Thrombocytopenia in Early Alcohol Withdrawal is Associated with Development of Delirium Tremens or Seizures

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Abstract — Aims: In several studies, possible risk factors/predictors for severe alcohol withdrawal syndrome (AWS), i.e. delirium tremens (DT) and/or seizures, have been investigated. We have recently observed that low blood platelet count could be such a risk factor/predictor. We therefore investigated whether such an association could be found using a large number of alcohol-dependent individuals (n = 384). Methods: This study is a retrospectively conducted cohort study based on data from female and male patients (>20 years of age), consecutively admitted to an alcohol treatment unit. The individuals had to fulfil the discharge diagnoses alcohol dependence and alcohol withdrawal syndrome according to DSM-IV. Results: During the treatment period, 3% of the patients developed DT; 2% seizures and none had co-occurrence of both conditions. Among those with DT, a higher proportion had thrombocytopenia. Those with seizures had lower blood platelet count and a higher proportion of them had thrombocytopenia. The sensitivity and specificity of thrombocytopenia for the development of DT during the treatment period was 70% and 69%, respectively. The positive predictive value (PPV) was 6% and the negative predictive value (NPV) was 99%. For the development of seizures, the figure for sensitivity was 75% and for specificity 69%. The figures for PPV and NPV were similar as those for the development of DT. Conclusions: Thrombocytopenia is more frequent in patients who develop severe AWS (DT or seizures). The findings, including the high NPV of thrombocytopenia, must be interpreted with caution due to the small number of patients who developed AWS. Further studies replicating the present finding are therefore needed before the clinical usefulness can be considered.

INTRODUCTION

The alcohol withdrawal syndrome (AWS) occurs in alcohol-dependent individuals who abruptly reduce or discontinue their alcohol consumption. The most severe manifestations of the AWS are alcohol withdrawal delirium (delirium tremens (DT)) and/or seizures. It has even been suggested that individuals with DT or seizures could represent a clinically, and maybe genetically, homogenous subgroup (Gorwood et al., 2003).

DT has been estimated to occur in ~5–20% of the individuals who undergo treatment for alcohol withdrawal (Mayo-Smith et al., 2004; Lee et al., 2005; Wright et al., 2006), although there is a great variation between studies ranging from 1.25% (Shaw et al., 1998) up to 33% (Lee et al., 2005). DT is a severe manifestation of the AWS and the mortality rate may be in the range of 5–15% (Lee et al., 2005) and historically it has even been reported to be as high as 20% (Victor, 1966). However, with appropriate detection and treatment, including the use of benzodiazepines, the mortality should be in the range of 1% or less (Ferguson et al., 1996; Mayo-Smith et al., 2004).

Alcohol-related seizures generally occur 6–48 h after the end of alcohol consumption and frequently in the absence of other signs of the AWS (Rathlev et al., 2006). Multiple seizures occur in more than half of the individuals but do rarely (<5%) progress to status epilepticus (Rathlev et al., 2006). Alcohol-related seizures are in >50% of the individuals associated with concurrent risk factors such as epilepsy, structural brain lesions related to stroke or trauma, and use of other drugs (Rathlev et al., 2006). It should be noted that the development of alcohol-related seizures is associated with ~4-fold increase in the mortality rate. This is primarily due to complications of alcohol dependence rather than a direct effect of seizures or status epilepticus (Bråthen et al., 1999).

Clinical experience suggests that the best way to prevent severe AWS, such as DT, is to monitor alcohol withdrawal closely and treat promptly (Myrick and Anton, 2000). It is therefore extremely important for clinicians to be able to identify individuals at high risk for developing a severe AWS. In several studies, possible risk factors/predictors for the development of severe AWS have been investigated. It appears that the most robust risk factor/predictor is a history of previous DTs and/or withdrawal seizures (Shaw et al., 1998; Palmstierna, 2001; Fiellin et al., 2002; Lee et al., 2005; Wright et al., 2006). In some studies, concurrent medical illness or infectious diseases have been found to be risk factors/predictors (Schuckit et al., 1995; Ferguson et al., 1996; Wojnar et al., 1999; Palmstierna, 2001; Wright et al., 2006). Furthermore, cardiovascular parameters in AWS such as heart rate, cardiovascular (Palmstierna, 2001), elevated systolic blood pressure of 145 or above (Fiellin et al., 2002) have been reported to be such risk factors/predictors. Additionally, the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale, which is a validated 10-item assessment tool, can be used to quantify the severity of the AWS (Paz and Stokes, 2005). It has been suggested that scores >15 points correspond to severe AWS and thus an increased risk of DT and seizures (Bayerd et al., 2004). Finally, the utility of several laboratory parameters as possible risk factors/predictors for severe AWS has also been investigated. Thus, low levels of serum potassium has been found to be associated with the development of DT (Wadstein and Skade, 1978; Wetterling et al., 1994) although this finding could not be replicated in a study using subsequent multivariate analysis (Lee et al., 2005). In studies using laboratory parameters, known to be associated with riskful/harmful alcohol consumption, not only elevated levels of the liver enzymes like alanine aminotransferase (ALT), aspartate
aminotransferase (AST) and gamma-glutamyltransferase (GGT) but also carbohydrate-deficient transferrin (CDT) and mean corpuscular volume (MCV) have been found to be associated with more severe alcohol withdrawal symptoms, as assessed by a specially designed rating scale (Wetterling et al., 1998). Furthermore, Brøthén et al. (2000) reported that elevated levels of ALT, AST, ALT/AST ratio, GGT and CDT were risk factors/predictors of alcohol-related seizures with CDT being the best single marker. However, the clinical utility of these laboratory parameters as risk factors/predictors for the development of a severe AWS is greatly hampered by their low sensitivity (Wetterling et al., 1998; Brøthén et al., 2000).

