Minimal Hepatic Encephalopathy in Patients with Alcohol Related and Non-alcoholic Steatohepatitis Related Cirrhosis by Psychometric Hepatic Encephalopathy Score and Critical Flicker Frequency

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Running Title: MHE in ALD and NASH Cirrhosis

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ABSTRAK

Latar Belakang: Alkohol mungkin memiliki efek samping neurotoksik tambahan selain ensefalopati hepatik pada pasien dengan sirosis terkait alkohol. Penelitian ini bertujuan untuk mengevaluasi terjadinya *minimal hepatic encephalopathy* (MHE) dengan skor *Psychometric Hepatic Encephalopathy* (PHES) dan *Critical Flicker Frequency* (CFF) pada pasien sirosis terkait alkohol (ALD) dan *non-alcoholic steatohepatitis* (NASH). **Metode:** Sebanyak 398 pasien diskrining pada periode Maret 2016-Desember 2018; yang terdiri dari 71 pasien kelompok ALD dan 69 pasien kelompok NASH. Semua pasien menjalani tes psikometri yaitu *number connection test* A dan B (NCT-A dan NCT-B), *serial dot test* (SDT), *digit symbol test* (DST), *line tracing test* (LTT) dan CFF. MHE didiagnosis ketika nilai PHES pasien < -4. **Hasil:** Prevalensi terjadinya MHE lebih tinggi pada kelompok ALD dibandingkan dengan kelompok NASH (69,01% vs 40,58%; P 0,007). Hasil tes psikometri individu secara signifikan lebih buruk pada kelompok ALD (P<0,05). Sensitivitas dan spesifisitas CFF masing-masing sebesar 76,62% (95%CI 65,59 – 85,52) dan 46,03% (95%CI 33,39 – 59,06). Rata-rata CFF secara signifikan lebih rendah pada kelompok ALD dibandingkan NASH (37,07±2,37 vs 39,05±2,40; P 0,001); demikian juga pasien dengan MHE (36,95±2,04 vs 37,96±1,87; P 0,033) dan tidak adanya MHE (37,34±3,01 vs 39,79±2,46, P 0,001) juga lebih rendah pada kelompok ALD dibandingkan dengan NASH. **Kesimpulan:** MHE lebih umum terjadi pada pasien dengan sirosis ALD dibandingkan dengan NASH. Nilai CFF secara keseluruhan lebih rendah pada sirosis terkait alkohol dibandingkan dengan sirosis terkait NASH, bahkan dengan ada atau tidak adanya MHE. Kami menyarankan untuk meningkatkan kewaspadaan dalam manajemen MHE pada pasien sirosis ALD.

Kata Kunci: ensefalopati hepatik minimal, alkohol terkait sirosis, steatohepatitis non-alkoholik, *critical flicker frequency, psychometric hepatic encephalopathy.*

ABSTRACT

Background and Aim: Alcohol may have additional neurotoxic ill-effects in patients with alcohol related cirrhosis apart from hepatic encephalopathy. We aimed to evaluate minimal hepatic encephalopathy (MHE) with Psychometric Hepatic Encephalopathy (PHES) score and Critical Flicker Frequency (CFF) in alcohol (ALD) and non-alcoholic steatohepatitis related (NASH) related cirrhosis. **Methods:** 398 patients were screened between March 2016 and December 2018; of which 71 patients were included in ALD group and 69 in NASH group. All included patients underwent psychometric tests which included number connection test A and B (NCT-A and NCT-B), serial dot test (SDT), digit symbol test (DST), line tracing test (LTT) and CFF. MHE was diagnosed when their PHES was < -4. **Results:** The prevalence of MHE was significantly higher in ALD group compared to NASH (69.01% vs 40.58%; P 0.007). The performance of individual psychometric tests was significantly poorer in ALD (P<0.05). Overall sensitivity and specificity of CFF was 76.62% (95%CI 65.59 – 85.52) and 46.03% (95%CI 33.39 – 59.06) respectively. Mean CFF was significantly lower in ALD than NASH (37.07 ± 2.37 vs 39.05 ± 2.40, P 0.001); also in presence of MHE (36.95 ± 2.04 vs 37.96 ± 1.87, P 0.033) and absence of MHE (37.34 ± 3.01 vs 39.79 ± 2.46, P 0.001). **Conclusion:** MHE is significantly more common in patients with ALD cirrhosis than NASH counterparts. Overall CFF values are less in alcohol related cirrhosis than NASH related cirrhosis, even in presence or absence of MHE. We recommend additional caution in managing MHE in ALD cirrhosis.

