Factors predictive of complicated or severe alcohol withdrawal in alcohol dependent inpatients


Service d’hépatogastroentérologie, service de pathologie digestive, hôpital d’Instruction des Armées Bégin, 69, avenue de Paris, 94160 St-Mandé, France
Centre de recherche du service de santé des Armées, 38000 Grenoble, France

Available online 30 August 2008

Summary

Objective. — In a department of hepatology and gastroenterology, a significant number of patients are hospitalized for alcohol withdrawal. The aim of this retrospective study was to identify factors predictive of severe or complicated alcohol withdrawal in order to improve patient management.

Methods. — Between June 2002 and June 2005, 182 patients admitted for alcohol dependence according to the DSM-IV classification were enrolled in this study. A unique management protocol for alcohol withdrawal was applied for all patients. The Cushman score was recorded on day 1, 2 and 3 to assess the severity of alcohol withdrawal. We searched for correlations between epidemiological, clinical and biological data and the Cushman score.

Result. — The study population included 136 (74.7%) men and 46 (25.3%) women, mean age 47.6 ± 10.1 years. One hundred and eighteen patients (64.8%) were referred from a specialized outpatient clinic and 64 (35.2%) patients were referred from the emergency unit. The mean and median Cushman scores on day 1, 2 and 3 were: 5.1 and 5; 3.9 and 4; 2.3 and 2, respectively. Twenty patients (11.0%) and five patients (2.7%) had scores greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002). Mean alanine aminotransferase level on day 1 was significantly higher in patients with a score greater than or equal to 8 and greater than 12, respectively. The proportion of patients with Cushman score greater than or equal to 8 on day 1 was significantly greater in patients referred from the emergency unit than in those referred from a specialized outpatient clinic (p = 0.002).
In conclusion, severe alcohol withdrawal (Cushman score ≥ 8) is significantly associated with initial management in an emergency unit and serum alanine aminotransferase level greater than 1.5-fold the upper limit of the normal range. These predictors should be monitored in order to appropriately adapt the therapeutic schedule.

Résumé
Introduction. — Le nombre d’hospitalisations dans un service d’hépatogastroentérologie pour le sevrage d’une alcoolo-dépendance est important. Le but de cette étude, retrospective, était de déterminer les facteurs prédictifs d’un sevrage alcoolique sévère ou compliqué afin d’améliorer la prise en charge de ces malades. De juin 2002 à juin 2005, 182 malades ayant une alcoolo-dépendance selon la classification DSM-IV pris en charge dans le service pour sevrage ont été inclus dans cette étude. Tous les malades recevaient un protocole de sevrage identique. La gravité du sevrage alcoolique était évaluée par le score de Cushman à j1, j2 et j3. Les paramètres épidémiologiques et biologiques ont été comparés avec les valeurs du score de Cushman. Cent trente-six hommes (74,7 %) et 46 femmes (25,3 %) âge moyen 47,6 ± 10,1 ans ont été inclus. L’hospitalisation a été réalisée à partir d’une consultation d’alcoologie pour 118 malades (64,8 %) et par le biais des urgences pour 64 d’entre eux (35,2 %). La moyenne et la médiane du score de Cushman étaient à j1, j2 et j3, respectivement, de 5,1 et 5 ; 3,9 et 4 ; 2,3 et 2. Vingt malades (11,0 %) et cinq malades (2,7 %) avaient un score, respectivement, supérieur à 8 et supérieur ou égale à 12 à j1. La proportion de malades ayant un score supérieur ou égale à 8 à j1 était supérieure chez les malades venant des urgences que chez ceux issus de la consultation d’alcoologie (p = 0,002). Les malades dont le score était supérieur ou égale à 8 avaient un taux sérique moyen de l’alanine aminotransférase significativement plus élevé à j1 que ceux qui avaient un score inférieur à 8 (respectivement, 112,1 ± 44,4 UI/L versus 78,4 ± 11,8 UI/L ; p = 0,046). L’admission par le biais des urgences ainsi qu’un taux sérique de l’alanine aminotransférase supérieur à 1,5 fois la limite supérieure de la normale étaient les deux variables indépendantes prédictives d’un score de Cushman supérieur ou égale à 8. En conclusion, un syndrome de sevrage sévère lors d’une alcoolo-dépendance est significativement plus associé à une hospitalisation directe par le biais des urgences et à un taux sérique de l’alanine aminotransférase supérieur à 1,5 fois la limite supérieure de la normale. La présence de ces facteurs à l’admission du malade nécessite une surveillance accrue et une éventuelle adaptation de la prise en charge thérapeutique.

