INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH & DEVELOPMENT

ISSN 2278 – 0211 (Online)

Related Risk Factors and Predictors of Occurrence of Delirium Tremens in Patients with Alcohol Dependence Syndrome Underwent Inpatient Detoxification Programme at Tertiary Care Hospital, Kolenchery, Kerala, India

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Abstract:
Introduction: Delirium tremens is the severe form of alcohol withdrawal state that carries a certain degree of mortality. It is important to understand the contributing factors for the development of this complicated withdrawal state.
Objectives of the Study: is to identify the related risk factors associated with the occurrence of delirium tremens and identify the risk factors predict the occurrence of delirium tremens.
Methodology: This analytical, cross sectional study was carried out to identify the related risk factors associated with the development of delirium tremens (DT) among patients admitted for detoxification treatment of Alcohol dependence syndrome that fulfills ICD-10 diagnostic criteria at MMM De-addiction and research centre, MOSC Medical College Hospital, Kolenchery, Ernakulam dist, Kerala, India.
*Results: Among the 104 patients admitted for detoxification treatment during the period of January 2014- June 2014; twenty-three subjects developed delirium tremens among these, 6 subjects developed withdrawal seizures. The factors significantly associated with delirium tremens are increasing age (p=0.001**), previous history of DT (p=0.001**), binge drinking pattern (p=0.001**), increased amount of alcohol consumption (p=0.02*), and delay in hospitalization (p=0.001**), and increased ASI score (severity of addiction) (p=0.001**). The significant predictors of Delirium tremens are binge drinking, alcoholic liver disease, and increased severity of addiction; among these the significant positive predictor of delirium tremens is increased severity of addiction (OR=1.9 p=0.008*)*
Conclusion: patient admitted for detoxification should be carefully evaluated for these risk factors; and the vulnerable subjects with the presence of these risk factors should be cautiously managed and carefully monitored by the nurses taking care of these patients to prevent the occurrence of the fatal complication associated with alcohol withdrawal syndrome. Environmental manipulation, close observation and monitoring of vital signs, front loading dose of benzodiazepines are essential for preventing the occurrence of Delirium tremens during detoxification period.

Keywords: *Delirium tremens, risk factors, predictive factors, alcohol withdrawal syndrome, detoxification*

1. Introduction

Delirium tremens is the severe form of alcohol withdrawal state that increases the risk of mortality. Complications related to alcohol withdrawal account for a significant demand in healthcare resources and are associated with an increase of morbidity and mortality [i]. The alcohol withdrawal seizure and delirium tremens (DT) do occur in the range of 6–15% and 4–15%, respectively.[ii] Slightly higher rates might be observed among those with excessively high levels of alcohol intake over relatively longer periods of time[iii] . Delirious patients have high morbidity and mortality rates. Mortality in the next 8 years after an episode of delirium tremens is 30.8% Delirium tremens may be complicated by several severe or life-threatening conditions. When diagnosed and managed insufficiently, the

morbidity and mortality rates increase, hospitalization prolongs and complications such as status epileptics, coma or other disorders such as Wernicke-Korsakoff syndrome, central pontine myelinolysis, chronic alcohol hallucinosis or even dementia may develop[iv].
Delirium tremens usually develops within 24-72hours as an acute or subacute complication of withdrawal syndrome. Throughout the day, the fluctuation of symptoms is typical with worsening in the evening and at night (disturbance of circadian rhythm or its inversion). The symptoms usually slowly subside within few weeks.

The neurobiological studies regarding the alcohol withdrawal reveals that with the sudden cessation of alcohol in the chronic user, the alcohol mediated CNS inhibition is reduced and the glutamate mediated CNS excitation is left unopposed, resulting in a net CNS excitation. This CNS excitation results in the clinical symptoms of alcohol withdrawal in the form of autonomic over activity such as tachycardia, tremors, sweating and neuropsychiatric complications such as delirium and seizures[v]. During alcohol use and withdrawal, the increase in CNS dopamine levels contribute to the clinical manifestations of autonomic hyper arousal and hallucinations. Repeated episodes of withdrawal and neuro-excitation results in a lowered seizure threshold as a result of kindling predisposing to withdrawal seizures.[vi]

The treatment strategy could be optimized if patients with a higher risk of developing withdrawal seizure or DT could be identified. Treatment with benzodiazepines significantly reduces the occurrence of withdrawal seizure and delirium tremens. Even when treatment is initiated at the onset of DT or withdrawal seizure the course is often volatile and unpredictable[vii,viii]. Thus prediction and prevention become the cornerstones of avoiding delirium tremens and withdrawal seizure[viii]. The purpose of this study was therefore to identify the risk factors associated with the development of Delirium tremens. The objectives of the study are to find out the related risk factors for developing delirium tremens and to find out the association between risk factors and occurrence of delirium tremens in patients in patients having alcohol dependence syndrome undergoing detoxification program at MOSC Medical College Hospital, Kolenchery, Kerala.