Keywords: Minimal Hepatic Encephalopathy; Alcohol Related Cirrhosis, Non-alcohol Steatohepatitis; Critical Flicker Frequency; Psychometric Hepatic Encephalopathy

Key Summary

1. Alcohol is neurotoxin and have additional ill-effects on neurological function independent of underlying liver disease

2. Prevalence of minimal hepatic encephalopathy is higher in alcohol related cirrhosis compared to non-alcoholic steatohepatitis related cirrhosis
3. Performance of each of psychometric tests is hampered more in the patients with alcohol related cirrhosis compared to NASH related cirrhosis
4. Critical flicker frequency values lower in alcohol related cirrhosis than NASH related cirrhosis.

INTRODUCTION

Minimal hepatic encephalopathy (MHE) refers to subtle cognitive and psychomotor abnormalities observed in patients with cirrhosis who have no clinical evidence of overt hepatic encephalopathy.[1-3] MHE adversely affects Health-related quality of life (HRQoL).[4,5] Complex activities requiring attention or information processing and psychomotor skills such as driving, quick decision making or reaction to an acute change in environment are usually affected. Early identification of MHE is important as it can increase the risk of development of overt hepatic encephalopathy.[3] HRQoL, driving performance and prognosis can be improved with early recognition and treatment.[6]

Alcohol abuse is capable of inducing multi-system injury including hepatic and neurological dysfunction.[7] Excessive and chronic alcohol consumption is associated with impaired memory and serious cognitive decline and a range of neuropsychiatric complications.[8] Apart from ammonia related development of hepatic encephalopathy, which causes neurocognitive decline, alcohol has its independent affects cognitive function due to the presence of withdrawal, depression and direct toxic effect on the nervous system which needs to be identified.[9] The prevalence of MHE is dependent on prior episodes overt HE, severity of underlying liver disease, age, presence of esophageal varices and surgical porto-systemic shunts. However etiology of cirrhosis is not considered as major determinant for MHE,[3] which is based on studies where only digit symbol test (DST) and number connection test (NCT) were used to diagnose MHE.[10,11] As NCT and DST are affected by compounding factors like level of education, age, presence of peripheral neuropathy. Another study demonstrated that the decrease in critical flicker frequency (CFF) was significantly more in alcohol related cirrhosis (ALD) than non-alcohol related cirrhosis (NASH).[12]

In present study, we aimed to evaluate the role of CFF in the patients with MHE along with a battery of five Psychometric Hepatic Encephalopathy (PHES) tests in alcohol (ALD) and non-alcohol steatohepatitis related (NASH) related liver cirrhosis.

PATIENTS AND METHODS

All cirrhotic patients attending the Liver Clinic of Asian Institute of Gastroenterology, Hyderabad March 2016 to December 2018 were screened for eligibility based on etiology and presence or absence of overt hepatic encephalopathy. The study was approved by the Institutional Ethic committee and the Institutional review board. After written informed consent, patients with ALD and NASH related cirrhotic patients between age 18 to 70 were included. The diagnosis of cirrhosis was established based on clinical history, laboratory testing and imaging. Patients were considered to have alcohol-related cirrhosis if daily alcohol intake was more than 80 g for more than 10 years after excluding viral hepatitis, metabolic disease or autoimmune hepatitis. Diagnosis of NASH related cirrhosis was made in the patient with/without diabetes mellitus (DM) and obesity, but with no h/o ethanol consumption with a previously documented evidence of NAFLD. Other etiologies of cirrhosis such as viral hepatitis, autoimmune hepatitis and Wilson's disease were excluded. Patients with present or past history of overt HE, spontaneous bacterial peritonitis (SBP) or sepsis, history of GI bleeding (within last 4 weeks), history of alcohol intake during the past 4 weeks, TIPSS or shunt surgery, significant co-morbid illness such as cardiac, respiratory, renal, neurologic diseases and visual or mental impairment were excluded. Patients with mini mental scale examination score (MMSE) less than 24 were excluded. All included patients underwent PHES tests which included number connection test A and B (NCT-A and NCT-B), serial dot test (SDT), digit symbol test (DST), line tracing test (LTT) and CFF on the same day along with laboratory and imaging studies.

