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PSYCHIATRY

TO STUDY PREDICTORS FOR WITHDRAWAL SEIZURES IN PATIENTS OF ALCOHOL WITHDRAWAL SYNDROME

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ABSTRACT

Introduction- The alcohol withdrawal seizure(WS) occurs during the early phase of withdrawal and is characterized by reduction in the seizure threshold and it emerges within 48 hours of cessation of prolonged drinking (Brathen G et al,1999;Victor M et al,1967.)The appearance of a withdrawal seizure represents a strong risk factor for progression into a severe withdrawal state with following development of DT in up to 30% of cases(Victor M et al,1967).

Aim- The purpose of the current study is to identify the most parsimonious collection of risk factors present at the time of hospital admission that were predictive for the development of WS.

METHODOLOGY- 102 subjects admitted at deaddiction centre, SMS hospital were selected using a screening performa which was followed by a comprehensive assessment of alcohol use followed by relevant laboratory investigations with blood pressure and pulse rate recording. Severity of alcohol withdrawal syndrome (AWS) was determined in analogy to the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. Patients were put on standard treatment based upon institute guidelines and withdrawal was assessed for 1 week. Patients were monitored for withdrawal seizure and diagnosis was made as per criteria of ICD 10.

RESULTS- Age of onset of drinking, duration of alcohol abuse and daily ethanol intake were found to be significantly correlated to the development of WS. Systolic BP, Diastolic BP, Heart rate had significant correlation to the occurrence of WS which can be attributed to the autonomic hyperactivity during the withdrawal state. CIWA-Ar score also came out to be a significant risk factor to the development of WS.Previous history of seizures, delirium tremens, previous alcohol withdrawal syndrome and previous detoxification episodes were also a significant risk factor for the occurrence of WS .

CONCLUSION- The various variables that were found to be significantly correlated to the occurrence of WS are mentioned as follows: age, duration of abuse, daily alcohol intake, CIWA-Ar score>15, systolic & diastolic BP, previous history of WS and DT, previous history of alcohol withdrawal syndrome and previous detoxification episodes.

KEYWORDS : Alcohol withdrawal syndrome, Withdrawal seizures, Delirium tremens

INTRODUCTION

Alcohol dependence syndrome was conceptualized as a cluster of seven psychological and physiological elements or processes that occur on a continuum of severity and lead to heavy drinking that is increasingly unresponsive to adverse consequences. ICD-10 (WHO, 1992) classifies alcohol dependence as the more severe of two categories of substance use disorder: ***harmful use and the dependence syndrome***. Instead, DSM-5 (APA, 2013) (1) combines the criteria for two separate alcohol use disorder (2) – 'alcohol abuse' (similar to ICD-10 harmful use) and 'alcohol dependence' (similar to ICD-10 alcohol dependence syndrome) – into a single disorder called '**alcohol use disorder**' (AUD) with mild, moderate and severe sub-classifications.

Alcohol withdrawal syndrome (AWS) is a well-known condition occurring after intentional or unintentional abrupt cessation of heavy/ constant drinking, and it occurs in about 8% of hospitalized AUD inpatients. (3). A complicated AWS includes epileptic seizures and/or delirium tremens (DT), the occurrence of which may be as high as 15% in AUD patients (4) (5).

The alcohol withdrawal seizure (WS) is a symptom occurring primarily during the early phase of withdrawal and is characterized by reduction in the seizure threshold. More than 90% of acute symptomatic seizures emerge within 48 h of cessation of prolonged drinking (6) (7).

Seizures frequently occur in the absence of other signs of the AWS. More than half of the individuals present with repeated seizures, and in up to 5%, they may progress to status epilepticus (8). More than 50% of withdrawal seizures are associated with concurrent risk factors such as prior epilepsy, structural brain lesions, or use of other drugs (8) (6). It is remarkable that the development of acute symptomatic seizures during an alcohol withdrawal episode is associated with a fourfold increase in the mortality rate that is due to complications of severe AUD rather than a direct effect of seizures (8) (9). The appearance of a withdrawal seizure represents a strong risk factor for progression into a severe withdrawal state with following development of DT in up to 30% of cases (7). Unprovoked seizures occurring later than 48 h after the last drink suggest other causes such as head trauma or combined drug withdrawal effects (10) (11).

In several studies, possible predictors for the development of a severe AWS have been investigated. Medical history and laboratory biomarkers serum ethanol, serum electrolytes, Aspartate transaminase(AST),Alanine transaminase(ALT), Gamma glutamyl transferase (γGT), and Mean corpuscular volume(MCV), are the two most important methods for the identification of patients at high risk. Clinical findings such as elevated heart rate, systolic blood pressure, and temperature are all easily verifiable in the initial patient assessment, although their predictive value to identify patients with AWS who are more likely to develop WS is not high (3) (12) (13).

