A CLINICAL STUDY OF HEPATIC ENCEPHALOPATHY IN CHRONIC LIVER DISEASE WITH REFERENCE TO SERUM AMMONIA IN A TERTIARY CARE HOSPITAL OF NORTH EAST INDIA

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ABSTRACT

INTRODUCTION

Hepatic encephalopathy is the term used to describe the complex, sometimes irreversible, and variable changes in neuropsychiatric status that can complicate both acute and chronic liver disease. A spectrum of neuropsychiatric abnormalities exists ranging from clinically indiscernible changes in cognition to clinically obvious changes in intellect behaviour, motor function, and consciousness.

METHODS

We conducted a hospital-based observational descriptive study comprising of 80 patients of chronic liver disease from June 2014-May 2015 who had been diagnosed on the basis of a thorough history, physical examination, including mini-mental status examination, Glasgow Coma Score, biochemical tests including arterial ammonia, radiological findings, EEG and CFF (critical flicker frequency) Tests after excluding other causes of neurological impairment. The patients were admitted in Gauhati Medical College and Hospital, Guwahati, Assam (India) and fulfilled the inclusion and exclusion criteria of the study. Statistical analysis was performed using one way ANOVA method of analysis.

RESULTS

In our study, 61 patients were male and 19 patients were female. 30% patients were in the third decade of life followed by 26.25% in the fourth decade and 18.75% in the fifth decade. Most of the patients were in Child-Pugh Class C (72.5%) followed by Class A (16.25%) and Class B (11.25%). The patients were assigned grades of hepatic encephalopathy according to the West-Haven classification. Majority of patients were in grade I hepatic encephalopathy (30%) followed by grade III (28.75%) and grade IV (21.25%). The lowest mean arterial ammonia level was found in grade 0 and grade I hepatic encephalopathy - 39.2±7.4 mg/dL and 58.7±9.8 mg/dL (mean±standard deviation) respectively and the highest values were found in the highest grades of hepatic encephalopathy - grade III and IV (98.4±10.7 mg/dL and 145.0±17.0 mg/dL respectively).

CONCLUSION

The arterial ammonia correlates with the grades of hepatic encephalopathy and interventions aimed at reducing the ammonia level improves the outcome and prognosis.

KEYWORDS

Chronic liver disease, Hepatic encephalopathy, Arterial ammonia.

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INTRODUCTION: Hepatic encephalopathy is a syndrome that is difficult to synthesize into an entity. It describes a wide spectrum of neuropsychiatric abnormalities that occur in people with chronic liver disease. It can be both reversible and irreversible. It affects several neurologic domains like cognition, emotion, biologic rhythms, and behaviour. The neuropsychiatric abnormalities in hepatic encephalopathy range from clinically indiscernible changes in cognition to clinically obvious changes in intellect, behaviour, motor function, and consciousness. The key components of the syndrome are portosystemic shunting and hepatocellular damage. It is most common in the third and fourth decades[(1),(2)] and there is a male preponderance of the disease.[(1),(3)]

30-45% of patients with cirrhosis[(4)] and 10-50% of patients with portosystemic shunts[(5)] will experience an episode of overt encephalopathy sometime during their illness.

Prognosis in hepatic encephalopathy is poor with 1 year survival of 40% following a first episode, which rapidly falls to about 15% in 3 years.[(6)] Even when mild, it is a marker

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of low survival expectancy.[7] It continues to be a major clinical problem. Its prognosis in patients with cirrhosis can be determined with the Child-Pugh classification.[8] The Organisation Mondiale de Gastroenterologie commissioned a Working Party to reach a consensus in this area at the 11th World Congress of Gastroenterology in Vienna (1998). Hepatic encephalopathy reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease. The definition of hepatic encephalopathy incorporates both the type of hepatic abnormality and the duration/characteristics of neurologic manifestations in chronic liver disease. The types of hepatic encephalopathy[9] are as given below:

Types of Hepatic Encephalopathy:

Type A: Encephalopathy associated with acute liver failure.

Type B: Encephalopathy associated with portal systemic bypass and no intrinsic liver disease.

Type C: Encephalopathy associated with cirrhosis and portal hypertension and/or portal systemic shunts.