Introduction
Complications related to alcohol dependence and alcohol withdrawal account for a significant proportion of hospital activity. In hepatology and gastroenterology departments in France, the rate reaches 4% for delirium tremens and 6% for convulsions, despite preventive treatment [1–3]. In the United States, the figures are even higher, 15% for delirium tremens and convulsions among patients hospitalized for alcohol withdrawal [4].

Management practices could be optimized if patients with a high risk of complications could be identified. The purpose of this retrospective study was to ascertain, among patients hospitalized in our unit for alcohol withdrawal and monitored with the Cushman clinical score, those factors associated with severe or complicated withdrawal [5,6].

Patients and methods
Patients
All adult patients hospitalized in the Bégin Army Instruction Hospital, hepatology and gastroenterology department for alcohol withdrawal, between June 2002 and June 2005 were eligible for inclusion in this study. Inclusion criteria were: alcohol dependence according to the DSM IV criteria and no contraindication for the use of benzodiazepines. Exclusion criteria were: retrospective data collection insufficient to evaluate the intensity of the withdrawal syndrome, active use of illicit drugs or substitution therapy, benzodiazepine dependence and presence of serious psychiatric comorbidity. Patients were recruited directly via our outpatient anti-alcohol clinic or referred from the hospital emergency unit.

Methods
Data were collected from the Bégin Hospital, hepatology and gastroenterology department archives. Data on the following variables are recorded at admission: gender, age at withdrawal, age at onset of excessive alcohol intake (> 60 g per day), number of prior alcohol withdrawal attempts (as inpatient or outpatient), history of convulsion or delirium tremens, number of consultations before hospitalization, initial management in the emergency unit, presence of cirrhosis (Child classification) or alcoholic pancreatopathy, mean corpuscular volume (MCV; < 9.8 μL), prothrombin (PT in percentage), and serum levels of aspar-
tate aminotransferase (AST; n < 35 IU/L), alanine aminotransferase (ALT; n < 45 IU/L), gamma-glutamyl transferase (γGT; n < 55 IU/L), and carbohydrate-deficient transferrin (CDT; n < 2.6%).

Withdrawal schedule

A standardized withdrawal schedule consisted in the administration of depressive doses of diazepam (Valium®), a benzodiazepine recommended for the prevention and treatment of withdrawal syndrome because of its effectiveness in reducing the duration of symptoms and mortality [7,8]. Diazepam was administered orally at the dose of 10 mg every hour for the first six hours then one tablet every four hours for the first 24 h. The dose was then tapered off to one tablet per day until interruption on the fifth day. The oral dose was not delivered if the patient was sleeping. If liver disease was suspected or known, diazepam was replaced by oxazepam (Seresta®) 30 mg (the equivalent to 10 mg diazepam). If however, the patient’s score was greater than 12 on day 1, the initial therapeutic schedule (10 mg every hour) was prolonged until the patient reached a score less and equal to 8. For patients with an initial score greater than 15, diazepam 10 mg hourly was prolonged and if the withdrawal score did not decline after six hours, diazepam was administered intravenously at the dose of 10 mg/h in the intensive care unit.

