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Post-Traumatic Stress Disorder in Patients with Heavy Alcohol Consumption and Alcoholic Hepatitis

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Abstract

Background: Lifetime prevalence of post-traumatic stress disorder (PTSD) in general population is reported to be 6.8%. Individuals with alcohol dependence and substance abusers have high prevalence of PTSD. However, the prevalence of PTSD in heavy drinkers with alcoholic hepatitis is not known.

Aim: To determine the prevalence of PTSD in heavy drinkers with and without alcoholic hepatitis.

Methods: We screened for PTSD using Primary Care -PTSD questionnaire among heavy drinkers with (n=115) and without (n=64) alcoholic hepatitis participating in a multicenter observational study in which participants were followed up to 12 months following their enrollment.

Results: The prevalence of PTSD in heavy drinkers with alcoholic hepatitis was 34% and was not different from heavy drinking controls without liver disease (34%). In the entire group screened for PTSD, the presence of PTSD was associated with higher alcohol consumption as reported by average drinks per last 30 days, and average grams of alcohol consumed per day ($p = 0.047$ for both tests), but not associated with relapse of heavy drinking or mortality. Similarly, patients with alcoholic hepatitis and PTSD did not have higher relapse rate, or higher mortality compared to patients with alcoholic hepatitis but no PTSD.

Conclusion: Compared to previously reported prevalence in general population, heavy drinking individuals with or without alcoholic hepatitis have significantly higher prevalence of PTSD. However, PTSD was not associated with higher relapse rate, or higher mortality in this population.

Keywords: Heavy alcohol drinkers, Alcoholic hepatitis, Alcoholic liver disease, Post-traumatic stress disorder

Introduction:

Excess alcohol consumption is associated with significant mortality and economic burden. (Rehm et al., 2009) About 88,000 deaths every year are attributable to excess alcohol consumption. (Esser et al., 2014) Alcohol attributable fractions (AAF) of deaths due to liver cirrhosis in heavy drinkers is 60.6% and 62.4% in males and females respectively. ("WHO: Alcohol Consumption in the United States of America," 2014)

Alcoholic liver disease (ALD) consists of a spectrum of histopathological changes ranging from simple steatosis, to alcoholic steatohepatitis, and cirrhosis. (Sozio and Crabb, 2008) Alcoholic hepatitis (AH); however, is a severe clinical presentation characterized by acute onset of jaundice- and liver-related complications in patients with AUD. The short term mortality of AH remains high with 15%-30% mortality within the first 30 days after the diagnosis. (Orntoft et al., 2014; Maddrey et al., 1978; Liangpunsakul, 2011) At present, there are no effective therapies for AH except for alcohol abstinence. Complete abstinence after an episode of AH significantly impacts long-term survival; suggesting that strategies aimed at promoting alcohol abstinence in AH patients are mandatory. (Altamirano et al., 2017)

It is known that AUD, a risk factor for AH, is more likely to develop in those with other psychiatric illnesses including post-traumatic stress disorder (PTSD). (Kessler et al., 1996; Regier et al., 1990) Co-occurrence of PTSD with AUD not only intensifies likelihood of mood disorders, neuropsychological challenges and other non-PTSD anxiety problems, but also increases suicidal risk. (Blanco et al., 2013; Bowe and Rosenheck, 2015; Flanagan et al., 2016; Hawkins et al., 2012; Marx et al., 2009; Ouimette et al., 2003; Pietrzak et al., 2010) PTSD appears to play an important role in perpetuating the vicious cycle leading to AUD and is associated with relapse to alcohol use among those who achieved abstinence. (Bradizza et al., 2006) Although this notion is not consistently seen in literature, as evident in a post-

hoc analysis combining study populations of two clinical trials, where alcohol consumption severity was found to be higher in the group with AUD alone compared to the AUD and PTSD group. (Fuehrlein et al., 2014)