Table 1. Proposed Nomenclature of HE

HE Type	Nomenclature	Subcategory	Subdivisions
A	Encephalopathy associated with acute liver failure		
B	Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease.		
C	Encephalopathy associated with cirrhosis and portal hypertension/or portal-systemic shunts	Episodic HE	Precipitated Spontaneous* Recurrent
		Persistent HE	Mild Severe Treatment-dependent
		Minimal HE	

The correlation between circulating blood ammonia concentrations and neuropsychiatric status is poor. This reflects at least in part the technical difficulties associated with its measurement and the differences in blood and brain ammonia concentrations, which can be explained by variation in the compartmental pH. Indeed, the pH - dependent partial pressure of gaseous ammonia in arterial blood correlates more closely with the clinical and neurophysiological changes observed than plasma ammonia concentrations.[10]

AIMS OF THE STUDY:

1. To study the correlation between the arterial ammonia level and the grades of hepatic encephalopathy.
2. To study the clinical profile of the patients of hepatic encephalopathy.

MATERIALS AND METHODS:

Patients: In this descriptive, observational study conducted from June 2014 to May 2015, a total of 80 patients with hepatic encephalopathy were included. These patients ranging in age from 19 years to 75 years had attended Medicine OPD/Ward or Gastroenterology OPD/Ward in Gauhati Medical College, Assam, India and had been diagnosed as described above.

Inclusion Criteria Were: All patients of chronic liver disease with hepatic encephalopathy. Exclusion criteria - (1) Patients with chronic kidney disease, (2) Dyselectrolytemias, (3) Uncontrolled hypertension, (4) Known CNS infections, and (5) Major illnesses like diabetes mellitus and tuberculosis. Ethical clearance was obtained from the ethical committee of Gauhati Medical College and Hospital.

Assessment: Data was collected by taking proper history from patients and attendants, thorough clinical examination, and relevant investigations. Data was recorded in preformed proforma. Clinical data mainly consisted of age, sex, date of onset of illness, date of presentation to the hospital, intake of alcohol and indigenous medicines, signs and symptoms, and determination of the grades of hepatic encephalopathy. In clinical examination, in addition to pulse and blood pressure, the presence or otherwise of jaundice, oedema, splenomegaly, ascites, spider naevi was determined. A thorough examination of the nervous system especially the mental status and reflexes was carried out. Laboratory data that was gathered consisted of a complete blood count, PT, APTT, INR, LFT including bilirubin, AST, ALT, albumin, RBS, RFT, routine urine examination, HIV ELISA, Chest X-ray, EEG, ECG, CT scan (brain), and upper gastrointestinal endoscopy.

STATISTICS: Statistical analysis was performed using one way ANOVA analysis.

RESULTS: Eighty patients with chronic liver disease and hepatic encephalopathy were selected for this study. Fig 1 shows the age distribution of the patients. The maximum number of patients were found in the third decade of life.

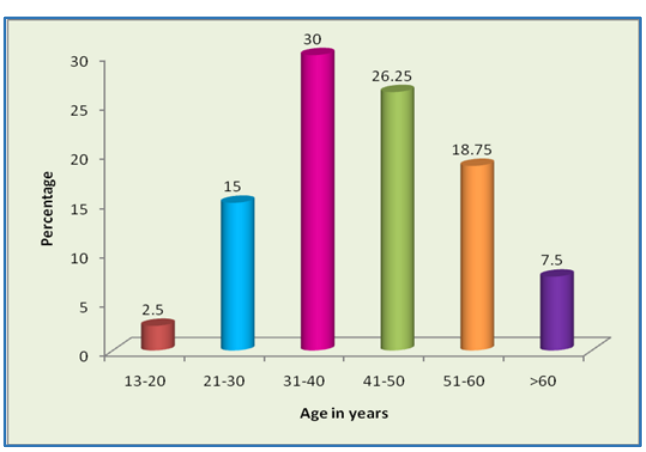

Fig. 1: Age Distribution of the Patients

Showing Sex Distribution of Patients:

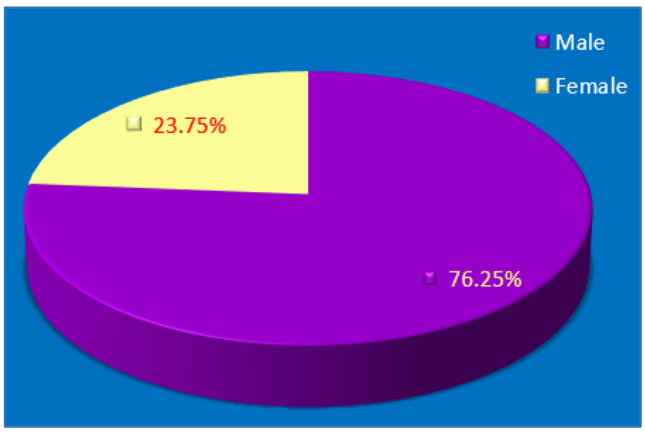

Fig. 2: Pie Diagram Most of the Patients were Male (76.25%) and the Rest were Female (23.75%)

Table 1 shows the aetiology of chronic liver disease. The major aetiology was found to be alcohol (66.25%).

