ORIGINAL ARTICLE

Prevalence And Correlates Of Delirium tremens In Alcohol Dependence Syndrome At Tertiary Hospital.

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Abstract

Introduction: *The prevalence of Delirium tremens (DT) is around 5-12%. Very few studies have looked into the prevalence of DT in general population and has shown varying results. The study aims at finding the prevalence of delirium tremens among alcohol dependents (AD) and a comparison of profiles of alcohol withdrawal syndrome (AWS) with DT and AWS without DT.*

Material And Method: *A case- control study was conducted in patients diagnosed as Alcohol dependent syndrome and admitted in Psychiatry in-patient ward for detoxification. Socio demographic and clinical variables were assessed and compared between alcohol dependents who developed DT and who did not developed DT.*

Results: *24% of the patients with AD had/developed delirium tremens. The multivariate regression analysis model shows variables like Age>50years (AOR= 75.7,95% C.I=7.8-730), Caste(Janjati: AOR=4.2, 95% C.I=1.329-13.23,) and unemployment(AOR=54.2, 95%C.I=3.8-765.254),longer length(years) of alcohol consumption >20 years(AOR= 305,95%CI=3.4-2711),presentation within 48-72 hrs since the last intake of alcohol (AOR=923,95%CI=38-22333),absence of nicotine consumption(AOR=40,95%C.I.=1.66-967) were significantly associated with development of delirium tremens. Similarly, those with educational status of higher secondary and above (AOR=0.7, 95% C.I =0.73-1.43), past history of absence of DT (AOR=0.013, 95% C.I=0.0002-0.77), less frequent intake of alcohol <3 times/week (AOR=0.001,95%C.I=0.001-0.07) had less likely developed DT. These significant variables were further assessed for their ability to predict the occurrence of delirium tremens in ROC and area under the curve for age, duration since last alcohol intake and years of intake of alcohol were respectively = 0.799, 0.843 and 0.765.*

Conclusion: *Three features findings (older Age, more years of intake of alcohol, more hrs since last intake of alcohol) were more likely seen in delirium tremens patients.*

Keywords: Alcohol withdrawal syndrome, clinical variables, Delirium tremens, socio-demographic variables.

INTRODUCTION

Delirium tremens is a severe form of alcohol withdrawal with symptoms most often occurring within 48-96 hours after the last drink. Sometimes they may occur up to 7 - 10 days after the last drink. Only 5% of patients with Alcohol withdrawal progress to delirium tremens.[1]However DT has its significance due to high mortality rate around 35%.Fortunately, In the past decades there has been a dramatic decline in mortality from DT almost 0 to 8% that

can be attributed to an improved understanding of pathophysiology and advances in the approach to management. (2,3,4)

Delirium tremens is not a uniform complication of AWS. Despite numerous studies seeking reliable predictors of complicated withdrawal (DT and withdrawal seizure), no standardized risk prediction model has been derived. Risk factors for delirium tremens among various studies, are previous history of DTs, Co-morbid illness, daily excess and prolonged alcohol

consumption, more numbers of days since last drink, severe symptoms of withdrawal at presentation, previous detoxification, older age group, high pulse rate 100 b.p.m, axillary temperature > 38 °C, hypokalemia. [2,3,5,6,7] However, studies have methodological differences, and thus a common consensus has not been arrived at as yet.

The purpose of this study was to find the prevalence and assess the socio-demographic and clinical correlates, available to clinicians at the time that patients present for alcohol detoxification, associated with the development of DT as well as to collaborate our findings with the existing ones.

MATERIAL AND METHOD

The study was a case -control study conducted in patients diagnosed as Alcohol dependent syndrome and admitted in Psychiatry Department at a private medical college in Bhairahawa within a period of 1 year (2019-2020). Total patients meeting criteria for ADS who were admitted in department of psychiatry and de-addiction unit were 356 in 12 months period. Out of 356 patients 86 were of Delirium tremens (presented/developed), after excluding few patients (as per exclusion criteria), 71 patients with DT were enrolled. Equal numbers of controls were randomly selected from the pool of remaining AWS patients who did not develop DT and reviewed for eligibility,with inclusion of those who met our criteria. Approval for the study was taken from the Institutional Review Committee.

