Research Report

PHENOMENOLOGY OF DELIRIUM IN DECOMPENSATED LIVER DISEASE PATIENTS-A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Decompensated liver disease (DCLD) is associated with various cognitive changes. The present study aimed to estimate the prevalence, phenomenology, and course of delirium in decompensated liver disease patients. **Methods**: This prospective observational study was done on 111 patients admitted to the gastroenterology department with the diagnosis of DCLD. Richmond Agitation Sedation Scale (RASS) and confusion assessment method (CAM) were used to detect delirium for the first five consecutive days. Patients detected to be having delirium were administered a delirium rating scale (DRS) for the next seven days to evaluate the features of delirium. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. For normally distributed quantitative parameters, the mean values were compared using an independent sample t-test. Categorical outcomes were compared between study groups using the chi-square test. coGuide version V.1.0 was used for statistical analysis. **Results:** The prevalence of delirium among patients with DCLD was 34 (30.63%). All delirious patients continued to have delirium symptoms for the initial three days. Six patients remitted as early as the fourth day of DRS assessment, while nine patients continued to have delirium symptoms even by the seventh day of evaluation. **Conclusion:** Nearly one-third of patients with DCLD presented with delirium. They presented with insomnia, cognitive deficits, motor retardation, and minimal psychotic symptoms. Many patients completely recovered from delirium within a week, but a few had delirium up to the seventh day.

Keywords: delirium, Hepatitis, hepatic encephalopathy, cirrhosis

Introduction

Delirium is a complex neuropsychiatric disorder and a potentially life-threatening acute brain dysfunction. Among the various causes of delirium, decompensated liver disease (DCLD) is an important one. [1] The literature on DCLD has dealt in-depth with various cognitive changes associated with it. Various terms are given for it as hepatic encephalopathy, minimal hepatic encephalopathy, episodic and persistent encephalopathy.[2] During the natural course of DCLD like fatty liver (steatosis), followed by inflammation ofthe liver tissue (hepatitis), scar tissue formation (fibrosis), and finally, destruction of liver architecture (cirrhosis) cause a decrease in the number of functional liver cells resulting in an inability to remove toxic substances from the blood. As a result, ammonia and manganese accumulate in the brain leading to structural

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changes in the astrocytes. These factors contribute to altered neurotransmission and brain dysfunction.

Based on psychomotor features, two clinical subtypes of delirium have been described; hyperactive and hypoactive.[3] Some patients fluctuate between these two and fall into the third subtype called mixed delirium.[4] Hyperactive delirium is characterized by agitated behaviour with increased psychomotor activity.[5] Alcohol withdrawal is a classic example of hyperactive delirium. Patients with hypoactive delirium are quiet and lethargic with decreased psychomotor activity.[5] Probably, these phenotypes signify different forms of neurologic dysfunction. However, as of now, clinically, there is no substantial understanding to pinpoint the aetiology.[6]

The prevalence of cognitive changes among patients with decompensated liver disease (DCLD) ranges from 30%-60%. The annual risk of a patient with DCLD developing hepatic encephalopathy is 20%, and 60%-80% of the patients with DCLD have some form of cognitive impairment during their lifetime.[7] Survival probability among DCLD patients who developed encephalopathy was 42% at one year and 23% at three years.[8] Prompt identification and management of this condition reduces mortality, morbidity and also shortens hospital stay.[9] Literature available includes studies on clinical profile, plasma ammonia levels in patients with liver failure with or without hepatic encephalopathy (HE) and prognostic factors associated with HE.[10–12] Longitudinal studies are found to be looking into the phenomena of all-cause delirium.[13] Though there are Indian studies on all-cause delirium [14], studies looking specifically at hepatic encephalopathy (HE) are rare. Hence, the current study aimed to study the phenomenology and course of delirium in decompensated liver disease patients. The objectives were to estimate the prevalence of delirium in patients admitted with decompensated liver disease and determine the association between delirium with clinical and laboratory parameters.