Despite epidemiological studies on the comorbidity of AUD and PTSD, not much is known about the prevalence of PTSD in patients with AH, a subgroup of AUD associated with high mortality. As PTSD is associated with relapse to alcohol and abstinence impacts survival in AH, understanding the magnitude of this problem is important as it may lead to screening and appropriate intervention for PTSD in patients with AH. The primary objective of our study is to determine the prevalence of PTSD in a well characterized cohort of patients with AH and their matched heavy drinking controls. Our secondary objectives include evaluation of alcohol consumption, severity of liver disease, mortality rates up to 12 months and relapse at 6 and 12 months in the entire cohort and AH subgroup based on PTSD status.

Methods:

Study cohort

The study is based on an ongoing prospective observational study of heavy drinking individuals with well characterized AH and matched heavy drinking controls without liver disease (**TREAT 001, NCT 02172898**). This study was approved by the Institutional Review Boards at each of the participating centers and all participants signed an informed consent. The diagnosis of AH was based on (i) average daily alcohol consumption of > 40 grams/day for women and > 60 grams/day for men for a minimum of 6 months and within the 6 weeks prior to study enrolment, and (ii) clinical evaluation and appropriate laboratory testing as defined by total bilirubin > 3 mg/dL and AST > 50 U/L. Liver biopsy was selectively obtained when the diagnosis was in doubt. Heavy drinking controls were those with average daily alcohol consumption as well as duration of drinking similar to that of AH cases but with normal hepatic panel and no prior history of alcoholic liver disease and absence of

hepatosplenomegaly or stigmata of chronic liver diseases. (Liangpunsakul et al., 2016; Puri et al., 2018) Relapse was defined as drinking on five or more days within one week or five or more drinks per drinking occasion. (O'Malley, 1992) All patients who were enrolled in TREAT from December 2014 to September 2017 and completed PC-PTSD questionnaire were included in the study.

Demographic data, past medical history, and blood samples were collected at the time of enrollment. Alcohol Use Disorders Identification Test (AUDIT) and the Time Line Follow-Back (TLFB) were used to characterize the alcohol consumption data. Four-question Primary Care-PTSD (PC-PTSD) questionnaire consisting of the following questions was used to screen for the presence of PTSD:

In your life have you ever had any experience that was so frightening, horrible, or upsetting that in the past month you:

- (a) Have had nightmares about it or thought about it when you did not want to?*
- (b) Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?*
- (c) Were constantly on guard, watchful, or easily startled?*
- (d) Felt numb or detached from others, activities, or your surroundings?*

Individuals with positive responses to ≥ 3 out of these 4 questions were considered to have PTSD. PC-PTSD has 78% sensitivity and 87% specificity in identifying individuals with PTSD compared to the gold standard, Clinician Administered PTSD Scale (CAPS). (Prins et al., 2004)

Statistical analysis

Pearson's chi-square test and two-sample t-tests were employed wherever appropriate to compare the groups. When sample sizes were extremely small, Fisher's exact test was applied instead of Pearson's chi-square test. The prevalence of PTSD and alcohol relapse at 6 and 12 months were calculated and the potential relationships between PTSD and alcohol relapse were determined. Among patients with AH, mortality rates were calculated using the Kaplan and Meier product limit estimator at 30 days, 60 days, 6 months, and 12 months by PTSD status. Mantel-Cox log rank test was employed to test for a difference in mortality rate by PTSD status. A p-value <0.05 was considered as statistically significant.

Results:

One hundred and fifteen patients with AH and 64 matched heavy drinking controls completed the PC-PTSD questionnaires. Baseline demographics and selected clinical characteristics of two groups are shown in **Table 1**. While age, gender, race, and BMI were comparable between two groups, as expected, liver tests were worse in patients with AH than in controls. The prevalence of PTSD in cases with AH was 34% and was not different from heavy drinking controls without liver disease (34%).