The inclusion criteria were (a) willingness to participate and giving informed consent, (b) meeting the criteria for Alcohol dependence syndrome as ICD-10 Diagnostic Criteria for Research (DCR) and (c) currently having withdrawal symptoms and having a Clinical Institute Assessment for Alcohol-revised (CIWA-Ar) score of eight or greater at the time of admission. Patients excluded were (a) patients who were already taking counter tolerant drugs at admission,(b) Patients suffering from other primary psychiatry conditions like schizophrenia, dementia, and bipolar affective disorder (c) Any cases of mixed delirium where alcohol withdrawal was one of the factors along with other factors that might have contributed to delirium (d) patients with dependence on other substances except nicotine and caffeine and (e) patients with mental subnormality.

After admission and informed consent taken, a semi- structured questionnaire was used to collect the data from the patients (a) socio demographic details, (b) Clinical variables details (alcohol start age, duration, frequency, type and amount of alcohol consumed, including details of the last drink,previous history of withdrawal symptoms, relevant history regarding medical illness, family history of alcohol consumption and medical illness and history of nicotine consumption. The ICD-10 (DCR) was used to diagnose alcohol dependence. CIWA-Ar was used to rate the withdrawal syndrome (8).The scale was applied at the time of admission and those with a score greater than eight, indicating definite need for detoxification treatment and increased chance of severe withdrawal, were included in the study. All patients brought in DT were followed up and data were collected after DT subsides. Treatment of all patients was done following standard protocol (thiamine, multivitamins, fluids, benzodiazepine).

DATA PROCESSING AND ANALYSIS: Data were entered and analyzed by using Statistical Package for Social Science (SPSS) software version 20. Frequency and Percentage were used as Descriptive statistics. Bivariate analysis was carried out to assess the association between Dependent Variables and Independent Variables. The ultimate effect measure (measure of association) was odds ratio, and 95% confidence intervals were used to determine statistical significance. Variables found to be associated in bivariate analysis were entered into the multivariate logistic regression model to find the risks factors of delirium tremens. To assess predictive capacity of results, a receiver operating characteristic (ROC) curve was constructed by standard procedure, using its graphic representation and the area under the curve.

RESULT

Total 356 patients meeting criteria for ADS were admitted in department of psychiatry and de-addiction unit in 12 months period. Out of 356 patients 86(24.15%) were of Delirium tremens (presented/developed).Using inclusion/

exclusion criteria 71 DT were taken as case and equal numbers of controls were randomly selected from remaining AWS patients who did not develop DT.

Table: 1 Socio-Demographic variables

Variables	Group	AWS (no DT)	AWS (with DT)	p-value
Age	18-28	18(90%)	2(10.0%)	<0.001
	29-39	26(81.2%)	6(18.8%)	
	40-50	18(40.0%)	27(60%)	
	>50	9(20%)	36(80%)	
Gender	Male	58(47.8%)	64(52.5%)	0.148
	Female	13(65.0%)	7(35.0%)	
Caste/Ethnicity	Khas- Arya	42(60.9%)	27(39.1%)	0.031
	Janjati	24(42.1%)	33(57.9%)	
	Others	5(31.2%)	11(68.8%)	
Marital Status	Single	13(76.5%)	4(23.5%)	0.039
	Married	52(49.5%)	53(50.5%)	
	Separated	4(36.4%)	7(63.6%)	
	Widowed	2(22.2%)	7(77.8%)	
Religion	Hindu	64(49.6%)	65(50.4%)	0.771
	Buddhist	7(53.8%)	6(46.2%)	
Occupation	Business	16(84.2%)	3(15.8%)	0.009
	Farmer	11(39.3%)	17(60.7%)	
	Labourer	22(41.5%)	31(58.5%)	
	Service	10(71.4%)	4(28.6%)	
	Housewife	6(50.0%)	6(50.0%)	
	Unemployed	6(37.5%)	10(62.5%)	
Education	Illiterate	4(26.7%)	11(73.3%)	0.011
	Can Read and Write	28(70.0%)	12(30.0%)	
	Primary	20(50.0%)	20(50.0%)	
	Secondary	10(33.3%)	20(66.7%)	
	Higher Secondary and Above	9(52.9%)	8(47.1%)	
Type of family	Nuclear	31(41.9%)	43(58.1%)	0.056
	Joint	38(61.3%)	24(38.7%)	
	Extended	2(33.3%)	4(66.7%)	

The 2 groups (alcohol dependents who developed delirium and who did not developed delirium tremens) are comparable on all sociodemographic variables. Variables like Age, caste, Marital Status, Occupation and Education are statistically significant(p<0.05). [Table 1].

