
<td>46.5 ± 89.9</td>
<td>113.6 ± 162.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>14.7 ± 18.7</td>
<td>32.2 ± 45.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>21.2 ± 41.0</td>
<td>28.4 ± 18.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>89.7 ± 5.6</td>
<td>93.0 ± 5.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>g alcohol/day (n = 176)</td>
<td>12.0 ± 19.4</td>
<td>78.3 ± 132.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SD. For abbreviations, see the text.

Elevated CDT serum levels (women > 26 mg/l; men > 20 mg/l) were detected in 43 cases (21.1%), indicating a recent increased alcohol consumption. The rate of increased CDT levels was much higher in males (31.5%) than in females (7.9%). Of these cases, 39.7% had elevated serum γ-GT concentrations (females > 19 U/l, males > 28 U/l), whereas 25.3% showed increased ASAT values (females > 15 U/l, males > 19 U/l) and 19.1% higher ALAT levels (females > 18 U/l, males > 22 U/l). Blood analysis revealed pathological MCV values (>95.0 fl) in 17.2% of the sample.

As shown in Tables 1–3, there were significant differences in all biochemical values between cases classified as alcohol-dependent or alcohol abuser and as non-alcoholics by the ICD-10 criteria (Table 1), or identified as abstainers or light drinkers and as heavy drinkers by the CAGE (Table 2) or MAST (Table 3) respectively. Since significant sex differences of many alcohol markers have been reported (Nilssen et al., 1992; Nyström et al., 1992; Anton and Moak, 1994; Gronbaek et al., 1995), the correlations of the biological parameters with the self-ratings were calculated separately for females and males (Table 4).

Table 4. Correlations of self-report tests (CAGE and MAST) with biochemical parameters, frequency, and amount of drinking

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>CAGE</th>
<th>MAST</th>
<th>Frequency</th>
<th>Amount</th>
<th>CDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>0.12</td>
<td>0.29*</td>
<td>0.35**</td>
<td>0.57***</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>0.44**</td>
<td>0.13</td>
<td>0.44**</td>
<td>0.23</td>
<td>0.30*</td>
</tr>
<tr>
<td>γ-GT</td>
<td>0.56***</td>
<td>0.54***</td>
<td>0.58***</td>
<td>0.52**</td>
<td>0.32*</td>
</tr>
<tr>
<td>ALAT</td>
<td>0.46**</td>
<td>0.56***</td>
<td>0.56***</td>
<td>0.56*</td>
<td>0.27</td>
</tr>
<tr>
<td>ASAT</td>
<td>0.49**</td>
<td>0.50**</td>
<td>0.41**</td>
<td>0.34*</td>
<td>0.22</td>
</tr>
<tr>
<td>Males:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>0.14</td>
<td>0.18</td>
<td>0.39***</td>
<td>0.48***</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>0.30**</td>
<td>0.22*</td>
<td>0.28**</td>
<td>0.20*</td>
<td>0.47***</td>
</tr>
<tr>
<td>γ-GT</td>
<td>0.47**</td>
<td>0.20</td>
<td>0.39**</td>
<td>0.30**</td>
<td>0.14</td>
</tr>
<tr>
<td>ALAT</td>
<td>0.13</td>
<td>0.04</td>
<td>0.31*</td>
<td>0.21</td>
<td>0.12</td>
</tr>
<tr>
<td>ASAT</td>
<td>0.02</td>
<td>0.03</td>
<td>0.19</td>
<td>0.10</td>
<td>0.01</td>
</tr>
</tbody>
</table>

For abbreviations, see the text. *P < 0.05; **P < 0.01; ***P < 0.001.
### Table 5. Sensitivity, specificity, and predictive values for alcohol dependence of the CAGE, MAST, and biochemical parameters