In the entire sample assessed for PTSD at baseline, those with PTSD were younger ($p = 0.034$), less likely to be white ($p = 0.015$), and had higher alcohol consumption as reported by average drinks per last 30 days, and average grams of alcohol consumed per day ($p = 0.047$ for both tests). However, the relapse of heavy drinking at 6 months and 12 months following enrollment as well as the mortality rate at 30 days, 60 days, 6 months, or 12 months were not different two groups (**Table 2**). The complete blood count, liver

biochemistries and Model for End Stage Liver Disease (MELD) were not different between the two groups (**Table 2**).

Compared to patients with AH but no PTSD, AH patients with PTSD were younger (42.5 vs 48.7 years, $p=0.006$), but their age, gender, and BMI were comparable. AH patients with PTSD had lower mean platelet counts (125.2 ± 54.8 cells/mm³ vs. 158.1 ± 92.8 cells/mm³, $p=0.04$), while other laboratory values were comparable. (**Table 3**) The relapse and mortality rates were comparable between AH patients with and without PTSD. (**Table 3**) Heavy drinking controls with ($n=22$) or without PTSD ($n=42$) had no difference in their relapse of heavy drinking at 6 months (33% vs 44%, $p=1.0$), or 12 months (80% vs 50%, $p=0.3$).

Discussion:

Based on DSM-IV/WHO mental health survey version of composite international diagnostic review, lifetime prevalence of PTSD in the general population was reported to be 6.8%. (Kessler et al., 2005) In our study, we found that a third of patients with AH and heavy drinkers have PTSD, which is an extremely high prevalence of PTSD compared to the general population (34% vs 6.8%). Although the prevalence of PTSD in patients with AH has not been specifically investigated previously, there is some evidence in the literature for enrichment of PTSD symptoms in individuals who participate in substance abuse. A quarter of subjects among a sample of 84 treatment-seeking substance abusers had PTSD symptoms. (Brown et al., 1995) In a study from Poland, 25% of 458 subjects with alcohol dependence were found to have criteria that met PTSD diagnosis. (Dragan and Lis-Turlejska, 2007) Published literature shows that patients with alcohol dependence have very high odds of having PTSD symptom clusters. (Tull et al., 2010) To our knowledge, this is the first report revealing high prevalence of PTSD in AH.

In our study, we also saw a higher alcohol consumption in subjects who had PTSD in the entire cohort compared to those who did not (440 vs 330 drinks per last 30 day period, $p=0.047$) and among subjects with AH, those who had PTSD drank an estimated average of 73 more drinks in the last 30 day period than those without presence of PTSD (353.2 vs 280.8), although this finding was not statistically significant ($p = 0.09$). As abstinence is an extremely important aspect of treatment in patients presenting with alcoholic hepatitis, addressing PTSD is very important in clinical care of patients with alcohol use disorders. (Pessione et al., 2003; Potts et al., 2013)

Previous studies suggested that PTSD is associated with worse outcomes in individuals with substance abuse. Substance dependent patients with PTSD not only relapsed faster, but indulged in heavier alcohol consumption (Brown et al., 1995) and had higher re-admission rates at one year for substance use relapse and mental health issues compared to those with substance abuse alone. (Ouimette et al., 1997) However, in our study, we did not find PTSD to be associated with higher relapse rate, or higher mortality. The reasons for this discrepancy are unclear but it could be due to limited number of participants returning for 6 and 12 month follow-up visits. We believe a study with larger sample size and more complete 6 and 12 month visit data are needed to firmly test the relationship between high prevalence of PTSD and relapse of heavy drinking in patients with AH.