Table: 2 Clinical Variables

Variables	Group	control	case	p-value
Family History	ADS	8(19.5%)	33(80.5%)	<0.001
	Others Psychiatry	10(58.8%)	7(41.2%)	
	None	53(63.1%)	31(36.9%)	
Past History	Complicated	2(11.1%)	16(88.9%)	<0.001
	Uncomplicated	9(31.0%)	20(69.0%)	
	Other pyschiatry along with medical	54(73.0%)	20(27.0%)	
	Similar and Medical	4(25.0%)	12(75.0%)	
	Uncomplicated and Medical	2(40.0%)	3(60.0%)	
Alcohol Start Age	<10 yrs	3(50%)	3(50%)	0.277(NS)
	10-20 yrs	43(45.2%)	52(54.8%)	
	20-30 yrs	24(63.1%)	14(36.9%)	
	30-40 yrs	1(33.3%)	2(66.7%)	
Type of alcohol	Local	22(37.9%)	36(62.1%)	0.007
	Beer	11(91.7%)	1(8.3%)	
	Vodka	3(60.0%)	2(40.0%)	
	Mixed	35(52.2%)	32(47.8%)	
Amount taken	0-15 units	33(63.5%)	19(36.5%)	0.015
	> 15 units	38(42.2%)	52(57.8%)	
Length	0-10 years	50(76.9%)	15(23.1%)	<0.001
	10-20 years	16(32.0%)	34(68.0%)	
	>20 years	5(18.5%)	22(81.5%)	
Frequency	Everyday	22(24.4%)	68(75.6%)	<0.001
	1-3 per week	49(94.2%)	3(5.8%)	
Duration of intake	0-24 hrs	53(89.8%)	6(10.2%)	<0.001
	24-48 hrs	8(42.1%)	11(57.9%)	
	48-72 hrs	4(8.7%)	42(91.3%)	
	> 72 hrs	6(33.3%)	12(66.7%)	
nicotine intake	Yes	58(58.0%)	42(42.0%)	0.03
	No	13(31.0%)	29(69.0%)	

Clinical variables like length of intake of alcohol, Amount of alcohol intake, duration of intake of alcohol, frequency of intake of alcohol, type of alcohol, use of nicotine, patient with past history of AWS and family history are also statistically significant among the patients with delirium tremens (P<0.05)[Table 2].