<table>
<thead>
<tr>
<th>Questionnaire/biochemical parameter</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAGE</td>
<td>49.1</td>
<td>98.0</td>
<td>90.0</td>
<td>83.9</td>
</tr>
<tr>
<td>MAST</td>
<td>47.3</td>
<td>98.7</td>
<td>92.9</td>
<td>83.5</td>
</tr>
<tr>
<td>CDT</td>
<td>47.3</td>
<td>88.6</td>
<td>60.5</td>
<td>82.0</td>
</tr>
<tr>
<td>γ-GT</td>
<td>57.6</td>
<td>69.5</td>
<td>47.5</td>
<td>77.4</td>
</tr>
<tr>
<td>ALAT</td>
<td>33.0</td>
<td>88.3</td>
<td>57.5</td>
<td>78.0</td>
</tr>
<tr>
<td>ASAT</td>
<td>40.9</td>
<td>81.9</td>
<td>51.9</td>
<td>74.3</td>
</tr>
<tr>
<td>MCV</td>
<td>33.3</td>
<td>88.4</td>
<td>52.8</td>
<td>77.9</td>
</tr>
</tbody>
</table>

For abbreviations, see the text.

4). Whereas in women CDT correlated only slightly with MAST, in men CAGE as well as MAST correlated with the CDT values. In females all the other alcohol markers correlated with both the CAGE and MAST quite well, whereas this was not the same for men.

The sensitivity, specificity, and the positive and negative predictive values (PPV/NPV) were calculated according to the following formulae:

- Sensitivity = true positives/(true positives + false negatives);
- Specificity = true negatives/(true negatives + false positives);
- PPV = true positives/all patients with positive test results;
- NPV = true negatives/all patients with negative test results.

The ICD-10 diagnosis of alcohol dependence or abuse was used as standard in Table 5, whereas reported harmful alcohol consumption [according to the definition used in a WHO study (Bohn et al., 1995)] was applied in Table 6. According to recent harmful alcohol intake, the positive predictive values were rather low in all tests (PPV <50%) (Table 6). With the ICD-10 diagnosis as standard (Table 5), the CAGE and MAST showed a rather high specificity (>0.95) and PPV (about 90%). CDT revealed the best PPV of all alcohol markers (60%). However, the sensitivities of the CAGE, MAST, and the alcohol markers for the ICD-10 diagnosis were rather low (<60%) both for ICD-10 diagnosis (Table 5) and for harmful alcohol consumption (Table 6).

### DISCUSSION

Screening medical patients for excessive alcohol drinking is important because: (1) minimal intervention by physicians is effective in reducing excessive consumption (Holder et al., 1991); and (2) severe complications (e.g. alcohol-withdrawal syndrome) can be prevented. Screening tests, such as biological markers of alcohol consumption or short self-ratings, should therefore be investigated to assess their validity to detect harmful alcohol consumption. However, there is a considerable disagreement in the literature on the terminology and the definition of alcohol problems, particularly the limits of harmful drinking. This lack of agreement makes it problematic to discuss the validity of different markers or instruments. As discussed in many articles (see, e.g. Nielsen et al., 1994), the most important factor in estimating the validity measures of biological parameters or instruments is the chosen 'gold standard'. As shown in some reviews, the PPV and NPV, the clinically most interesting measures, depend particularly on the applied diagnostic standard method (Storgaard et al., 1994), and the prevalence of alcohol problems in the population.

In the first part of the present study, the ICD-10 diagnosis of alcohol dependence was taken as 'standard', and in the second part the self-reported recent alcohol consumption. However, the use of recent alcohol consumption from medical patients as a standard for the evaluation of biological alcohol markers or short self-report tests may be questionable. By contrast, standardized quantity and frequency questionnaires investigating the...
average weekly alcohol intake have been shown to be the most reliable instruments to measure alcohol consumption (Babor et al., 1987).

A variety of laboratory tests are available to assist in the diagnosis of harmful alcohol consumption (Conigrave et al., 1995). In most studies (for review, see Wetterling and Kanitz, 1996), however, the validity measures of so-called alcohol markers have been calculated by contrasting their values in clearly alcohol-dependent patients with those in abstainers or very light drinkers. It is apparent that most laboratory parameters are relatively insensitive markers of short-term heavy alcohol drinking due to their time course. Thus, a single alcohol bout could not be detected by the main alcohol markers γ-GT, MCV, and CDT and so only 65% of ethanol-intoxicated alcohol-dependent subjects showed elevated CDT levels (Lesch et al., 1996a). CDT values also do not correlate with alcohol-related disabilities or severity of the withdrawal syndrome (Lesch et al., 1996a). In a drinking experiment, healthy males consuming 80 g of alcohol daily for 3 weeks were not detected through any significant changes in CDT values (Lesch et al., 1996b). In a study of subjects who drank over 80 g of alcohol daily for at least 3 weeks immediately prior to the measurements, the CDT levels were elevated in only 31%, MCV values in 14%, and γ-GT in 11% (Bisson and Milford-Ward, 1994). Our results revealed a slightly higher proportion of pathological values in persons with harmful alcohol consumption during the previous 4 weeks (CDT 35%, γ-GT, 26.8%, and MCV, 31.3%). It is likely therefore that subjects with excessive alcohol consumption for periods shorter than 4 weeks may not be detected by these laboratory parameters.