MATERIALS AND METHODS

Study population and study site: The study was conducted on patients admitted in the ward and ICU of a PSG Institute of Medical Science and Research, Coimbatore, with decompensated liver disease (DCLD) (based on clinical examination and supportive laboratory test reports).

Study design: Prospective observational study.

Study duration: Eight months from May 2013 to January 2014.

Inclusion Criteria:

1. Patients who were diagnosed with decompensated liver disease (DCLD).
2. Age between15 to 80 years.

Exclusion criteria:

1. Patients who were having severe mental disorders and mental retardation.
2. Patients on ventilators.
3. Patients were having severe impairment in vision (blindness) and hearing as they could not undergo the psychological tests.

Sample size: The sample size was calculated assuming the prevalence of delirium as 20% as per the study by FF Poordad et al.[15] The other parameters considered for sample size calculation were 8% absolute precision and a 95% confidence level. The following formula was used for sample size calculation.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n = Sample size, Z= Z statistic for the level of confidence, P= Expected prevalence of proportion (if the expected prevalence is 20%, then P= 0.2), and d = Absolute precision (if the precision is 8%, then d=0.08). The required number of subjects as per the calculation mentioned above was 97. To account for a non-participation rate of about 4% (four subjects), it was decided to sample about 111 subjects into the study.

Sampling method: All the eligible subjects were recruited into the study by consecutive sampling until the sample size was reached.

Ethical considerations: The Institutional Human Ethics Committee, PSG Institute of Medical Sciences & Research , Coimbatore approved the study, and the proposal approval number is 13/064. Written informed consent was obtained from the patient, and most were not capable of giving informed consent due to episodes of delirium at entry. Consent from the nearest key family member was taken in these cases.

Data collection tools and clinical examination

Patient proforma: Consists of data regarding socio-demographic profile, substance use details, clinical and laboratory parameters. A single examiner (psychiatrist) administered all the scales.

Various scales used for measurement:

SADQ (severity of alcohol dependence questionnaire)

The Severity of Alcohol dependence questionnaire was developed by Addiction Research Unit at Maudsley Hospital in 1983. It covers five aspects of alcohol dependence like Physical withdrawal symptoms, Affective withdrawal symptoms, relief in drinking, the frequency of alcohol consumption, and the speed with which onset of withdrawal symptoms occurs. It focuses on the last six months of heavy alcohol drinking. It takes 2-5 minutes to administer this questionnaire.[16]

RASS (Richmond Agitation Sedation Scale)

In our study, we use this scale to assess the level of consciousness of the patient. The Richmond Agitation Sedation Scale was developed at Virginia Commonwealth University in Richmond by a multidisciplinary team, and it can be performed in less than 20 seconds and requires minimal training.

CAM-ICU (confusion assessment method)

Confusion Assessment Method- ICU was developed by Sharon Inouye et al. in 1990, subsequently revised in October 2010. It is a bedside assessment tool, even usable by non-psychiatrists. This was designed mainly for ICU patients who are critically ill, with or without a ventilator, and unable to talk. It takes 5-8 minutes to assess the presence or absence of Delirium.[17]

The Delirium Rating Scale-Revised 98 (DRS-R-98) and administration of various scales:

The timings for data collection were scheduled between 5-7 pm because it is well known that delirium worsens during evening hours. The severity of alcohol dependence questionnaire (SADQ) was used on patients with a history of alcohol use. Each of the patients was administered RASS and CAM-ICU scales daily for five days to detect delirium. If a patient was detected to be having delirium on any of those five days, from that day onwards DRS-R-98 scale was administered. The onset of delirium was considered as the primary outcome variable. Data collection was scheduled between 5-7 pm of all the seven days of the study period (every 24 hours) to avoid overlap of symptoms and better capture of signs. DRS-R-98 scale is a validated scale with a high inter-rater reliability score ranging from 0.66–0.99, specificity ranging from 79%-88%, and sensitivity of 83%-88%. It is a 16-item clinician-rated scale, and it has two sections. First, 13 items are for assessing delirium symptoms severity, and the next 3 are diagnostic items. First, 13 items are rated from 0-3 points, and diagnostic items are rated from 0-2.[18]