The purpose of the current study is therefore to identify, among patients hospitalized in our centre, the most parsimonious collection of risk factors present at the time of hospital admission that were predictive for the development of WS.

METHODOLOGY

Objectives:

1) To identify socio-demographical and clinical variables for withdrawal seizures.
2) To find out relationship between patient variables and withdrawal seizures. 102 subjects admitted at deaddiction centre, SMS hospital were selected using a screening performa which was followed by a comprehensive assessment of alcohol use followed by relevant laboratory investigations with blood pressure and pulse rate recording. Severity of alcohol withdrawal syndrome(AWS) was determined in analogy to the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. Patient was put on standard treatment based upon institute

guidelines and withdrawal was assessed for 1 week. Patients was monitored for withdrawal seizure and diagnosis would be made as per criteria of ICD 10.

SELECTION CRITERIA

Inclusion criteria:

Patients qualifying the ICD 10 criteria for alcohol dependence, patients requiring inpatient treatment for detoxification, Age 18 years and above, either sex.

Exclusion criteria :

Dependence on Benzodiazepines,use of other psychoactive substance except tobacco, patient presented in condition of delirium or withdrawal seizure,patients poorly adherent to treatment protocol,declining to provide informed consent,patient with objective findings of a general medical cause of delirium.

Instruments of study:

1. Consent form
2. Screening performa
3. Comprehensive assessment of alcohol use.
4. Laboratory investigations like Ethanol concentration in blood ,pulse rate and blood pressure at the time of admission – laboratory investigations will include serum GGT, sodium, potassium, creatinine and platelet count.
5. **Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)**

Statistical Analysis

Statistical analysis was done with the help of software SPSS 20.0. Group comparison for socio-demographic variables and clinical variables was done with the help of appropriate application of independent t-test and chi square test. For the group comparison one way ANOVA was applied. Group comparisons were done with the help of non parametric test i.e. Independent-Samples Kruskal-Wallis Test. Further group differences were obtained with the help of Post Hoc Analysis

Results

Table 1 Sociodemographic Profile of WS Group

		WS	No WS	X2	P value		
		N=14	%	N=88	%	Value	
Marital Status	**1.Married**	10	71.43	76	86.36	16.112	***<0.001***
	2. Unmarried	0	0.00	10	11.36		
	3. Divorced	4	28.57	2	2.27		
Occupation	**1. Unemployed**	0	0.00	12	13.64	16.919	***0.001***
	2. Retired	0	0.00	0	0.00		
	3. Professional	10	71.43	22	25.00		
	4. Businessman	4	28.57	16	18.18		
	5. Farmer/Skilled Worker/Semi-Skilled Worker/Unskilled Worker	0	0.00	38	43.18		
Education	**1. Upto Middle**	4	28.57	24	27.27	0.918	***0.632***
	2. Middle to Sr. Sec.	4	28.57	36	40.91		
	3. Graduate/Post Grad.	6	42.86	28	31.82		
Income	**1.NIL-6000**	0	0.00	18	20.45	11.313	***0.003***
	2. 6001-15000	4	28.57	46	52.27		
	3. >15000	10	71.43	24	27.27		
Religion	**1. Hindu**	10	71.43	74	84.09	27.605	***<0.001***
	2. Muslim	0	0.00	14	15.91		
	3. Others	4	28.57	0	0.00		
Family	**1. Nuclear**	10	71.43	24	27.27	11.209	***0.004***
	2. Nuclear Extended	4	28.57	48	54.55		
	3. Joint	0	0.00	16	18.18		
Locality	**1. Urban**	14	100.00	52	59.09	8.851	***0.003***
	2. Rural	0	0.00	36	40.91		
Family History	**1.Negative**	4	28.57	30	34.09	0.166	***0.684***
	2.Positive	10	71.43	58	65.91		

Table 2 Laboratory Parameters of WS Group.

	WS	NO WS	P value		
	Mean	Std Deviation	Mean	Std. Deviation	
N=102	**N=14**		**N=88**		
Age	42.71	4.28	37.28	8.01	0.015
Duration of alcohol abuse (years)	24.28	9.5	15.65	7.64	<0.001
Daily alcohol intake (g/l)	207.25	46.74	140.81	109.39	0.028
Duration of last alcohol Intake (in hrs)	32.57	25.96	30.48	31.93	0.817
Duration of abstinence (months)	1.28	0.46	3.44	9.4	0.395
CIWA-Ar Score	33.42	8.64	23.36	6.39	<0.001
BP(Systolic) mmHg	154.28	13.42	134.54	15.88	<0.001
BP(Diastolic) mmHg	97.14	3.48	88.5	11.11	0.005
Heart rate (bpm)	100.57	3.27	94.36	10.19	0.027
GGT (U/l)	188	75.69	150.73	139.03	0.331
Na (mmol/l)	137.28	3.95	137.56	2.91	0.75
K(mmol/l)	4.1	0.21	4.14	0.38	0.715
Creatinine (mg/dl)	0.92	0.04	5.63	21.16	0.409
Platelet (lakhs/mm3)	1.74	0.86	2.03	0.98	0.306
Ethanol in serum (mg/ml)	0	0	0.061	0.15	0.154