Aetiology	No. of patients	Percentage (%)
Alcohol	53	66.25
Hepatitis B	11	13.75
Hepatitis C	3	3.75
NAFLD	13	16.25
Total	80	100

Table 1: Aetiology of the Cases

Symptoms	No. of patients	Percentage (%)
Abdominal distension	59	73.75
Constitutional symptoms	53	66.25
Haematemesis/Melaena	39	48.75
Sleep disorders	80	100
Neuropsychiatric manifestations	80	100
Jaundice	75	93.75
Pain abdomen	23	28.75
Leg swelling	55	68.75
Fever	36	45.0

Table 2: Symptoms Present in the Patients

The most common symptoms were neuropsychiatric manifestations like disorientation, drowsiness, mood fluctuations, lack of concentration, and sleep disorders (100%). This is shown in Table 2.

The most common signs in the present study were ascites (100%).

Signs		No. of patients	Percentage (%)
Pallor		69	86.25
Icterus		63	78.75
Oedema		58	72.5
Gynaecomastia		29	36.25
Fetor hepaticus		8	10.0
Caput medusae		1	1.25
Ascites		80	100.0
Splenomegaly		73	91.25
Hepatomegaly		39	48.75
Testicular atrophy		33	41.25
Asterixis		31	38.75
Deep tendon Reflexes	Exaggerated	46	57.5
	Diminished	34	42.5
Plantar Reflexes	Flexor	25	31.25
	Extensor	23	28.75
	Mute	32	40.0

Table 3: Signs Present in the Patients

The most common precipitating factors were found to be haematemesis/melaena (52.5%) followed by infection (42.5%) and constipation (41.25%) as shown in Table 4.

Precipitating factors	No. of patients	Percentage (%)
Haematemesis/Melaena	42	52.5
Infection	34	42.5
Constipation	33	41.25
Diarrhoea/Vomiting	21	26.25
Excessive diuresis	20	25.0
Sedatives	3	3.75
Herbal medicines	23	28.75
Large volume paracentesis	33	41.25
Hyponatraemia	32	40.0
Hypernatraemia	3	3.75
Hypokalaemia	14	17.5
Hyperkalaemia	2	2.5

Table 4: Precipitants of Hepatic Encephalopathy

Most of the patients were anaemic (97.5%) and had low platelet counts (91.25%) as shown in Table 5.

Investigations	No. of patients	Percentage (%)
Anaemia	78	97.5
Leucocytosis	34	42.5
Leucopenia	15	18.75
Thrombocytopenia	73	91.25
Raised ESR	58	72.5
Raised PT	74	92.5

Table 5: Haematological Abnormalities of Patients

Hypoalbuminaemia (100%), hyperammonaemia (100%), elevated bilirubin (83.75%), elevated transaminases (86.25%), and elevated BUN (48.75%) were the common biochemical abnormalities found (Table 6).

Investigations	No. of patients	Percentage (%)
Raised T. Bilirubin	67	83.75
Raised AST	69	86.25
Raised ALT	35	43.75
Raised ALP	38	47.75
Raised GGT	25	31.75
Hypoalbuminaemia	80	100
Hyperammonaemia	80	100
Hyponatraemia	32	40.0
Hypernatraemia	3	3.75
Hypokalaemia	14	17.5
Hyperkalaemia	2	2.5
Raised BUN	39	48.75
Raised Creatinine	15	18.75
HBsAg Positivity	11	13.75
Anti-HCV positivity	3	3.75

Table 6: Biochemical Abnormalities in the Patients

Chronic hepatic parenchymal changes were the most common USG findings (100%). This is shown in Table 7.

USG findings	No. of patients	Percentage (%)
Chronic hepatic parenchymal changes	80	100
Ascites	80	100
Splenomegaly	80	100
Hepatomegaly	38	47.5
Pleural effusion	24	30.0
Cholelithiasis	6	7.5
Renal calculi	5	6.25
Prominent portal vein	8	10.0

Table 7: USG Findings in the Patients

EEG abnormalities appeared to roughly correspond to the grades of hepatic encephalopathy with grade I showing predominantly alpha waves and grades II, III, and IV showing predominantly theta, triphasic, and delta waves (Table 8).