2. Methodology

Among 104 patients admitted for detoxification treatment during the period of January to June 2014 in the de-addiction centre; among them 23 patients developed delirium tremens either during hospital stay or at the time of admission. Patients were diagnosed to develop Delirium tremens by the treating psychiatrist based on ICD 10 diagnostic criteria. The present study was conducted in the inpatient unit of MMM integrated rehabilitation centre for addicts, MOSC Medical college hospital Kolenchery, Ernakulam; Kerala is a tertiary care hospital in Kerala, India. Subjects were requested to participate in the study and were enrolled in the study on 15th day of withdrawal. Approval for the study was obtained from the Institutional ethics committee. All patients who agreed to participate in the study signed the written informed consent form. These Subjects were assessed for their Socio demographic profile, drinking parameters, co morbid medical and psychiatric disorders, severity of addiction inpatient medical records were also analyzed.

2.1. Statistical Analysis

Data were entered and analyzed using R software. Continuous variables were summarized as means (M) and standard deviations (SDs). Categorical variables were presented as the frequency (%) for each variable. For categorical variables chi-square test or Fisher's exact test (χ^2) (where the frequency in a category was small) were used to find the association between the variables and the occurrence of DT. Continuous variables were compared using Student's *t* test (*t*) for independent samples and the Mann-Whitney test (*U*). Normality of the data was assessed using the Kolmogorov-Smirnov test. The predictive factors for the occurrence of DT were analyzed using binary logistic regression with odds ratio (OR) with 95% confidence intervals (CI). All significance tests were performed using a two-sided significance level of 5% ($p < 0.05$)

3. Results

Among the 104 patients admitted for detoxification treatment during the six months period; 23 subjects were identified with delirium tremens. Out of subjects with DTs, six patients developed withdrawal seizures.

3.1. Socio demographic Profile of Subjects

Data are expressed as mean (SD), Range for continuous variables and as frequency (%) for categorical variables

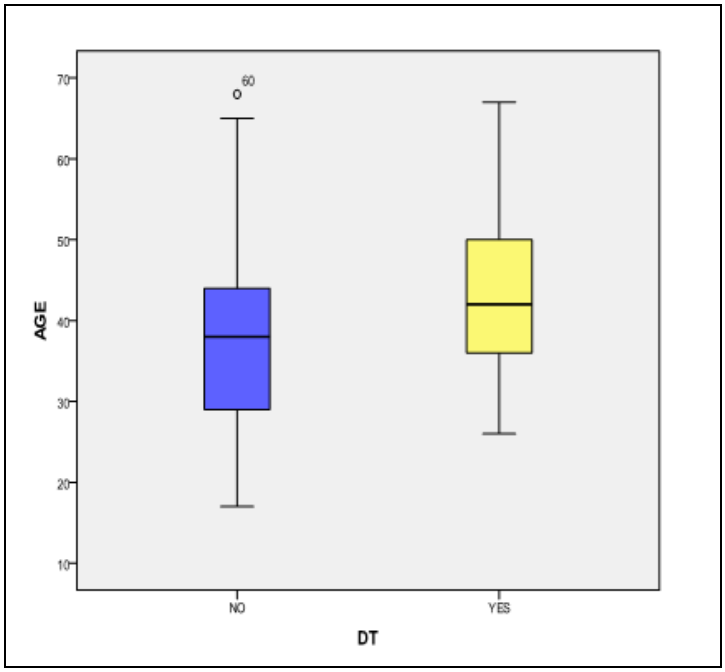

Figure 1: 1 Box Plot Showing the Mean Age & SD among patients with DT & Non DT

Figure No: 1 box plot shows that Mean age of the patients with DT is 43.2±11.29years which are significantly higher than Non DT patients 37.14±11.24 years (t= -2.292 p= 0.001*).

Table 1 reveals the Socio demographic profile of the subjects. It shows that all patients were males. Majority of the patients in both the group belongs to Hindu religion (52.1%& 49.9%) DT and Non DT group respectively.