Table - 3 OTHER ANALYTICAL CORRELATES OF WS GROUPS

Complications of drug use		WS	No WS	X2	P Value		
		N=18	%	N=88	%	Value	
Co-morbid medical illness	1. Yes	14	33.33	28	66.67	23.182	***<0.001***
	2. No	0	0.00	60	100.00		
Co-morbid Psychiatric illness	1. Yes	4	20.00	16	80.00	0.827	***0.363***
	2. No	10	12.20	72	87.80		
Structural Brain Lesion	1. Yes	10	100.00	0	0.00	69.68	***<0.001***
	2. No	4	4.35	88	95.65		

Table 4 CLINICAL CORRELATES OF WS GROUP

		WS	No WS	X2	P Value		
		N=14	%	N=88	%	Value	
Prev Seizures	1. Yes	14	100.00	4	4.55	75.72	<0.001
	2. No	0	0.00	84	95.45		
Prev Dilerium	1. Yes	4	28.57	6	6.82	6.46	0.011
	2. No	10	71.43	82	93.18		
Prev AWS	1. Yes	14	100.00	28	31.82	23.18	<0.001
	2. No	0	0.00	60	68.18		
Previous detoxification episodes	1. Yes	14	100.00	36	40.91	16.87	***<0.001***
	2. No	0	0.00	52	59.09		
DT	1. Yes	14	100.00	24	27.27	27.33	<0.001
	2. No	0	0.00	64	72.73		

Table 1 shows the sociodemographic profile of the patients in the WS group. All the patients in the sample were males. Majoriy of the patients in DT+(71.4%) and in the DT- group(86.3%) were married. Most of the patients in the DT+ group were professionals (71.43%) while in the WS- group,25% of the patients belonged to professional group. Majority of the patients in the WS+ group were either graduate or postgraduate(42.86%) while majority of the patients in the WS- group studied till middle to senior secondary (40.9%). Patients in the WS+ group belonged to higher socioeconomic status(71.43%) and in the WS-group belonged to middle socioeconomic status(52.27%). Majority of the patients in both the groups belonged to the hindu community. Patients in the WS+ belonged to the nuclear families(71.43%) while patients majorily in the WS- group belonged to the nuclear extended families(54.55%). All the patients in the Ws+ group resided in the urban community while 59.09% in the WS- group belonged to the urban locality. Both the groups had positive family history for alcohol use disorder and it didnot have any correlation the occurrence of WS.

Table 2 shows that significant correlation was found with the age of patient and the development of WS(p value=0.015). Duration of alcohol abuse(p value<0.001) and daily alcohol intake(p value=0.028) were significant predictors for occurrence of WS. CIWA-Ar score also significant correlated (p value<0.001) to the occurrence of WS.Cardiovascular parameters like Systolic BP(p value<0.001), Diastolic BP(p value=0.005) and Heart rate(p value=0.027) were significant risk factors for the occurrence of WS.

Table 3 shows the comparison of consequences of alcohol use in WS+ and WS- patients. Significant correlation was found between financial (p value=0.013) , social(p value=0.013) and legal(p value= 0.011) consequences and occurrence of WS. Comorbid medical illness in AWS patients was significantly associated with the development of WS. Structural brain lesions was also inferred as a significant predictor for the occurrence of withdrawal seizures.

Table 4 shows different clinical correlates in the WS+ and WS- group. Significant correlation was found between history of prev seizures, prev delirium, prev AWS, previous detoxification episodes and occurrence of WS. Development of DT was also inferred as a significant predictor for the development of WS.

DISCUSSION

The present study corroborates the importance of the addiction-related history of an individual patient that adds significantly to our appraisal of which patients should deserve our special attention during their course of withdrawal.