Normative Value

The normative values for the PHES tests were derived from a group of 110 healthy persons of which 85 were males and 25 were females. The mean age of this group was 43.74 ± 8.83 years (range 22–74 years), and the mean duration of formal education was 11.28 ± 4.04 years. The normative values for the PHES tests were as follows: NCT-A = 44.43 ± 11.59 s; NCT-B = 87.63 ± 24.04 s; DST = 47.13 ± 9.16

s; SDT = 56.65 ± 9.64 s; and LTT = 76.26 ± 11.46s. MHE was diagnosed if PHES score was less than -4 based on the normograms of healthy volunteers.[12,13]

Critical Flicker Frequency Test

CFF was measured by HEPAtonorm analyzer (R & R Medi Business Freiburg GmbH, Freiburg, Germany). It was measured in a quiet, semi-darkened room. Patients were first instructed and trained about the procedure with five measurements of CFF. Subsequently, flicker frequencies were measured nine times and the mean value was calculated. Measurement of the CFF thresholds was done by intrafoveal stimulation with a luminous diode. Decreasing the frequency of the light pulses from 60 Hz downward, the CFF threshold was determined as the frequency when the impression of fused light turned to a flickering one. CFF value < 39 was considered abnormal.[12]

Statistics and Sample Size Calculation

Based on previous study,[12] it is assumed to get a mean difference of CFF as 1.2 between two groups with 1.35 and 1.59 as standard deviations. The sample size required for the present study is 32 per each group with 90 % power and 0.05 as type 1 error using Medcal C software.

The data was presented as mean ± SD for continuous variables and as percentage for categorical variables. Mann-Whitney test and Chi-square tests were applied to test the statistical significance between the two groups for different parameters. Baseline characteristics including age and level of education were matched between study groups. A p value of <0.05 was considered as significant. The analysis was carried out using the statistical package for social sciences (IBM SPSS 24th version) and Medcal C software (version 18.6).

RESULTS

A total of 398 outpatients were screened for eligibility (**Figure 1**), out of which 71 patients were included in the ALD group [100% male; mean age (SD) – 50.37 (4.78) years] and 69 were included in NASH group (84.4% male; mean age (SD) – 51.58 (5.32) years). The mean years of formal education was 12.59 ± 2.01 years in ALD group and 13.25 ± 3.10 years in NASH group. Baseline characteristics are depicted in the **table 1**. There is no significant statistical difference between both groups with respect to age, level of education, baseline characteristics including CTP score and MELD score (p value >0.05).

By using PHES score, the point prevalence of minimal hepatic encephalopathy was significantly higher in the ALD group as compared to the NASH group: [49/71 patients (69.01%) vs. 28/69 patients (40.58 %), p value 0.007]. Even performance of individual PHES test was significantly poorer in the ALD group (p value <0.05) which is depicted in the **table 2**.