Table:3 Multivariate logistic of Socio-demographic variables with Case Control

Variables	Group	Control	Case	COR	95% C.I	AOR	95% CI
Age	18-28	18(90%)	2(10.0%)	1.0		1.0	
	29-39	26(81.2%)	6(18.8%)	2.1	.376-11.477*	0.6	.059-6.926**
	40-50	18(40.0%)	27(60%)	13.5	2.786-65.406	23.1	3.014-176.38
	>50	9(20%)	36(80%)	36.0	7.030-184.34	75.7	7.842-730.439
Caste/Ethnicity	Khas- Arya	42(60.9%)	27(39.1%)	1.0		1.0	
	Janjati	24(42.1%)	33(57.9%)	2.1	1.047-4.369*	4.2	1.329-13.230**
	Others	5(31.2%)	11(68.8%)	3.4	1.070-10.943	10.6	1.358-82.848
Marital Status	Single	13(76.5%)	4(23.5%)	1.0		1.0	
	Married	52(49.5%)	53(50.5%)	3.3	1.014-10.825*	2.8	.359-21.677
	Separated	4(36.4%)	7(63.6%)	5.7	1.078-29.997	0.7	.062-7.634
	Widowed	2(22.2%)	7(77.8%)	11.4	1.651-78.378	1.1	.057-21.064
Occupation	Business	16(84.2%)	3(15.8%)	1.0		1.0	
	Farmer	11(39.3%)	17(60.7%)	8.2	1.938-35.057*	10.0	1.118-89.579**
	Laborers	22(41.5%)	31(58.5%)	7.5	1.951-28.953	20.5	2.961-142.36
	Service	10(71.4%)	4(28.6%)	2.1	.393-11.592	3.4	.318-35.931
	Housewife	6(50.0%)	6(50.0%)	5.3	1.000-28.435	13.8	1.052-179.89
	Unemployed	6(37.5%)	10(62.5%)	8.9	1.803-43.820	54.2	3.841-765.254
Education	Illiterate	4(26.7%)	11(73.3%)	1.0		1.0	
	Can Read and Write	28(70.0%)	12(30.0%)	0.2	.041-0.589*	0.1	.011-0.813**
	Primary	20(50.0%)	20(50.0%)	0.4	.099-1.336	0.2	.026-2.0
	Secondary	10(33.3%)	20(66.7%)	0.7	.184-2.871	1.3	.165-9.516
	Higher Secondary and Above	9(52.9%)	8(47.1%)	0.3	.073-1.433	0.7	.060-8.838

Table 3: shows association between Sociodemographic variables with Delirium tremens of respondents. Sociodemographic Variables such as Age, Caste, Marital Status, Occupation and Education were found to be associated with Delirium tremens (p<0.05) and these associated variables were further entered into multivariate logistic regression model for adjusting confounding Variables. Results from the multivariate regression analysis model excluded marital status as risk factor of DT. Age group (40-50) years were more likely about twenty three times & Age group (>50 years) were more likely about 76 times to have delirium tremens. Similarly the odds of having delirium tremens for different caste were (Janjati: AOR=4.2, 95% C.I=1.329-13.23; Others: AOR=10.6, 95% C.I=1.358-82.84) as compared to Khas- Arya. Those whose educational status was higher secondary and above were 30% less likely to develop delirium tremens as compared to illiterate (AOR=0.7, 95%C.I =0.73-1.43).Results also showed that patients who were unemployed were fifty four times(AOR=54.2 ,95%C.I=3.9-765) and those who were laborers were twenty times(AOR=20.5,95%C.I=2.9-142.3) more likely to have delirium tremens as compared to business men. Variables like gender, religion, type of family, income of head of family did not show any significance.

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Table 4: Multivariate Logistic Regression of Clinical Variables

Variables	Group	control	case	COR	95% C.I	AOR	95% CI
Family History	ADS	8	33	1		1	
	Others Pyschiatry	10	7	.17	.05-0.58*	12.363	.069-2202.15
	None	53	31	.14	.06-0.35	.422	.030-5.98
Past History	Complicated	2	16	1		1	
	Uncomplicated	9	20	.28	.05-1.47*	.013	.0002-.77**
	Other pyschiatry along with medical	54	20	.05	.01-0.22	.031	.001-1.12
	Similar and Medical	4	12	.38	.06-2.40	.059	.001-6.50
	Uncomplicated and Medical	2	3	.19	.02-1.90	.270	.0001-36.65
Type of alcohol	Local	22	36	1		1	
	Beer	11	1	.06	.01-0.46*	.096	.0004-13.20
	Vodka	3	2	.41	.06-2.63	.269	.001-98.86
	Mixed	35	32	.56	.27-1.14	.216	.015-3.10
Amount taken	0-15 units	33	19	1		1	
	> 15 units	38	52	2.38	1.18-4.98*	4.568	.253-82.52
Length	0-10 years	50	15	1		1	
	10-20 years	16	34	7.08	3.09-16.22*	8.99	.355-227.62**
	> 20 years	5	22	14.67	4.74-45.38	305.29	3.433-2711.61
Frequency	Everyday	22	68	1		1	
	1-3 per week	49	3	.020	0.06-0.7*	.001	0.001-0.07**
Duration since last intake	0-24 hrs	53	6	1		1	
	24-48 hrs	8	11	12.15	3.51-42.05*	86.13	1.40-5291.85**
	48-72 hrs	4	42	92.75	24.57-350.12	923.3.	38.17-22333.5
	> 72 hrs	6	12	17.67	4.85-64.40	15.98	0.70-364.03
Tobacco	Yes	58	42	1		1	
	No	13	29	3.08	1.43-6.66*	40.06	1.66-966.96**

Table 4 : shows the association between Clinical variables and delirium tremens.