Besides the above-mentioned rather well-established risk factors/predictors, we have recently observed in a small number of patients that low blood platelet count could also be such a risk factor/predictor. We therefore decided in the present study to investigate whether such an association could be found using a large number of alcohol-dependent individuals treated for AWS (n = 334). In addition, other known risk factors/predictors such as histories of previous DT and/or seizures as well as blood pressure, pulse rate and laboratory parameters (serum potassium level, haemoglobin, white blood cell counts, MCV, AST, ALT, GGT and CDT) at admission were also examined.

MATERIAL AND METHODS

Individuals
This study is a retrospectively conducted cohort study based on data from female and male patients (above 20 years of age), consecutively admitted to an alcohol treatment unit of a university hospital during the years 1997–1998. The reasons for admittance were generally long-term periods of heavy alcohol consumption necessitating treatment for alcohol withdrawal symptoms. To be included in this study, individuals had to fulfill the discharge diagnoses alcohol dependence and alcohol withdrawal syndrome according to DSM-IV (American Psychiatric Association, 1994).

Treatment period
In the morning, the day after admission, blood samples were collected for routine laboratory parameters. A psychiatrist examined the individuals psychiatically and physically. All patients were treated with standard schemes of either benzodiazeines (diazepam) or chlomethiazol in decreasing doses during the treatment period. Additional doses were only given when considered necessary.

During their treatment period, a hospital record was established or new data added into earlier records. Information of alcohol intake, psychiatric or somatic treatments prior to admission was also recorded and individuals were asked whether treatments in other hospital had occurred previously. Copies of records from other hospitals were collected and relevant data added to the patient’s record. After discharge, mostly after a treatment period of 5–6 days, summary about the latest admission and diagnoses was added and registered.

Concerning the amount of alcohol intake prior to admission, it was not possible to receive reliable information from the patients. They gave varying reports of their alcohol intake at the time point for admission and also when interviewed later during the treatment period. However, most of the patients had ended their alcohol intake shortly (the same day) before admission. Lee et al. (2005) found that in their patients, who were also admitted to hospital for treatment of alcohol withdrawal, the reports on amount and duration of alcohol consumption were frequently not in agreement with those of the patients’ relatives. Therefore, in agreement with Lee et al. (2005), we considered that the patients’ self-reports on alcohol consumption before admission could not be regarded as valid or reliable data and therefore not be used in the analyses. Since most of the patients had ended their alcohol intake at the same day when they were admitted, blood platelet counts were determined within 1 day after the end of alcohol intake. Consequently, the influence of length of abstinence prior to the determination of blood platelet count was eliminated.

Evaluation of the hospital records
An independent and experienced research assistant performed examination of the hospital records for the treatment period 1997–1998. The examination covered the occurrence of DT and/or seizures for the time period when patients were treated in the hospital as well as preceding time periods (often several years). Discharge diagnosis rather than admission diagnosis was used to increase the sensitivity of cohort identification (see Lee et al., 2005).

Laboratory parameters
The following data were collected for the treatment period 1997–1998: blood platelet counts (reference range: 150–400 × 10⁹/L), haemoglobin (135–175 g/L), white blood cell count (4–10 × 10⁹/L), serum potassium (3.5–5.0 mmol/L), MCV (80–100 fl), AST (0.2–0.8 μkat/L), ALT (0.2–0.8 μkat/L), GGT (<0.8 μkat/L), CDT (<1.7%), pulse and blood pressure levels.