Clinical monitoring

The Cushman score [5,6] was used to assess the severity of the withdrawal syndrome. This score, which has been validated in this indication [7], takes into consideration the following clinical variables: pulse, systolic blood pressure, respiratory rate, tremor, sweating, agitation, and sensorial disorders (Table 1). The withdrawal syndrome is considered severe for a Cushman score greater than or equal to 8 and complicated for a Cushman score greater than or equal to 12 and/or the presence of criticized hallucinations. A score of greater than or equal to 15 corresponds to the diagnosis of delirium tremens. The nursing team used a standard chart to determine the Cushman score at each intake of benzodiazepines during the first three days of hospitalization. For the purpose of this study, the highest Cushing scores recorded on these charts for day 1, 2, and 3 were retained.

Statistical analysis

A descriptive analysis of the study population was performed. We searched for a relation between the Cushman scores on day 1, 2 and 3 and the different variables recorded. This phase of the analysis consisted in determining the degree of correlation between patient variables and withdrawal scores to identify factors predictive of complicated withdrawal. Non-parametric tests were applied, Spearman’s rank correlation (r) for discrete variables and the Mann-Whitney test for indiscrete variables, \( p < 0.05 \) was considered significant.

Results

General characteristics

During the study period, 200 patients were hospitalized in our department for alcohol withdrawal. Eighteen patients presented an exclusion factor and were not retained for study. The study population thus included 182 patients. Nineteen of these patients were included twice and six patients three times because of repeated hospitalizations for alcohol withdrawal.

The study population included 136 males (74.7%) and 46 females (25.3%). Mean age was 47.6 ± 10.1 years. One hundred and eighteen patients (64.8%) were referred from the unit’s specialized outpatient clinic and 64 patients (35.2%) from the hospital emergency unit. Mean age at onset of excessive alcohol intake was 33.8 ± 11.2 years (range: 25—60). Data were available on withdrawal history in 166 patients: the recorded hospitalization was the first attempt for 56 (33.7%) and 110 (66.3%) who had tried to stop drinking at least one other time in an outpatient or inpatient setting. Twenty-one patients (19.1%) had experienced a complicated withdrawal. The highest daily alcohol intake reported by the patients the day before hospital admission ranged from 80 to 480 g per day (mean 180 ± 105 g per day). Thirty-eight patients (20.9%) had cirrhosis (nine Child A, 11 Child B and 18 Child C) and seven patients (3.8%) had alcoholic pancreatitis (Table 2).

<table>
<thead>
<tr>
<th>Table 1 Cushman score. Score de Cushman.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>Pulse (beats per minute)</td>
</tr>
<tr>
<td>Systolic blood (mmHg)</td>
</tr>
<tr>
<td>Respiratory rate (cycles per minute)</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Perspiration</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Sensorial disorders</td>
</tr>
</tbody>
</table>

Factors predictive of complicated or severe alcohol withdrawal

Table 2  Characteristics of the study population.
Caractéristiques de la population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at withdrawal (years) (range)</td>
<td>47.6 ± 10.1 (25–70)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>136 (74.7)</td>
</tr>
<tr>
<td>Mean age at onset of excessive alcohol intake (years) (range)</td>
<td>33.8 ± 11.2 (14.6–60.9)</td>
</tr>
<tr>
<td>First withdrawal attempt (%)</td>
<td>56a (33.7)</td>
</tr>
<tr>
<td>History of prior withdrawal attempts (%)</td>
<td>110a (66.3)</td>
</tr>
<tr>
<td>History of seizure or delirium tremens (%)</td>
<td>21 (19.1)</td>
</tr>
<tr>
<td>Referral from a specialized outpatient clinic (%)</td>
<td>118 (64.8)</td>
</tr>
<tr>
<td>Referral from emergency unit (%)</td>
<td>64 (35.2)</td>
</tr>
<tr>
<td>Average daily alcohol intake (g per day) (range)</td>
<td>180 ± 105 (80–480)</td>
</tr>
<tr>
<td>Alcoholic cirrhosis (%)</td>
<td>38 (21.0)</td>
</tr>
<tr>
<td>Pancreatopathy (%)</td>
<td>7 (3.8)</td>
</tr>
</tbody>
</table>

a Data missing in 16 patients.