Comparing the sociodemographic profile of patients with WS+ and WS-, we found wide range of variabilities. Amongst all the patients, WS appeared mostly in the professionals(71.43%) from higher socioeconomic status(71.43%)with educational background higher than senior secondary(42.86%).From the point of view of religion, the findings were similar to those of the patients with DT+ i.e. mostly hindus developed WS(71.43%). Out of all, the maximum number of patients who developed WS belonged to nuclear families (71.43%) whereas no case of WS was reported in patients living in joint families. This can be attributed to the strong social fabric and early recognition of withdrawal symptoms by the family members and early interventions. In the present study, around 14% of the patients who developed WS were from the urban background while none from the rural background which is complementary to our findings of no WS in the patients living in joint families. As we know, in India it is a social norm to live in a joint or nuclear-extended family, compared to the scenario in the western countries.

The present study had also compared various biochemical markers in the patients of WS+ and WS- group. Age was found to be a significant predictor (p value = 0.015) for WS. Thus, older age does correlate with a longer duration of abuse and an increased risk of severe withdrawal (14) (15).

On comparing the duration of addiction years and daily ethanol consumption in the WS+ and WS- group, both these had significant correlation for occurrence of WS. The association between grams per day of ethanol consumption and seizure prevalence is unexpected and in conflict with the other studies performed on a similar population done by Brown ME et al, 1988 (23), Eyer et al, 2011 (17), Bleich et al, 2006 (15). Presumably toxic effects of ethanol acting over the course of months or years lower an individual's seizure threshold.

In the current study, CIWA-Ar score (Mean-33.42±8.64) also came out to be a significant risk factor(p value<0.001) for the development of WS.

The cardiovascular parameters, systolic and diastolic blood pressure and heart rate were evaluated and both systolic blood pressure (154±13.4)mmHg and diastolic blood pressure (97±3.4)mmHg had significant correlation (p value<0.001;p value=0.005) to the development of WS. This can probably be attributed to the phenomena of autonomic hyperactivity occurring in this population during the withdrawal state (19). W.A Mortan et al, 1994 (20) also assessed heart rate and in his study, the seizure patients had a greater elevation in mean pulse rate (93 f 12) during the first 48 hour period compared to the controls (85 f 10) (P < .05).

In patients with WS+ group, comorbid medical illness was a significant predictor (<0.001) for the occurrence of WS.On analysing the structural brain lesions in patients in WS+ group,71.4% had history of structural brain lesion like epilepsy, head injury, etc. and this had significant correlation(p value<0.001) with the occurrence of WS. This finding was also found significant in the study conducted by W.A Mortan et al, 1994 (20) and Eyer et at, 2011 (17) replicated the above finding.

All the patients in the WS+ group had previous history of WS and previous history of alcohol withdrawal syndrome and 28.5% had a previous history of DT. These parameters were a significant predictor (p value<0.001, p value=0.011) for the occurrence of WS, an observation well studied in the previous studies. A progressive increase in the severity of alcohol withdrawal with prolonged continuous abuse is termed "kindling". A previous history of alcohol-related seizures is a strong predictor of future events. In the current study, patients who had experienced a seizure in the past were identified, but no attempt was made to differentiate between the type of seizures Similar results have been given by Rathlev et al., 2000 (21), Wojnar et al., 1999 (22), Morton et al., 1994 (20). Brown et al., 1988 (23) in their study found the previous history of alcohol withdrawal seizures as a best predictor of subsequent withdrawal seizure susceptibility.

In continuation with the above findings, previous history of detoxification episodes also came out to be a significant predictor (p value <0.001) for the occurrence of WS and all the patients in the WS+ group had a previous history of multiple detoxification episodes. Brown et al.,1988 (23); concluded that that alcoholics with greater than five previous medical detoxifications may be at a higher risk for withdrawal seizures due to the accumulated kindling effect of repeated alcohol withdrawals.

Finally, comparing patients with DT+ and WS+ by multivariate regression analysis, it was inferred that both DT and WS are independent significant risk factors (p value<0.001) for each other i.e. occurrence of WS increases the risk for occurrence of DT and vice versa.

LIMITATIONS

Even though in this study we analyzed parameters of patients at admission (e.g. withdrawal history, laboratory parameters) being certainly independent of the given treatment protocol, we have yet to consider differences in the baseline parameters of these two groups that were not necessarily balanced in all respects. The information about prior WS was according to patient's report and we were unable to verify the accuracy of these reports. Only those experiencing alcohol withdrawal in an inpatient setting were included. In addition, this study excluded female gender, previous studies have shown differences in the amount of alcohol leading to intoxication as well as medical sequelae from chronic alcohol use in females.

CONCLUSION

Following conclusions were drawn from the present study that the various variables that were found to be significantly correlated to the occurrence of WS are mentioned as follows: age, duration of abuse, daily alcohol intake, CIWA-Ar score>15, systolic & diastolic BP, comorbid medical illness, structural brain lesion, previous history of WS and DT, previous history of alcohol withdrawal syndrome and previous detoxification episodes.

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