Blood platelet counts, haemoglobin, MCV and white blood cell counts were determined using an automatic counter, Sysmex SE-9000 (Sysmex, Kungsbacka, Sweden). Serum potassium concentration and catalytical concentrations of AST, ALT and GGT were determined on a Hitachi 917 instrument (Boehringer Mannheim, Mannheim, Germany). The proportion (%) of CDT in relation to the total transferrin concentration in serum was determined by ion exchange chromatography using a Dionex HPLC instrument (Dionex, Gothenburg, Sweden).

All biochemical methods were approved according to standards for routine laboratory assessments defined by the Swedish Board for Accreditation and Conformity Assessment. Units are reported according to the International System of Units.

Statistical analyses
An unpaired t-test for continuous variables and Fisher’s exact test for categorical variables were used when appropriate. One-way analysis of variance followed by Tukey’s post hoc test was also used for comparisons of continuous variables. P < 0.05 was considered as statistically significant. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated according to standard formulae (see e.g. Wetterling et al., 1998). SPSS version 15.0 was used for all statistical analysis.
This study was approved by the Ethics Committee of the University of Gothenburg, Sweden, and was in compliance with the Helsinki Declaration of 1975. Informed consent was obtained from all subjects. None of the subjects were paid for their participation in the study.

RESULTS

Subjects and development of DT and seizures

The study sample comprised 334 patients, 57 females (17%) and 277 males (83%), admitted to the alcohol treatment unit of the university hospital during the years 1997–1998. The mean age of the patient group was 49 ± 11 years; ns.

Seven percent (22/306) had a history of previous DT and 9% (31/317) a history of previous seizures. During their treatment period, 3% (10/334) of the patients developed DT, 2% (8/333) developed seizures and none had co-occurrence of both conditions.

Risk factors/predictors for the development of DT

As seen in Table 1, among those who developed DT during their treatment period, a significantly higher proportion had thrombocytopenia (<150 × 10^9/L, according to the lower reference limit of the laboratory) for those who did not develop DT (70% versus 30%; P < 0.05). Furthermore, in those who developed DT during the treatment period, a significantly higher proportion had a history of previous DT in comparison to those who did not (40% versus 7%; P < 0.01). Patients who developed DT had also significantly lower systolic blood pressure (t[1,310] = 2.02; P < 0.05) and serum potassium (t[1,327] = 2.70; P < 0.01), and higher levels of the liver function tests AST (t[1,331] = 2.81; P < 0.01) and GGT (t[1,323] = 4.27; P < 0.001).

Risk factors/predictors for the development of seizures

Those who developed seizures during their treatment period (see Table 2) had significantly lower blood platelet count (t[1,331] = 2.72; P < 0.01) and a higher proportion of these patients had thrombocytopenia in comparison to those who did not develop seizures (75% versus 25%; P < 0.05). In those who developed seizures, a significantly higher proportion had a history of previous seizures in comparison to those who did not (37% versus 9%; P < 0.05). They had significantly higher levels of the liver function tests AST (t[1,330] = 7.49; P < 0.001) and GGT (t[1,322] = 2.44; P < 0.01), and also of %CDT (t[1,321] = 3.32; P < 0.001).

The group consisting of patients with neither DT nor seizures was compared in an analysis of variance with the two above-mentioned groups. In this calculation, the results did not change with the exception that the serum potassium level was not significantly lower in patients who developed DT.

Predictive power of thrombocytopenia

The sensitivity and specificity of thrombocytopenia for the development of DT during the treatment period was 70% and 69%, respectively. The PPV was 6% and the NPV 99%. For the development of seizures, the figure for sensitivity was 75% and for specificity 69%. The figures for PPV and NPV were similar as those for the development of DT (6% and 99%, respectively).

Gender effects

Male patients had significantly lower blood platelet count than female patients (male: 189 ± 87 × 10^9/L; female: 249 ± 85 × 10^9/L; t[1,332] = 4.75; P < 0.001) and a significantly higher proportion of the males had thrombocytopenia (<150 × 10^9/L; male: 37% [102/277]; female: 12% [7/57]; χ²[1,334] = 12.95; P < 0.001). Male patients had also a higher %CDT than female patients (male: 4.1 ± 3.4; female: 2.4 ± 1.7; t[1,321] = 3.73; P < 0.001). None of the other independent variables differed significantly between male and female patients (data not shown).