Statistical Methods: The onset of delirium was considered as the primary outcome variable. Symptoms at different follow-up periods were considered as the primary explanatory variable. Demographic variables (like age, gender), clinical variables, and laboratory parameters were considered other study-relevant variables. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. For normally distributed quantitative parameters, the mean values were compared using an independent sample t-test. Categorical outcomes were compared between study groups using the chi-square test. P-value <0.05 was considered statistically significant. The coGuide version V.1.0 was used for statistical analysis.[19]

RESULTS

In our study, the prevalence of delirium among patients with DCLD was 30.63% (34). 94 (84.7%) were males in the study sample, and 17(15.3%) were females. More than half of the study group had been diagnosed with alcohol-induced DCLD 64(57.7%). The majority of patients with DCLD had portal HTN91(82%), ascites 43(38.7%), and oesophagal varices 36 (32.4%) were almost equally distributed in the entire sample. Among111 patients, 71 patients (64%) had a history of alcohol consumption in their lifetime. The number of patients using nicotine in the form of smoking was 48(43.2%), and in the form of tobacco, chewing was noted only in 10 (9%) of patients. Among the patients who had a history of alcohol consumption in their lifetime, around 36 (50%) consumed alcohol within one month before hospital admission. (Table 1)

Patients continued to have sleep disturbance throughout one week of delirium. Sleep disturbances seen were sleep-wake cycle disruption, insomnia, day-night

reversal, and frequent daytime naps. From the fourth day onwards, psychotic symptoms (delusions, perceptual abnormalities, and thought disorder) started

Table 1: Summary of demographic variables and clinical parameters (N=111)

Petameters	Summary
Gender	
Male	94 (84.7%)
Female	17 (15.3%)
Age	53.6 ± 8 years
DCLD subtypes	
DCLDalcohol-induced	64 (57.7%)
DCLD-cryptogenic	15 (13.5%)
DCLD- other types	32 (28.8%)
Manifestations of DCLD	
Portal hypertension	91 (82%)
Ascites	43 (38.7%)
Esophageal varices	36 (32.4%)
Mean total bilirubin	6.58 ± 0.25
Mean SGPT	49.31 ± 5.33
Mean SGOT	84.38 ± 9.45
Mean alkaline phosphatase	133 ± 20.15
Mean proteins total	6.27 ± 0.18
Substance use	
Alcohol	71 (64%)
Nicotine (smoking)	48 (43.2%)
Nicotine (Chewable)	10 (9%)
Last drink of Alcohol consumption (n=71)	
0 to 30 days of admission	36 (50.7%)
between 30 to 90 days of admission	8 (11.2%)
>90 days of admission	27 (38.0%)
SADQ severity of alcohol dependence (no=51)	
Mild	3 (5.8%)
Moderate	28 (54.9%)
Severe	20 (39.2%)
The onset of Delirium (no=34)	
Day 1	23 (67.6%)
Day 2	7 (20.5%)
Day 3	4 (11.7%)
Last drink (N=71)	
<7 days	26 (36.62%)
>7 days	45 (63.38%)

Patients continued to have sleep disturbance throughout one week of delirium. Sleep disturbances seen were sleep-wake cycle disruption, insomnia, day-night reversal, and frequent daytime naps. From the fourth day onwards, psychotic symptoms (delusions, perceptual abnormalities, and thought disorder) started reducing and were absent on the sixth and seventh days. On day 7, patients continued to have the following symptoms; sleep disturbance 9 (100%), motor retardation 4(44.4%). The cognitive deficits which continued were disorientation, inattention, visuospatial deficits, short-term memory loss, and long-term memory loss. (Table 2)