Our data also shows that heavy drinking control group consumed more alcohol compared to AH group. This data was previously published by our group and the difference in alcohol consumption was believed to suggest a threshold effect of alcohol consumption, beyond which variations in alcohol consumption may not predict risk of AH. It could also point to factors other than quantity of alcohol that predispose heavy drinking individuals to develop AH. (Liangpunsakul et al., 2016)

Some limitations of our study deserve further comments. We screened subjects using PC-PTSD questionnaire based on Diagnostic Systems Manual-IV, but did not subject them to confirmatory PTSD testing. Furthermore, these patients could have co-existing mental health disorders in addition to PTSD, but we did not collect the information regarding the subject's mental health history or if the subjects were receiving treatment for the same. Finally, our study consisted of a modest sample size and a sizable proportion not returning for their follow-up visits. Notwithstanding these limitations, our observation that heavy drinking individuals with or without AH have high prevalence of PTSD is clinically important and merits further inquiry.

In summary, in this study we have shown that there is high prevalence of PTSD in patients with AH and heavy alcohol drinkers. Although screening positive for PTSD in the entire cohort was associated with higher alcohol consumption, it was not associated with higher relapse rate, or higher mortality. Studies with larger sample size and more complete follow-up are needed to fully understand the clinical relevance of PTSD in heavy drinkers with AH.

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Table 1: Selected Characteristics and Outcomes of Heavy Drinking Individuals with and without Hepatitis

	Cases (n=115)	Controls (n=64)	P value
Gender: male (%)	62	67	0.5
Race: white (%)	84	81	0.6
Age (years)	46.6 ± 11.3	45.9 ± 12.2	0.7
BMI (kg/m ²)	29.6 ± 7.5	27.7 ± 5.9	0.09
Average Drinks per Drinking Day	11.1 ± 7.5	17.2 ± 13.2	0.0001
Drinks per last 30 day period	305.4 ± 218.2	465.1 ± 385.9	0.0005
Average grams of alcohol consumed per Drinking Day (Gram)	166.6 ± 112.2	257.6 ± 197.9	0.0001
Average grams of alcohol consumed per Day (Gram)	152.7 ± 109.1	232.5 ± 192.9	0.0005
WBC (cells/cumm)	11.9 ± 7.3	6.8 ± 2.0	<.0001
Hemoglobin (gram/dl)	10.5 ± 2.8	13.0 ± 2.0	<.0001
Platelet (cells/cumm)	147.0 ± 83.2	226.8 ± 69.5	<.0001
Total Bilirubin (mg/dl)	13.8 ± 10.2	0.5 ± 0.3	<.0001
INR	1.8 ± 0.6	1.0 ± 0.2	<.0001
AST (units/L)	146.2 ± 85.5	29.7 ± 8.8	<.0001
ALT (units/L)	59.6 ± 50.4	27.2 ± 11.1	<.0001
Albumin (gram/dl)	2.8 ± 0.7	4.0 ± 0.6	<.0001
Creatinine (mg/dl)	1.1 ± 1.1	0.9 ± 0.3	0.26
MELD score	23.1 ± 7.2	7.3 ± 2.1	<.0001
PTSD (%)	34	34	0.95
Relapse (6 months)	10 of 41	11 of 27	0.17
Relapse (12 months)	9 of 21	10 of 17	0.33

Abbreviations: BMI- body mass index; WBC-white blood cells; INR-International Normalized Ratio; MELD score- Model for End Stage Liver Disease.

Table 2: Selected Characteristics and Outcomes in Heavy Drinking Individuals with and without PTSD