Overall sensitivity and specificity of CFF was 76.62% (95%CI 65.59 – 85.52) and 46.03% (95%CI 33.39 – 59.06) respectively. In subgroups; sensitivity and specificity of CFF in ALD was 75.51% and 36.36%; while in NASH it was 78.57% and 51.22% respectively. The diagnostic performance of the CFF for detecting MHE is summarized in the **table 3**. Overall CFF values were significantly lower in the ALD group compared to NASH group (**Figure 2** - 37.07 ± 2.37 vs. 39.05 ± 2.40, p value 0.001). CFF values in the patients with MHE (36.95 ± 2.04 vs. 37.94 ± 1.87 p value 0.033) and in patients without MHE (37.33 ± 3.01 vs 39.79 ± 2.46 p value 0.001) were also lower in ALD subgroup compared to NASH counterparts.

DISCUSSION

In the present study, we found that prevalence of MHE in the patients with alcohol related cirrhosis is higher than that of the NASH related cirrhosis; using psychometric tests as gold standard to detect MHE. Overall CFF values in the patients with alcohol related cirrhosis was lower than NASH related cirrhosis. Also in the presence or absence of MHE, CFF values were lower in alcohol related cirrhosis. This could be explained by neurotoxicity caused by alcohol itself.[8,9] Alcohol intake increases reaction time, decreases motor and cognitive functions. Alcohol affects visual functions by impairing depth perception, contrast sensitivity and visual temporal processing.[14] These neurological functions are essential during performance of CFF.

There is large variation in the prevalence of MHE among various Indian studies ranging from 22 to 74%.[15,16] This large variation is due to difference tests with different cut-offs.[3] Our study overall prevalence of MHE was 55% which is comparable with previously published studies.[17,18] Though a previous study[19] demonstrated that etiology of cirrhosis may not affect prevalence of MHE, we found that prevalence of MHE is higher in the alcohol related cirrhosis. We also found that overall CFF values were lower in the alcohol related cirrhosis compared to NASH counterparts. It could be explained by difference between diagnostic criteria for MHE between two studies. Current study used battery for five PHES tests to calculate PHES score. If score is less than -4 then is it diagnosed as MHE; while Li YY et al[19] used only NCT-A and DST for the same. Even in the presence or absence of MHE, CFF value were lower in alcohol related cirrhosis, which was also demonstrated in the previous study by Kircheis G, et al.[12] CFF is considered as easy to perform, cheap test, being reproducible parameter with limited bias with adequate sensitivity (76.62% in present study) and can be used for quantification of HE.[12, 20] As CFF is having adequate sensitivity compared to PHES tests to detect MHE, it can be used as single test instead of using five different PHES tests.[21] However, in one of the previous study, sensitivity of CFF was found to be low (39%) with specificity of 82% and diagnostic accuracy of 70.6% for detecting MHE, suggestive that CFF should be PHES for evaluation of MHE.[22]

We also evaluated individual psychometric test's performance in the alcohol related cirrhosis and their NASH counterparts. In present study, we found that performance of all the psychometric tests was significantly poor in the alcohol related cirrhosis. Though previous study by Li YY et al[19] demonstrated that performance of the NCT and DST was not statistically different in the both study groups, though the numerically values in the alcohol related group was poorer. Previous studies[23,24] have shown age and education as significant independent predictor for the PHES, our study these parameters are matched in both groups to avoid their effect on PHES tests and CFF.

Alcohol intake has many negative effects on neurological function, which are not only immediate but also long term. Neurological dysfunctions in the alcohol abusers are multiple and multifactorial.[9] Alcohol itself and its metabolites may probably directly causes toxic damage of the brain. Alcohol induced neurological dysfunction is usually characterized by a slowly progressing cognitive deficit along with brain tissue loss particularly Purkinje cells in cerebellar vermis.[9, 25-27] White matter atrophy, neural inflammation and toxicity, and impairment in synaptogenesis occurs mainly due to harmful effects of alcohol on the astrocytes, oligodendrocytes and synaptic terminals.[27] These effect might be independent of the alcohol induced liver injury, which leads to production of toxic, metabolic and inflammatory mediators that can cause neurological injuries.[28,29] Similarly, chronic alcohol intake increases reaction time, decreases motor function, affects attention and reduces CFF.[14,30]

Apart from being single center study, this study is having certain limitations. We do not have established histological diagnosis of NASH in study group; but we have included patients who have metabolic syndrome with documented evidences of fatty liver in previous ultrasound report after ruling out other causes of cirrhosis. We did not evaluated effect of nutritional deficiencies such as thiamine in patients with ALD, but we included patients with MMSE score >24. This could eliminate patients with major neuro-cognitive dysfunction secondary to nutritional and structural diseases.