We looked for association with hepatic encephalopathy by considering various parameters like age, gender, the severity of DCLD presentation, alcohol use, and LFT values. We compared these parameters between delirious and non-delirious patients. There were no statistically significant differences between delirious and non-delirious in various parameters like age, gender, the severity of DCLD presentation, and LFT parameters like (SGPT, SGOT, alkaline phosphatase, total protein, GGT) (p-value >0.05) except for bilirubin, which showed statistical significance. (Table 3)

DISCUSSION

In our study, the prevalence of delirium in patients with decompensated liver disease was 30.63%. Among the various causes of decompensated liver disease, alcohol-induced DCLD was seen in most patients (57%). While analyzing the association, none of the factors like age, gender, alcohol, or severity of liver dysfunction was associated with delirium except for bilirubin in DCLD patients.

The mean age of the participants was 53.6±8 years, and 84.7% were males, and 15.3% were females. A study on cirrhotic hepatitis C patients had a mean age of 57.8 ± 7 and 63%, and 37% were males and females, respectively.[20]

Our study was comparable to other studies on cognitive changes in decompensated liver disease (30%-60%) in the prevalence of delirium.[21] Overt hepatic encephalopathy occurs in approximately 30%–45% of cirrhotic patients and 10%–50% of patients with the transjugular intrahepatic portosystemic shunt.[22] Minimal hepatic encephalopathy, characterized by

Table 2: Course of each symptom of delirium in 7days period

SL. No	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Insomnia	34(100%)	29 (96.6%)	25 96.1%)	17 (94.4%)	9 (81.8%)	10 (90.9%)	9 (100%)
Perceptual isturbance	10 (29.4%)	7 (23.3%)	4 (15.3%)	2 (11.1%)	0	0	0
Delusions	10 (29.4%)	7 (23.3%)	3 (11.5%)	0	0	0	0
Affect disturbances	31 (91.1%)	23 (76.6%)	12 46.1%)	10 (55.5%)	5 (45.4%)	3 (27.2%)	1 (11.1%)
Language deficits	18 (52.9%)	12 (40%)	4 (15.3%)	2 (11.1%)	1 (9%)	0	0
Thought disorder	11 (32.3%)	6 (20%)	4 (15.3%)	1 (5.5%)	1 (9%)	0	0
Motor agitation	18 (52.9%)	16 (53.3%)	10 38.4%)	8 (44.4%)	5 (45.4%)	2 (18.1%)	2(2 2.2%)
Motor retardation	32 (94.1%)	22 (73.3%)	16 61.5%)	10 (55.5%)	5 (45.4%)	4 (36.3%)	4 (44.4%)
Disorientation	34 (100%)	26 (86.6%)	14 53.8%)	8 (44.4%)	4 (36.3%)	2 (18.1%)	2 (22.2%)
Inattention	30(88.2%)	21 (70%)	11 42.3%)	4 (22.2%)	4 (36.3%)	2 (18.1%)	2 (22.2%)
Short-term memory	25 (73.5%)	15 (50%)	9 (34.6%)	5 (27.7%)	3 (27.2%)	2 (18.1%)	2 (22.2%)
Long-term memory	19 (55.8%)	13 (43.3%)	6 (23%)	4 (22.2%)	1 (9%)	1 (9%)	1 (11.1%)
Visuo-spatial deficits	17 (50%)	12 (40%)	6 (23%)	4 (22.2%)	1 (9%)	1 (9%)	1 (11.1%)
Total D-pts	34	30	26	18	11	11	9 (26.4%)