The variables like length (years)of intake of alcohol, duration(hrs) since the last intake of alcohol of intake of alcohol/decrease in dose of alcohol, frequency of intake of alcohol, type of alcohol intake, patient with past history of DT and family history of ADS were statistically significant among the patients with delirium tremens. However after adjusting confounding variables multivariate regression analysis model found variables like past history of DT, length(years) of alcohol intake, frequency of alcohol intake, duration(hrs)since the last intake of alcohol of intake of alcohol/decrease in dose of alcohol, nicotine use were significantly

associated with for causation of delirium tremens.

Patient who had past history of uncomplicated withdrawal were 98.7 % less likely to develop delirium tremens than those with past history of complicated withdrawal and those who took alcohol for 1-3 times per week were 99 % less likely to develop DT(AOR=0.001,C.I.=0.001-0.07) compared to those who took everyday. The odds of having DT in those who took alcohol for more than 20 years were significantly higher (AOR=305.29,95% C.I = 3.43-2711.61) than those who took for lesser years 10 years and less. similarly The odds of having DT in those who took alcohol 48-72hrs back were 932 times more (AOR=923,95% C.I= 38-22333) than who

presented within 24hrs of intake of alcohol .However those who presented more than 72 hrs after last intake of alcohol were only 16 times likely (AOR=15.98,95%C.I=0.70-364.03) to develop DT than whose who presented within 24hrs. The data also shows that those who did not consume nicotine were 40 times more likely to develop DT than who consumed,(AOR=40.06,95%C.I=1.66-966.96)
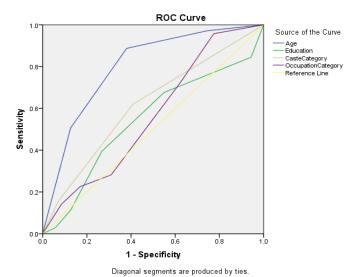

Figure 1. Receiver operating characteristic (ROC) curve predicts that among significant socio-demographic variables age is more likely predicted factor for DT as compared to other factors like caste, occupation , education. Area under curve AUC of age is .799.
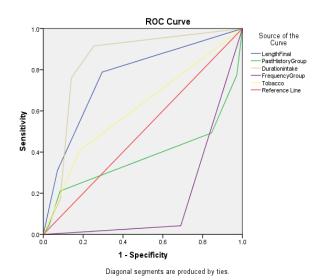

Figure 2. similarly, among the clinical variables which are significant, ROC predicts Duration (hrs)since last intake and length of intake(years)to be important risk factors. AUC for duration since last intake =0.843 and AUC For length of intake = 0.76.

DISCUSSION:

The prevalence of delirium among alcohol withdrawal patients was 24.15% (86/356 patients),higher than expected probably due to the fact that only moderate to severe alcohol withdrawal were admitted and those who were already in DT were brought for treatment by family members. This however is in keeping with an earlier study which reported prevalence of delirium tremens in moderate to severe alcohol use of 22.3%(9),33%(3).The study showed that the patients of age 50 years and above were more likely to develop complicated withdrawal(DT) compared to younger age group. Previous researches also indicated that the elderly are more vulnerable to severe withdrawal events. (10,11) Chronic co-morbid conditions, limited physiological reserve, longer period of alcohol consumption and adverse effects of drug treatment all may increase the risk of complicated alcohol withdrawal in people with older age.