In current study, we have shown that there is higher prevalence of MHE in the patients with alcohol related cirrhosis than NASH related cirrhosis using both

psychometric tests and CFF tests. We recommend additional caution in dealing with MHE in patients with alcohol related cirrhosis for better outcome. These findings need to be validated in the external cohort to establish the role of underlying etiology of cirrhosis in the MHE.

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Figure Legends

Figure 1: Study consort diagram

Figure 2: Comparison of critical flicker frequency in ALD and NASH group

Table 1: Baseline characteristics of study populations

Parameters	ALD (n= 71)	NASH (n = 69)	p value
Age (years)	50.37 ± 4.78	51.58 ± 5.32	0.158
Education (years)	12.59 ± 2.01	13.25 ± 3.10	0.139
Hemoglobin (gm/dl)	10.35 ± 1.48	10.99 ± 1.48	0.011
Platelet count (lakhs/mm^3)	1.18 ± 0.29	1.21 ± 0.31	0.644
INR	1.40 ± 0.17	1.36 ± 0.19	0.281
Bilirubin (mg/dl)	2.69 ± 2.43	2.10 ± 0.69	0.054
Albumin (gm/dl)	2.90 ± 0.30	3.03 ± 0.35	0.016
Creatinine (mg/dl)	0.92 ± 0.17	0.94 ± 0.17	0.437
Na (meq/L)	136.7 ± 2.10	136.6 ± 1.32	0.646
Ammonia (mmol/L)	47.82 ± 21.32	45.49 ± 22.30	0.529
CTP score	7.93 ± 1.41	7.48 ± 1.29	0.081
MELD	13.25 ± 1.92	12.58 ± 2.30	0.061
MELD Na	15.06 ± 2.24	14.32 ± 2.10	0.096

ALD: Alcohol related cirrhosis, NASH: non-alcoholic steatohepatitis related cirrhosis, INR: international normalized ratio, Na: sodium, CTP: Child-Pugh-Turcotte, MELD: model for end stage liver disease

Table 2: Psychometric tests in the ALD and NASH group

Psychometric test	ALD (N-71)	NASH (N-69)	p value
NCT-A (seconds)	83.21 ± 37.89	67.54 ±15.19	0.002
NCT-B (seconds)	155.59 ± 60.23	114.75 ±14.99	0.001
DST (numbers)	30.27 ± 7.85	34.22 ± 7.63	0.003
SDT(seconds)	67.99 ±12.27	61.01 ± 9.99	0.001
LTT(seconds)	79.27 ± 12.38	65.26 ±17.11	0.001
CFF	37.07 ± 2.37	39.05 ± 2.40	0.001

All values are expressed as mean ± standard deviation. NCT – A and B: number connection test A and B, DST: digit symbol test, SDT: serial dot test, LTT: line tracing test

Table 3: Diagnostic performance of CFF for detecting minimal hepatic encephalopathy

	True Positive/ Total Positive	True Negative/Total Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
ALD	37/51	8/20	75.51% (61.13 – 86.66)	36.36% (17.20 – 59.34)	72.55 % (64.98 – 79.01)	40.00% (24.14- 58.28)
NASH	22/42	21/27	78.57 % (59.05 - 91.70)	51.22 % (35.13 – 67.12)	52.38 % (43.21 – 61.39)	77.78% (61.85 – 88.31)
Overall	59/93	29/47	76.62% (65.59 – 85.52)	46.03% (33.39 – 59.06)	63.44% (57.25 – 69.22)	61.70 % (49.80 – 72.35)

ALD: alcohol related cirrhosis, NASH: non-alcoholic steatohepatitis related cirrhosis, PPV: positive predictive value, NPV: Negative predictive value

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