Socio demographic variables	**DELIRIUM TREMENS**		
	NO (n=81) F (%)	YES (n=23) F (%)	Statistical value
Religion status			
Hindu	38(49.91%)	11(52.17%)	χ^2= 2.462
Christian	35(43.20%)	11(47.8%)	p=0.292
Muslim	7(8.6%)	1(4.34%)	
Gender			
Male	81(100%)	23(100%)	
Educational status			
Secondary school and below	62(76.54%)	21(91.3%)	Fisher's exact test
Higher secondary and above	19(23.45%)	2(8.69%)	P=0.001*
Occupational status of patient			
Employed	73(90.12%)	21(91.3%)	Fisher's exact test
Unemployed due to alcohol use	8(9.87%)	2(8.69%)	P=0.6
Monthly income (in rupees)			
Mean±SD	11498.9±9617.8	11695.6±4456.2	Mann Whitney U
Range	0-65000	3000-20000	test p=0.9
Marital status			
Married	54(66.6%)	15(65.2%)	χ^2=0.178
Unmarried	22(27.16%)	7(30.4%)	P=0.915
Separated due to alcohol use	5(6.1%)	1(4.3%)	
Living arrangements			
Living with wife	50(61.7%)	15(65.2%)	χ^2==0.178
Living with parents	31(38.3%)	8(34.8%)	P=0.915

Table 1: Socio demographic profile of the study subjects N=104

Education level is significantly lower in DT Group compared no Non DT group (91.3% and 76.5%) respectively with value of (p=0.001). Majority in both the groups and married, employed and living with their spouses. Nine percent of the Non DT patients and 8.67% of DT group Patients were unemployed due to drug use and 6.1% of Non DT Patients and 4.3% DT patients are living separately from their spouse due to alcohol use.

Clinical Variables	**Delirium Tremens**		
Variables	**No(n=81)**	**yes(n=23)**	**Statistical value**
Previous history of DT			
Yes	0(0%)	16(69.6%)	Fishers exact test
No	81(100%)	7(30.4%)	P=0.001*
Alcohol liver disease			
Yes	6(7.4%)	14(60.9%)	χ^2=32.96
No	75(92.6%)	9(39.1%)	P=0.001*
Co morbid psychiatric illness			
Yes	42(51.9%)	14(60.9%)	χ^2=0.586
no	39(48.2%)	9(39.1%)	P=0.44
Binge Drinking			
Yes	19(23.5%)	19(82.6%)	χ^2=27.03
no	62(76.5%)	4(17.4%)	P=0.001*
Hours of withdrawal before hospitalization (hours of delay)			
Mean±SD	47± 32.5	76± 51	t=-3.2
Range	24-154	24-154	p=0.001*
Age of initiation of alcohol in years			
Mean±SD	17.13±4.4	15.6±3.4	t=1.484
Range	9-20	10-23	p=.141
Duration of alcohol use in years			
Mean±SD	18.8±11.5	23.2±11.2	t=-1.604
Range	2-55	3-47	p=0.112
Duration of excessive use			
Mean±SD	6.53±5.8	9.24±7.8	t=-1.477
Range	1-30	2-32	p=0.151
Addiction severity index(ASI)score			
Mean±SD	5.7±1.6	7.5±1.4	t=-4.836
Range	2.3-8.9	2.4-8.8	p=.001*
Quantity of Alcohol(Rum/brandy) consumed (per day in ml)			
Mean±SD	531.18±208.6	543.5±159.9	t=-.300
Range	120-1000	180-720	p=0.766
Maximum amount of alcohol consumed per day in ml			
Mean±SD	946.7±342.8	1198.8±483.9	t=-.2.31
Range	360-1500	360-2000	p=0.02*

Table 2: Related risk factors associated with the occurrence of Delirium tremens among patients N=104

As shown in Table2 Sixty-nine percent of patients in the DT group had previous history of DT while comparing with the non DT group and found to be highly statistically significant (p=0.001**). Presence of alcoholic liver disease in DT Group (60.9%) when compared with non DT group (7.4%) diagnosed by gastroenterologist was also found to be highly significant factor contributing DT (p=0.001**). Presence of co-morbid psychiatric illness was comparable between the DT and Non DT group (p=0.4). Eighty-two percent of the subjects in the DT group had binge drinking pattern whereas only 23.5% of non DT subjects followed binge drinking pattern, which was found to be significant factor contributing to the occurrence of DT (p=0 .001**). DT group subjects had delay in hospitalization after their withdrawal (Mean ± SD 76 ± 51 hours respectively) which also is a contributing factor for the development of DT (p=0.001**). Mean age of initiation of alcohol use is comparable between DT and Non DT subjects (p=0.1). The mean duration of alcohol consumption (p=0.1) and duration of excessive use (p=0.2) in DT group was relatively higher but does not found to be statistically significant. Severity of addiction which was assessed using addiction severity index (ASI), the mean ASI score was significantly greater in the DT group while compared with the non DT group (p=0.001**). Subjects in the DT group consumed

significantly higher amount of alcohol (maximum use/day) i.e. Mean ± SD 1198± 483.9ml per day(p=0.02*); whereas usual daily consumption of alcohol was comparable between the group(p=0.7) respectively.