Ethinicity wise majority of patients were khas-arya 48.6% as shown in other studies as well. (12,13) However multivariate logistic regression shows Janjati (newar, tamang, magar, rai, gurung, etc) and others(apart from janajati) has high risk than khas- arya to develop delirium tremens. As per our knowledge no studies has been done in severity of AWS with ethnicity in Nepal. One possible explanation of our finding could be that in Janajati and few other ethinc groups, alcohol especially home brewed: Jaand, chhyang, thumba (local names) use is accepted as culture and traditional so early start and longer duration of intake of alcohol could be the reason of high risk for developing DT. This study showed that those who are unemployed were at high risk of developing delirium tremens which was found in others study as well which showed that those who developed delirium tremens were more likely to be unemployed, and homeless (2).The study showed that those who were educated upto

higher secondary and above were 30 % less likely to develop DT then illiterate. Another study also found similar result which showed that alcoholism is slightly more common in lower income and less educated groups.(14)

We found that the patients who presented within 48 hrs-72hrs since their last drink had increased risk of developing delirium tremens than who presented early within 1-2 days of abrupt cessation of alcohol. Similar result has been supported by another study (2). Length of time a person has been consuming alcohol was considered as risk factor for developing DT. Study shows that those who took alcohol for more than 20 years are at 305 times more at risk of developing DT than those who took for only 10 years and less. Chronic exposure to alcohol results in a compensatory decrease of GABA-A neuroreceptor response to GABA, evidenced by increasing tolerance of the effects of alcohol. Alcohol also inhibits NMDA neuroreceptors, and chronic alcohol exposure results in up-regulation of these receptors. Abrupt cessation of alcohol after chronic exposure, results in brain hyperexcitability, resulting in AWS including delirium tremens.(15) The study found that the patient with past history of AWS with no DT were about 98.7% less likely to develop DT compared to those who has past history of complicated AWS. This finding relates to a meta- analysis finding which identify that an incident occurrence of DT or alcohol withdrawal seizures was significantly predicted by history of a similar event in past.(3,5,16) An important concept for this probably is the "kindling" phenomenon. The term refers to long-term changes that occur in neurons after repeated detoxifications which explains the observation that subsequent episodes of alcohol withdrawal tend to progressively worsen.(17)

Another contradictory finding in the study was that those who did not use nicotine were 40 times more likely to develop DT than those who consumed nicotine. It shows taking alcohol and nicotine together lead to less severe withdrawal symptoms. similar result was found in another study which concluded that nicotine use with ethanol likely confers some "benefit" to the ethanol abuser.(18)however this may not influence the choice to combine smoking and drinking. one possible explanation is as explained in Prendergast et al, Nicotine preexposure is known to protect neurons against overactivity of NMDA receptors, possibly by increasing expression of Ca2+buffering proteins (19).Our study showed that the odds of developing DT in those who drank alcohol >15units/day in last month was 4.5 times more than whose drank less. However after adjusting the confounding factors association was not statistically significant. The non-significance of amount of alcohol intake variables in the multivariate models was surprising since other studies have found these to be predictive of severe withdrawal symptoms (20).This difference was probably due to the fact that the study explained amount of alcohol consumption of 1 month only. The advantage of the current study was that it was performed on patients hospitalized exclusively for alcohol detoxification so any other acute medical conditions which would increase the risk for DT were already excluded unlike other studies.(2) The study was a prospective study, not patient's recorded histories of the event. (20) Since the study showed many risk factors for DT so to be more precise ROC was constructed which showed the factors like older age, duration since last intake of alcohol and length of time patient has been taking alcohol are at more risk of developing delirium tremens. Some important limitations of the study is that the confidence intervals of few variables are wide, this may mean that the sample size is small, if the dispersion is high, the conclusion is less certain . Another important aspect that is missing here is correlation with laboratory findings of patient which definitely somehow affect the course and outcome of delirium tremens.

CONCLUSION:

The study shows that the socio-demographic factors like age group 50 years and above, illiterate , being unemployed were more likely to have deliriums tremens. Variables like gender, religion, type of family, income of head of family did not show any significance. Clinical variables like past history of DT, longer length(years) of alcohol consumption, frequency of alcohol intake, duration(hrs)since the last intake of alcohol of intake of alcohol/decrease in dose of alcohol, nicotine use were significantly

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associated with risk of delirium tremens. These significant variables were further assessed for their ability to predict the occurrence of delirium tremens which concluded the three features older age, more years of intake of alcohol, more hrs since last intake of alcohol were more likely seen in delirium tremens patients. These results are preliminary and need further development and validation, particularly in different populations and settings.

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