As in epidemiological studies (Nilssen et al., 1992; Nyström et al., 1992), the sensitivity of CDT and other alcohol markers in detecting alcoholics is rather poor in our unselected clinical sample. In a similar survey, CDT and γ-GT showed little higher sensitivity in men (Yersin et al., 1995). The sensitivity of CDT is particularly low in females (Nyström et al., 1992; Löf et al., 1994; Gronbaek et al., 1995; Yersin et al., 1995). However, for clinicians, the PPV and NPV are the most important parameters. As shown in Tables 5 and 6, all alcohol markers were invalid with low PPVs (<60%). Thus, single alcohol markers do not provide an early and sufficient discrimination of heavy from light drinkers in a clinical setting.

The short questionnaires CAGE (Mayfield et al., 1974) and MAST (Selzer, 1971) have been applied in many studies. Thus far, only a few studies compared the validity measures of different tests for alcohol abuse by using DSM-III or DSM-III-R criteria (American Psychiatric Association, 1987) as standard (for review, see Storgaard et al., 1994). In our sample, those cases classified as alcohol-dependent or having high CAGE or MAST scores revealed pathological laboratory findings and, like those with elevated CDT values, reported a significantly higher alcohol intake. Thus, our data (Tables 1–3) show internal consistency.

The PPV of the MAST in unselected clinical samples as well as in epidemiological surveys was rather low (Nielsen et al., 1994). In our sample the PPV and sensitivity of the CAGE and MAST for recent harmful alcohol consumption were rather low (sensitivity <60%; PPV <50%). With the ICD-10 diagnosis as standard, the CAGE and MAST showed a high specificity (>95%) and PPV (about 90%), but the sensitivity of the CAGE and MAST for the ICD-10 diagnosis was rather poor (<50%). It is noteworthy that the CAGE and MAST only assess the lifetime risk of severe alcohol problems, whereas laboratory tests can detect a recent elevation in alcohol consumption.

As in some other studies, we found that the specificity of the MAST (or modifications) and CAGE in detecting either excessive drinking or alcoholism was much higher than γ-GT (Bisson and Milford-Ward, 1994; Girela et al., 1994; Gronbaek et al., 1995) and MCV (Bisson and Milford-Ward, 1994; Girela et al., 1994). However, the positive and negative predictive values of alcohol markers were low in all tests (Nyström et al., 1992; this study). Recent data suggested that another method of measuring CDT (relative % of total serum transferrin) may offer some advantages in identifying heavy drinkers (Lesch et al., 1996c).

In summary, the application of short questionnaires, like the CAGE or MAST, as well as laboratory alcohol markers, do not provide a good prediction of the risk of alcohol-related complications, which are mostly associated with recent hazardous alcohol consumption (>21 days). Thus, further clinical investigations are urgently needed.
in order to find a good indicator of harmful alcohol intake. For the identification of alcohol dependence or abuse, a refined instrument combining CAGE and MAST items was recently evaluated: the Lübeck Alcohol Dependence and Abuse Screening Test or LAST (Rumpf et al., 1997). For identifying hazardous levels of alcohol consumption the Alcohol Use Disorders Identification Test, AUDIT (Bohn et al., 1995) and the TWEAK test (Chan et al., 1993) are promising. However, different cut-off values have been recommended for the AUDIT (e.g. Schmidt et al., 1995; Volk et al., 1997), which impedes the usefulness of this instrument. One aim of future research might be to develop screening tools that differentiate between alcohol dependence, alcohol abuse, and at-risk drinking.

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