Complicated withdrawal syndrome

Monitored on day 1, 2, and 3, the mean and median Cushman scores were, respectively: 5.1 and 5; 3.9 and 4; 2.3 and 2. On day 1, the Cushman score was greater than or equal to 8 in 20 patients (11.0%) and greater than or equal to 12 in five (2.7%). The score was greater than or equal to 15 in one patient with delirium tremens who was then transferred to intensive care. None of the patients developed seizures during the withdrawal period.

Predictive factors

The search for factors predictive of a complicated withdrawal syndrome failed to identify any correlation between the severity of the withdrawal syndrome and the following variables: patient age at hospitalization, age at onset of excessive alcohol intake, number of prior withdrawal attempts, history of delirium tremens or seizures, number of consultations before withdrawal attempt, presence of cirrhosis or pancreatopathy. The intensity of the withdrawal syndrome was not correlated with alcohol intake level 24 h before hospitalization, but there was a nearly significant correlation with higher mean maximum Cushman scores (days 1 + 2 and days 1 + 2 + 3) (p = 0.063 and 0.056, respectively). Initial Cushman scores were available for 50 of the 64 patients referred from the emergency unit. Their mean Cushman score was significantly higher on day 1, day 3, days 1 + 2, and days 1+2+3 than in patients referred from the unit’s outpatient clinic (p = 0.0001, 0.006, 0.003 and 0.002, respectively) (Table 3). A Cushman score greater than or equal to 8 was more frequent among patients referred from the emergency unit than those referred from the outpatient clinic (p = 0.002). There was no correlation between mean Cushman score and certain blood test results (MCV, PT, CDT). There was, however, a statistically significant positive correlation between the mean Cushman score and serum AST, ALT and γGT levels on day 1, 2 and 3 (Table 4). ALT levels were significantly higher in patients with a Cushman score greater than or equal to 8: 112.1 ± 44.4 versus 78.4 ± 11.8;

Table 3  Correlation between the Cushman score and referral from emergency unit (Mann-Whitney test).
Corrélation entre le score moyen de Cushman et le passage par le Service d’accueil des urgences (SAU) (test de Mann-Whitney).

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Cushman Score</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Days 1 + 2</th>
<th>Days 1 + 2 + 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient clinic</td>
<td>Mean</td>
<td>4.56</td>
<td>3.59</td>
<td>2.02</td>
<td>4.07</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>102</td>
<td>102</td>
<td>102</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>Emergency unit</td>
<td>Mean</td>
<td>6.14</td>
<td>4.24</td>
<td>3.00</td>
<td>5.21</td>
<td>4.48</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>50</td>
<td>49</td>
<td>49</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td>0.006</td>
<td>0.003</td>
<td>0.002</td>
</tr>
</tbody>
</table>

n: number of patients.
NS: Not Significant.
Discussion

This retrospective study was conducted among a department of hepatology and gastroenterology inpatients. The clinical features of our study population were comparable to those reported in a multicentric prospective study conducted in the alcohology units of the Société française d’alcoolologie which included 1043 alcohol dependent patients (EVA study) [9]. The only difference was the mean daily alcohol intake which was lower in our population (223.8 g per day versus 180 g per day) and mean reported age of excessive alcohol intake which was later (21.3 days versus 33.8 days). This difference might be related to the absence of serious psychiatric comorbidity in our population and thus a later onset of excessive alcohol intake. Cirrhosis was also more frequent in the hepatology–gastroenterology unit (5.4% versus 21.0%).