Haemoglobin, MCV and white blood cell counts

For the total group, the mean value for haemoglobin was 143 ± 15 g/L, for MCV 93 ± 7 fl and for the mean white blood cell counts 7 ± 3 × 10^9/L. There was no difference in haemoglobin values, MCV values or white blood cell counts in patients who developed DT or seizures when compared to those who did not. The mean haemoglobin, MCV and white blood cell

| Table 1. Data for individuals with or without development of DT during their treatment period |
|-----------------------------|-----------------------------|
|                             | DT (n = 10)                | No DT (n = 324)               |
| Blood platelet count (× 10^9/L) | 149 ± 100                  | 201 ± 88                     |
| Patients (%) with           |                            |                             |
| Thrombocytopenia (<150 × 10^9/L) | 70 (7/10)                  | 30 (102/324)*               |
| Past history of DTs         | 40 (4/10)                  | 7 (22/306)**                |
| Past history of seizures    | 0 (0/10)                   | 10 (31/307)                 |
| Pulse rate (beats/min)      | 88 ± 15                    | 87 ± 18                     |
| Systolic blood pressure (mmHg) | 120 ± 22                   | 136 ± 23*                   |
| Diastolic blood pressure (mmHg) | 77 ± 12                    | 84 ± 15                     |
| Serum potassium level (mmol/L) | 3.6 ± 0.7                  | 3.9 ± 0.4**                 |
| ALT (μkat/L)                | 2.3 ± 1.8                  | 1.5 ± 4.4                   |
| AST (μkat/L)                | 3.2 ± 3.0                  | 1.5 ± 1.9**                 |
| GGT (μkat/L)                | 14.4 ± 28                  | 3.6 ± 6.2**                 |
| %CDT                        | 5.2 ± 6.6                  | 3.8 ± 3.2                   |

Values are presented as mean ± SD or percentage (frequency within parentheses).

*P < 0.05; **P < 0.01; ***P < 0.001 (unpaired t-test and Fisher’s exact test).

| Table 2. Data for individuals with or without development of seizures during their treatment period |
|-----------------------------|-----------------------------|
|                             | Seizures (n = 8)            | No seizures (n = 325)        |
| Blood platelet count (× 10^9/L) | 116 ± 52                   | 202 ± 89**                  |
| Patients (%) with           |                            |                             |
| Thrombocytopenia (<150 × 10^9/L) | 75 (6/8)                   | 25 (102/325)*              |
| Past history of DTs         | 0 (0/8)                    | 9 (28/308)                  |
| Past history of seizures    | 37 (3/8)                   | 9 (28/308)*                 |
| Pulse rate (beats/min)      | 93 ± 24                    | 87 ± 18                     |
| Systolic blood pressure (mmHg) | 144 ± 29                   | 135 ± 23                    |
| Diastolic blood pressure (mmHg) | 84 ± 19                    | 83 ± 15                     |
| Serum potassium level (mmol/L) | 3.7 ± 0.5                  | 3.9 ± 0.4                   |
| ALT (μkat/L)                | 4.0 ± 1.4                  | 1.4 ± 4.4                   |
| AST (μkat/L)                | 6.2 ± 4.0                  | 1.4 ± 1.7***                |
| GGT (μkat/L)                | 10.4 ±12.8                 | 3.7 ± 7.5**                 |
| %CDT                        | 7.8 ± 6.0                  | 3.7 ± 3.2**                 |

Values are presented as mean ± SD or percentage (frequency within parentheses).

*P < 0.05; **P < 0.01; ***P < 0.001 (unpaired t-test and Fisher’s exact test).
counts were within the normal range and thus not associated with thrombocytopenia.

**DISCUSSION**

In the present study, we found that thrombocytopenia was more frequently observed in alcohol-dependent individuals who developed a severe AWS, i.e. DT or alcohol-related seizures. Furthermore, blood platelet count was lower in those who developed alcohol-withdrawal seizures. The present finding of an association between thrombocytopenia and the development of severe AWS has to our knowledge not been reported earlier. The mechanism(s) for this association is unknown. One possibility may be that thrombocytopenia and the development of severe AWS are so called parallel phenomena. That is, they both reflect effects of long-term and heavy alcohol consumption. Thus, excessive alcohol consumption has been reported to be associated with thrombocytopenia, possibly mediated by a toxic influence on the bone marrow resulting in reduced platelet production (Latvala et al., 2004). The finding of mean haemoglobin values and white blood cell counts within the normal range may support the notion that the thrombocytopenia was alcohol-related and not due to non-alcohol-related causes. The development of a severe AWS may also be a consequence of long-term and heavy alcohol consumption (Cushman, 1987; Schuckit et al., 1995) and its effect on the brain function. In addition, severe AWS may be associated not only with thrombocytopenia but also with the functioning of platelets (Takahashi et al., 1976; Berggren et al., 2000). The finding of more markedly elevated levels of the liver function tests, AST and GGT, and CDT in the individuals who developed a severe AWS may also support such possibility of a parallel phenomenon, since these laboratory parameters are markers for excessive alcohol consumption. It may also be of clinical importance that blood platelet count is assessed before start of treatment for alcohol withdrawal, since thrombocytopenia and the subsequently rebound thrombocytopenia has been reported to be associated with the onset of brain infarction in alcoholics (Numminen et al., 1996).