3.2. The High Risk Factors Predict the Occurrence of Delirium Tremens

Predictive Variables	B	S.E.	Wald	p value	OR	R^2
Binge drinking	-2.01	0.7	7.8	0.005	0.13	0.612
ALD	-2.6	0.8	11.1	0.001	0.07	
Severity of addition (ASI)	0.6	0.3	6.9	0.008	1.9	

Table 3: Factors predicting the occurrence of Delirium tremens by binary logistic regression analysis

As shown in Table 3. Severity of addiction is the strongest predictor of delirium tremens with (OR=1.9) with R^2 value of 0.612. I.e. Odds of occurring DT is 1.9times high as the mean ASI score increases. The factors such as binge drinking, and the presence of alcoholic liver disease in patients increases their vulnerability to develop DT but is considered as a weak predictor.

4. Discussion

Many studies focus on severe alcohol withdrawal syndrome from the point of view of possible risk factors associated with the occurrence of delirium tremens. Patients suffering from delirium tremens are usually males in their mid-forties or fifties [4]. In our study also Mean age of the patients with DT is 43.2±11.29 (p=0.001**).

A previous episode of delirium and/or seizures during withdrawal in the patient's history seems to be the greatest risk factor for the development of DT[ix]. In our study also previous history of DT were found to be significantly related to the occurrence of DT i.e. 69.6% of the patients experienced previous episodes of complicated withdrawal (p=0.001**) developed DT during the current withdrawal state.

Previous study findings reported that high respiratory rate [12], tachycardia of more than 100 or 120 beats per minute and hypertension – systolic blood pressure over 145 mmHg [x] were identified as predictors of DT; Hemodynamic parameters were not included as a study variable in the present study.

Lower initial platelet count and low serum potassium level [13, 14] high blood level of homocysteine, and low blood level of pyridoxine, high BUN, low albumin level [xi]were associated with the subsequent development of DT. Elevated liver enzymes - alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) - or carbohydrate-deficient transferrin (CDT) and mean corpuscular volume (MCV) can predict more severe alcohol withdrawal [8]. Present study revealed that60.9% of patients were diagnoses as suffering from alcoholic liver disease by the gastroenterologist based on the symptoms, ultrasound and liver profiles(p=0.001**), subjects who developed DT all had elevated liver enzymes; this may be due to the long term excessive consumption of alcohol.

Patients who developed delirium tremens were found to be unemployed, and homeless, and were more likely to have gone more days since their last drink, co- morbid medical illness found to be significant predictor of delirium tremens [xii]. In our study there was no significant association with employment status with DT. Delay in hospitalization or longer hours of withdrawal before hospitalization were found to be significantly associated with the occurrence of DT (p=0.001**). Co-morbid medical illness except alcoholic liver disease (p=0.001**) were not found to be significantly associated with the occurrence of DT in the present study.

Heavy episodes or binging episodes predict Delirium tremens [9]. In our study 82.6% of patients had relatively higher level of alcohol consumption with mean amount of alcohol consumed per day of 1.2litres following binge drinking pattern (p=0.001**) Prevalence of structural brain lesions [xiii], ataxia and polyneuropathy at the neurological examination, indicate a higher risk for the development of DT [xiv]. Severity of addiction (high ASI score) found to be a strong predictor of delirium tremens in our study (OR 1.9 p-0.008*)

5. Conclusion

Twenty-two percent of patients treated for alcohol withdrawal developed delirium tremens. Delirium tremens is the most severe complication of alcohol withdrawal which usually appears after longer periods of heavy drinking. Increased severity of dependence, binge drinking significantly contributes to the occurrence of delirium tremens. This severe condition may be life-threatening and may lead to death or severe morbidity when not managed properly. The most important issue of the treatment is its prevention by early recognition of the potential risk of alcohol withdrawal and its management. Control of agitation should be achieved using parenteral rapid-acting sedative-hypnotic agents that are cross-tolerant with alcohol. Adequate doses should be used to maintain light somnolence for the duration of delirium. Vigilant observation, management and supportive medical care would be highly effective in preventing morbidity and mortality.

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