Grades of HE	Predominant EEG Changes
Grade 0	Alpha waves
Grade I	Alpha waves, Theta waves
Grade II	Theta waves
Grade III	Triphasic waves, Delta waves
Grade IV	Delta waves

Table 8: EEG Changes

Upper gastrointestinal endoscopy was done in 43 patients. The most common findings were oesophageal/gastric varices (88.4%) followed by gastric erosions (18.6%) as shown in table 9.

UGI Endoscopy findings	No. of Patients	Percentages (%)
Oesophageal/Gastric varices	38	88.4
Congestive gastropathy	6	13.95
Gastric erosions	8	18.60
Gastric/Duodenal ulcer	7	16.27
Normal	3	6.97

Table 9: Upper GI Endoscopy Findings

13 patients with MMSE scores of more than 24 underwent critical flicker frequency test.

38.46% patients had abnormal test results (Table 10).

CFF	No. of patients	Percentage (%)
Normal (>39 Hz)	8	61.54
Abnormal (< 39Hz)	5	38.46
Total	**13**	**100**

Table 10: Critical Flicker Frequency (CFF) Test

Most of the patients (72.5 %) were in Child-Pugh class C. The rest of the patients were divided among class A (16.25%) and class B (11.25%).

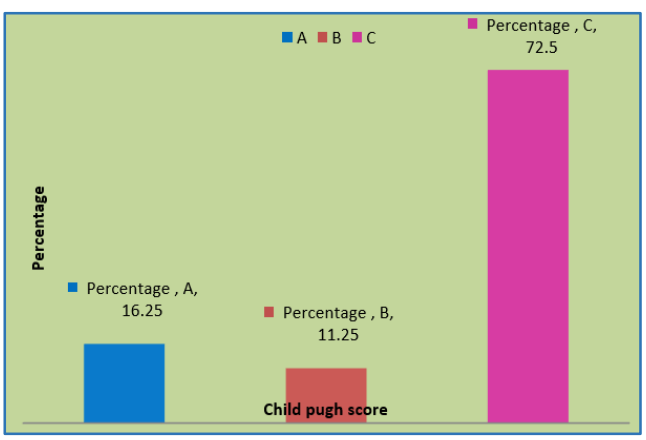

Fig. 3: Histogram Showing Child-Pugh Classification of the Patients

Most of the patients were placed in grade IV of the West-Haven classification (21.25%) followed by grade III (28.75%), grade I (30.00%), grade 0 (6.25%), and grade II (13.75%). The table 11 shows this.

Grade of HE	No. of patients	Percentage
0	5	6.25
I	24	30.0
II	11	13.75
III	23	28.75
IV	17	21.25

Table 11: Distribution of the Different Grades of Hepatic Encephalopathy (HE) Based on West Haven Classification

The arterial ammonia level in the milder grades of hepatic encephalopathy were lower compared to the higher grades. The lowest mean ammonia level was found in grade 0 and grade I hepatic encephalopathy - 39.2±7.4 mg/dL and 58.7±9.8 mg/dL (mean±standard deviation) respectively and the highest values were found in the highest grades of encephalopathy - grade III and grade IV (98.4±10.7 mg/dL and 145.0±17.0 mg/dL respectively. Grade II hepatic encephalopathy had a mean ammonia level of 71.1 mg/dL ± 8.1 mg/dL. By one way analysis of variance (ANOVA), the P value was found to be <0.0001 considered extremely significant.

Response to Treatment: In our study, the patients were put on rifaximin 1100 mg/day and lactulose 30 mL four times daily starting on the day of admission. After 14 days, the majority of patients (77.5%) showed an improvement in their condition as determined by improvements in mini-mental status examination and reduction in blood ammonia levels. Previous studies by Mas A et al in 2003[11] reported an improvement in outcomes in 81.6% patients on rifaximin 1200 mg daily and in 80.4% patients on lactitol 60 gm daily. Sharma BC et al in 2013[12] has also reported improved outcomes on treatment with rifaximin and lactulose.