	With PTSD (n=61)	Without PTSD (n=118)	P value
Gender: male (%)	59	66	0.35
Race: white (%)	74	88	0.015
Age (years)	43.8 ± 11.1	47.6 ± 11.7	0.03
BMI (kg/m ²)	29.0 ± 7.1	28.9 ± 7.0	0.95
Average Drinks per Drinking Day	15.2 ± 12.7	12.3 ± 8.7	0.07
Drinks per last 30 day period	424.0 ± 362.8	330.7 ± 255.1	0.047
Average grams of alcohol consumed per Drinking Day	227.7 ± 190.1	184.3 ± 130.8	0.07
Average grams of alcohol consumed per Day	212.0 ± 181.4	165.3 ± 127.5	0.047
WBC (cells/mm ³)	9.0 ± 5.9	10.7 ± 6.6	0.09
Hemoglobin (gram/dl)	11.1 ± 2.2	11.5 ± 3.1	0.31
Platelet (cells/mm ³)	165.5 ± 83.6	181.2 ± 89.0	0.26
Total Bilirubin (mg/dl)	8.1 ± 9.2	9.6 ± 10.9	0.36
INR	1.5 ± 0.6	1.6 ± 0.6	0.12
AST (units/L)	113.3 ± 103.7	100.1 ± 79.8	0.35
ALT (units/L)	51.1 ± 48.2	46.4 ± 41.3	0.50
Albumin (gram/dl)	3.3 ± 0.7	3.2 ± 1.0	0.91
Creatinine (mg/dl)	1.0 ± 0.9	1.0 ± 0.9	0.67
MELD score	16.2 ± 8.7	18.1 ± 10.0	0.22

Relapse (6 months)	6 of 17	13 of 46	0.58
Relapse (12 months)	6 of 11	13 of 27	0.72
Mortality Rate (%)			
30 days	3.3	7.7	0.99
60 days	8.2	8.55	
6 months	11.6	10.3	
12 months	11.6	11.4	

Abbreviations; BMI- body mass index; WBC-white blood cells; INR-International Normalized Ratio; MELD score- Model for End Stage Liver Disease.

Table 3: Selected Characteristics and Outcomes in Alcoholic Hepatitis Patients with & without PTSD

	With PTSD (n=39)	Without PTSD (n=76)	P value
Gender: male (%)	56	65	0.4
Race: white (%)	77	88	0.12
Age (years)	42.5 ± 10.1	48.7 ± 11.4	0.006
BMI (kg/m ²)	30.0 ± 7.8	29.4 ± 7.4	0.66
Average Drinks per Drinking Day	12.3 ± 7.8	10.5 ± 7.3	0.21
Drinks per last 30 day period	353.2 ± 240.9	280.8 ± 202.9	0.09
Average grams of alcohol consumed per Drinking Day (Gram)	185.0 ± 117.4	157.1 ± 109.1	0.21
Average grams of alcohol consumed per Day (Gram)	176.6 ± 120.5	140.4 ± 101.5	0.09
WBC (cells/mm ³)	10.5 ± 6.9	12.7 ± 7.4	0.14
Hemoglobin (gram/dl)	10.3 ± 2.2	10.5 ± 3.0	0.72
Platelet (cells/mm ³)	125.2 ± 54.8	158.1 ± 92.8	0.046
Total Bilirubin (mg/dl)	12.3 ± 9.1	14.6 ± 10.6	0.25
INR	1.7 ± 0.5	1.9 ± 0.6	0.16
AST (units/L)	160.6 ± 102.7	138.8 ± 75.0	0.19
ALT (units/L)	65.6 ± 54.8	56.5 ± 48.0	0.36
Albumin (gram/dl)	2.9 ± 0.6	2.8 ± 0.8	0.26
Creatinine (mg/dl)	1.0 ± 1.2	1.1 ± 1.1	0.78
MELD score	21.6 ± 6.1	23.9 ± 7.6	0.11

Relapse (6 months)	4 of 11	6 of 30	0.41
Relapse (12 months)	2 of 6	7 of 15	0.66
Mortality Rate			
30 days	5.13	12.00	0.97
60 days	12.82	14.71	
6 months	18.19	16.18	
12 months	18.1	17.96	

Abbreviations; BMI- body mass index; WBC-white blood cells; INR-International Normalized Ratio; MELD score- Model for End Stage Liver Disease.

Table Legends

Table 1: Selected Characteristics and Outcomes of Heavy Drinking Individuals with and without Alcoholic Hepatitis

Table 2: Selected Characteristics and Outcomes in Heavy Drinking Individuals with and without PTSD

Table 3: Selected Characteristics and Outcomes in Patients with Alcoholic Hepatitis with and without PTSD