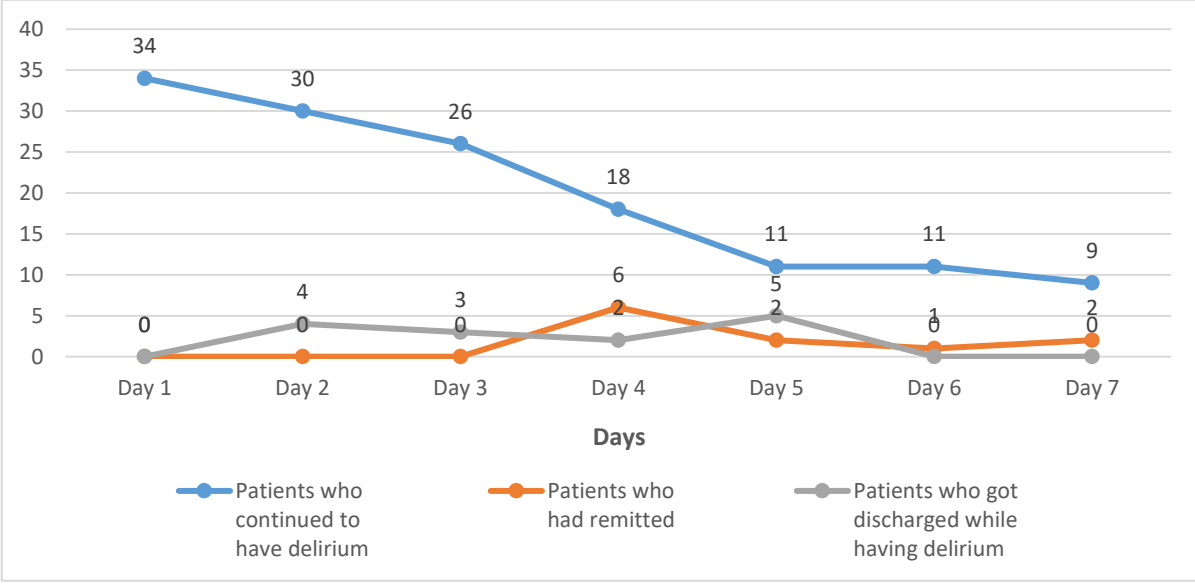
Table 3: Comparison of demographic variables and clinical parameters between delirium and non-delirium (N=111)

Parameters	Delirium (N=34)	Non-delirium (n=77)	P value
Mean age	55.09	52.96	0.372‡
Gender			
Male	30(88.2%)	64(83.1%)	0.476†
Female	4(11.8%)	13(16.9%)	
The severity of DCLD presentation			
Portal HTN	26(76.5%)	65(84.4%)	0.422†
Esophageal varices	13(38.2%)	23(29.9%)	0.382†
Ascites	11(32.4%)	32(41.6%)	0.404†
LFT parameters			
Total Bilirubin	8.65 ± 0.13	5.67 ± 0.09	0.010‡
SGPT	38.53 ± 3.08	51.88 ± 5.11	0.908‡
SGOT	77.88 ± 8.90	87.25 ± 7.78	0.482‡
Alkaline Phosphatase	144.26 ± 12.33	128.16 ± 11.45	0.435‡
Total Protein	6.30 ± 1.01	6.26 ± 0.99	0.828‡
GGT	96.68 ± 3.34	141.61 ± 2.56	0.954‡
Last drink			
<7days	9(34.6%)	17(65.4%)	0.797†
>7days	14(31.1%)	31(68.9%)	

‡*Independent sample t-test, † chi-square test*

subtle motor and cognitive deficits, affects approximately 20%–60% of patients with liver disease.[8] The true incidence and prevalence of hepatic encephalopathy is difficult to establish because of

Figure 1: Course of Delirium as evaluated by Delirium rating scale (DRS)



considerable differences in the aetiology and severity of hepatic encephalopathy and the varying tools in diagnosing.

Unlike the previously used scales like West-Haven Criteria, PSE-syndrome test (Portosystemic encephalopathy Syndrome Test and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test, which detects cognitive changes rather than delirium, we have used RASS and CAM-ICU, which detect delirium due to any cause. Unlike previous scales (which need physicians and psychologists to assess), nursing staff can administer these scales with minimal time and monetary resources.

To the best of our knowledge, this is the first study to look into the breadth of the phenomenology of delirium in patients with DCLD. Our study describes delirium in detail by tracing out and defining 13 of its symptoms over seven days (Table 3). By unfolding how exactly each of these symptoms remitted in a week, this study also portrays the course of delirium.