In this study, levels of the liver function tests, AST and GGT, and CDT were elevated in individuals with a severe AWS. However, there was a great overlapping in these test results between individuals who developed a severe AWS and those who did not. This finding thus supports the notions from earlier studies that the clinical utility of liver function tests and CDT as risk factors/predictors for development of a severe AWS is hampered by their low sensitivity (Wetterling et al., 1998; Bråthen et al., 2000). Nevertheless, the finding of elevated levels of the liver function tests and CDT in the present study are thus in agreement with findings in these latter studies and may therefore be regarded as a validation of the finding in the present study of an association between thrombocytopenia and the development of severe AWS. In the present study, we also found that low serum potassium levels were associated with the development of a severe AWS that replicates findings from some earlier studies (Wådstein and Skude, 1978; Wetterling et al., 1994).

The cardiovascular parameters, pulse rate and diastolic blood pressure were not different between the groups, whereas systolic blood pressure was lower in those who developed DT. This finding is thus in contrast with observations from some other studies reporting elevated pulse rate or systolic blood pressure in individuals who developed a severe AWS (Palmstierna, 2001; Fiellin et al., 2002; Lee et al., 2005). Finally, in the present study, histories of previous DT were more common among those who developed DT during their treatment period and similarly were histories of seizures more common among those who developed seizures.

The sensitivity and specificity for thrombocytopenia as a risk factor/predictor for development of severe AWS (DT or seizures) were moderately high (~70%). The figure for PPV was very low (6%), whereas NPV was extremely high (99%). Such a high figure for NPV may be of apparent clinical importance but must be interpreted with caution given the low prevalence of AWS in the study population, which per se favours high NPV of any test (Grimes and Schulz, 2002). Nevertheless, it is possible that subjects with blood platelet counts within normal range (in the present study about 2/3) indeed do run a low risk for the development of severe AWS. If verified in other studies, preferentially in populations with higher AWS incidence, such individuals could be considered for outpatient and thus less expensive treatment regimes. When comparing these figures for thrombocytopenia as a risk factor/predictor for the development of severe AWS with those of well-established risk factors/predictors such as histories of previous DTs and/or withdrawal seizures (see the ‘Introduction’ section), these are relatively similar, although the PPV is lower whereas the NPV is somewhat higher. Thus, in the present study, the sensitivity and specificity for past history of DT for the development of DT were 40% and 92%, respectively. Corresponding figures for PPV and NPV were 15 and 98%. For past history of seizures, these figures were 37%, 91%, 10% and 97%, respectively (data not shown in results).

There are, however, some limitations to this study. First, it is a retrospective cohort study without a control group. Second, a relatively small number of individuals developed a severe AWS, i.e. DT or seizures, during their hospitalization period (in total 18 out of 334 patients; 5%). Due to this large difference in size between groups (those who did and did not develop severe AWS), logistic regression analyses could not be performed. As mentioned above, the low prevalence also affects the predictive values favouring high NPV. The low prevalence of severe AWS in comparison to other studies (see the ‘Introduction’ section) might have been due to long experience among staff members in the treatment of alcohol withdrawal symptoms and also that they had personal knowledge of most of the patients. In addition, the staff members had been thoroughly educated to evaluate the presence of risk factors/predictors for the development of a severe AWS. Thus, they regularly collected information on earlier episodes of severe AWS (obtained from patients and/or medical records) and measured cardiovascular parameters (pulse rate and blood pressure). Nevertheless, despite these rigorous treatment procedures, some patients developed severe AWS. This indicates a need of additional predictors to further decrease the prevalence of DT and/or seizures. Another limitation in this study is the number of female patients, which was too low to allow firm conclusions on gender effects.

To sum up, the present study has two main findings. Firstly, thrombocytopenia is more frequent in patients who develop severe AWS (DT or seizures). Secondly, when using thrombocytopenia as a risk factor/predictor for the development of severe AWS, this biological marker has a high NPV. That is,
individuals with blood platelet count within the normal range have a low risk for the development of severe AWS. Future studies are needed to determine if this biological marker may be suitable for treatment allocation procedures. i.e. if patients with blood platelet counts within the normal range can be considered for out-patient and thus less expensive treatment regimes.

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