Reports in the literature have been highly variable regarding complications of alcohol withdrawal. Most studies define such complications as the development of epileptic seizure and/or delirium tremens, but very few provide precise information about the severity of the symptoms using a standard clinical scale as was used in our study. In our population, delirium tremens was uncommon (0.5%) and none of the patients had a seizure. Most other studies report rates of ranging from 3.1 to 18.6% [10–13] but also as high as 25–33% [14,15]. Only one other report [16] had such a low rate of complications (1.1%). This low rate of complications might be related to systematic application, as was the case in our study, of a standard therapeutic schedule, independently of the clinical presentation [16]. In our population, only 11.0% of the patients had severe withdrawal (Cushman score ≥ 8) and only 2.7% signs of complicated withdrawal (Cushman ≥ 12). If we had used a protocol linked to the Cushman score, giving benzodiazepine only to patients with a score greater than or equal to 8, the number of patients with complicated withdrawal might well have been higher.

Several factors predictive of severe withdrawal syndrome have been described in the literature. As also reported by other authors [17,18], the duration of alcohol dependence was not found to be a significant factor in our population. This is not in agreement with another study [4] where alcohol dependence greater than six years was predictive of complicated withdrawal. We were unable to identify any correlation between the severity of the withdrawal syndrome and age, as was previously reported [19]. In our population, severity of withdrawal syndrome was not correlated with alcohol intake the day before hospitalization. The mean of the maximum Cushman score recorded during the first three days of hospitalization was, however, higher in patients with higher alcohol intake. This direct relationship between daily alcohol intake and the development of a complicated withdrawal has been reported in three other studies but with a low level of significance [4,20,21]. Other studies have failed to find any correlation between these two variables [19,22–24].

The prevalence of delirium tremens in alcohol dependent patients would increase with increasing number of withdrawal attempts [21,22]. We were unable to find this correlation reported by others [17–19]. A history of delirium tremens was found to be predictive of complicated withdrawal in two studies [4,11,14,17], but not in our analysis. The presence of liver disease at the time of withdrawal might increase the risk of delirium tremens for some authors [10] but not for others [17]. Our standard protocol used oxazepam to avoid the risk of hepatic encephalopathy in patients with liver disease. The fact that these patients (21% of the study population) did not develop a complicated withdrawal syndrome confirms the non-deleterious effect of this compound and its efficacy in preventing withdrawal complications in patients with liver disease.

We demonstrated that patients with a Cushman score greater than or equal to 8 had significantly higher serum ALT levels on day 1 than patients with a Cushman score less than 8 (p = 0.046). Serum ALT greater than 1.5 fold the upper limit of normal was an independent factor predictive of more complicated withdrawal. In the literature, higher γGT and ALT levels [17] or elevated AST [4] are reported as predictive of delirium tremens. The severity of the withdrawal syndrome has not however been compared with the level of the elevation. Patients with more severe liver disease appear to have a greater risk of complicated withdrawal. This would probably be explained by the fact that these patients are seen later since management of withdrawal is considered to be a secondary problem, though further complicated by the compromised liver metabolism.

The observation that patients referred from the emergency unit had more severe withdrawal is logical since hospitalization is proposed for more serious conditions. The management of withdrawal is more difficult in these patients who have a higher prevalence of organic disease. Moreover, signs of withdrawal syndrome was more pronounced in these patients who did not have the proven benefit of a motivated consultation [25]. We thus found objective evidence (mean score ≥ 8) that Cushman scores are significantly higher on day 1 among patients referred from an emergency unit than among those who attended a specialized outpatient consultation. Consequently, referral from an emergency unit was thus an independent factor predictive of more severe withdrawal.

Conclusion

This study, conducted in a hepatology and gastroenterology department demonstrated that systematic use of a standard therapeutic schedule can reduce the development of complicated alcohol withdrawal syndrome. Prudent use of oxazepam in patients with cirrhosis could prevent complicated withdrawal without favoring the development of hepatic encephalopathy.

At admission, several factors should be carefully recorded: high alcohol intake the day before hospitalization, referral from the emergency unit, ALT greater than 1.5 fold the upper limit of normal. These factors are predictive of greater risk of complicated alcohol withdrawal.
Factors predictive of complicated or severe alcohol withdrawal

References