On meticulously observing the symptoms of delirium, sleep disturbance is present in all patients, and it is present throughout delirium. Sleep disturbance includes sleep-wake cycle disturbance, day-night reversal, nocturnal disturbance only, or frequent daytime naps. Sleep-wake inversion or the combination of restless nights and excessive daytime sleepiness were first described as a sign of overt HE by Sherlock et al.[23] Similar findings were recorded in studies with both insomnia and fragmented sleep with multiple night awakening sin cirrhosis patients.[24]

The next glaring symptom is disorientation, where the person is disoriented to time, place, and person in increasing order of severity. While recovering, the patient first gets oriented to person, and the last thing he gets oriented to is time. Almost 100% of the patient had disorientation on day one. Similar results were shown in studies where almost all participants showed disorientation features.[25] A recent longitudinal study of the phenomenology of delirium showed the prevalence of disorientation in all visits to be 81% with DRS-R-98 and 69% with the cognitive test for delirium (CTD).[13] Another longitudinal study (Fan et al. 2005) has suggested that psychomotor abnormalities and sleep-wake cycle disturbances present mainly in the early course of a delirium.[26] In contrast, disorientation, inattention, impaired memory, and sleep disturbances are present throughout delirium (McCusker et al., 2003).[27]

Another important area in delirium symptoms is cognitive deficits. Cognitive deficits consist of inattention, memory impairment, visuospatial disturbances. The cognitive symptom was one of the persistent symptoms patients had while getting discharged. Studies were done in the past, giving weightage on how to detect delirium in patients with a

subclinical presentation, mainly in cognitive deficits.[9] A study done to assess all-cause delirium's phenomenology using the MDAS scale showed an increased prevalence of perceptual disturbances (e.g., hallucinations) and delusions. In contrast, the present study showed less prevalent symptoms for perceptual disturbances and delusions.[28] The difference may be due to the scales used in both studies and the latter used only for DCLD patients.

Psychotic symptoms experienced were thought disorder, delusions, and perceptual abnormalities. Delusions predominantly seen were persecutory. Perceptual abnormalities ranged from illusions to hallucinations, predominantly auditory. We also found that psychotic symptoms were the first to remit among all the delirium symptoms. More prevalent symptoms such as hallucinations, illusions, and delusions were seen in patients with the activated subtype in a study done by Ross et al.[14]

Delirium was fully remitted in 11 patients within a week, but 14 patients got discharged within seven days while still having some features of delirium. Three of these patients requested discharge for personal reasons, and four patients got discharged against medical advice. The remaining seven patients were discharged from the hospital side when they still had minimal delirious features (like motor retardation and cognitive deficits).

This study also tried to analyze the association of delirium following hepatic encephalopathy with other factors. Age, gender, marital status, socio-economic status, and education did not significantly affect delirium. Moreover, on generally comparing LFT results between delirious and non-delirious patients, patients with delirium showed significantly more deranged bilirubin values. This is also supported by previous studies.[29]

The main strength of our study was that the participants were followed up by a week to assess the course of delirium in decompensated liver disease in detail.

Limitations: We don't have data on patients who had a more extended hospital stay in which delirium could have developed after five days (stopped visiting DCLD patients on the fifth day itself according to our study protocol). We did not consider other parameters associated with delirium, like biochemical parameters (electrolyte, ammonia, arterial blood gas, etc.), cardiac or renal parameters. Also, pharmacotherapy was not assessed, such as benzodiazepines for alcohol withdrawal that could have precipitated encephalopathy in some patients.

Conclusions: We conclude by saying that a significant number of patients having DCLD present with delirium. They present with insomnia, cognitive deficits, motor retardation, and minimal psychotic symptoms. Many patients completely recovered from delirium within a week, but few had delirium for more than one week. No significant association was seen in delirium patients with liver function tests and alcohol consumption except for bilirubin.

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Conflict of interest:

None declared.

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