DISCUSSION: In our study, most of the patients were found in the third decade of life. Similar findings were reported by Dhiman et al in 2000[1] and Weissenborn et al in 2001.[2] The majority of patients were male, the male:female ratio being 3.2:1. These findings are similar to those reported by Dhiman RK et al in 2000[1] and Das A et al in 2001.[3] The major aetiology of chronic liver disease was found to be alcohol related (66.25%) followed by NAFLD (16.25%) and others. This correlated with the findings of Amodio P et al,[13] Gomez et al,[14] Dhiman RK et al.[15] Among clinical features, the most common symptoms were neuropsychiatric manifestations like disorientation, drowsiness, mood fluctuations, lack of concentration, and sleep disorders (100%). Summerskill et al in 1956,[16] Resnik et al in 1968[17] and C.S. Landis et al in 2016[18] also reported similar findings. The most common signs in the present study were ascites (100%), splenomegaly (91.25%), pallor (86.25%), icterus (78.75%), haematemesis and melaena (48.75%), and asterixis (38.75%). C.S. Landis et al in 2016[18] reported asterixis in 45% of their patients. Resnick et al in 1968[17] have reported ascites, jaundice, hepatomegaly, splenomegaly, and asterixis to be common findings in cirrhosis of liver. Most of the episodes of encephalopathy were precipitated by haematemesis/melaena (52.5%) and infection (42.5%). Sheikh A et al in 2001[19] and Conn HO et al in 1980 have also reported similar findings.[20] Almost all the patients were anaemic (97.5%) and also had thrombocytopenia (91.25%), raised ESR (72.5%) and leucocytosis (42.5%). Stahl et al (1963) and Layrargues et al (1994) reported anaemia in all cases of cirrhosis of liver and hepatic encephalopathy.[21],[22] In the present study, hypoalbuminaemia (100%), hyperammonaemia (100%), elevated bilirubin (83.75%), elevated transaminases (86.25%), and elevated BUN (48.75%) were also common. In previous studies, Elsass et al in 1978,[23] Layrargues et al in 1994[21] found hypoalbuminaemia in all patients (100%). Layrargues et al also reported hyperbilirubinaemia in all patients (100%). Gitlin et al (1985) reported elevated values of transaminases, total bilirubin, and alkaline phosphatase.[24] Simmons et al (1970) Read et al in 1967[25] found hyperammonaemia in 100% of patients studied[26],[27] and Marchesini et al in 1996[28] Abou AS et al in 2001 found elevated ammonia in their patients. In our study, the most common endoscopic findings were oesophageal/gastric varices (88.4%). Karki et al in 2013 [29] and Dhiman et al in 2010 [30] also reported similar findings. EEG abnormalities appeared to roughly correspond to the grades of hepatic encephalopathy with grades 0 and I showing predominantly alpha waves and grades II, III, and IV showing predominantly theta, triphasic, and delta waves. Studies conducted by P. Marchetti et al in 2011 and Amodio P et al in 2001 concluded that the EEG changes corresponded to the severity of hepatic encephalopathy.[31],[4]

38.46% patients of liver cirrhosis had abnormal CFF test results. This is similar to the previous findings reported by Kircheis et al in 2002, Gomez et al in 2007, and Sharma et al in 2007.[32],[33],[34] Most of our patients had overt hepatic encephalopathy (72.5%), most being found in child's class C. 16.25% and 11.5% patients were found in child's A and B respectively. A previous study by Ong JP et al in 2003,[35] had the maximum number of patients in child's class C (69%) followed by class B (26%) and class A (4%). Most of the patients (38.75%) of liver cirrhosis were found in grade IV followed by grade III (31.25%), grade I (16.25%), and grade II (13.75%). Our findings are different from those previously reported. In studies conducted by Ong JP et al in 2003 and Mahmood MA et al in 2013, most of the patients were in lower grades of hepatic encephalopathy.[35],[36] The arterial ammonia level in the milder grades of hepatic encephalopathy was lower compared to the higher grades. The mean ammonia in grade 0 was 40.7±5.5 mg/dL (mean± SD), in grade I it was 59.2±10.4 mg/dL, in grade II it was 71.1±8.1 mg/dL, in grade III it was 98.7±11.4 mg/dL, in grade IV it was 145.4±17.9 mg/dL. On comparing the values of the milder grades of hepatic encephalopathy (0, I, II) with those of the severe grades (III, IV) it is seen that in the milder grades the mean ammonia level is 56.5±14.6 mg/dL (mean±SD) and in the severe grades it is 118.74±27.4 mg/dL (mean±SD). The two tailed p value was <0.0001 considered extremely significant. In our study, we have found that the arterial ammonia level correlated with the grades of hepatic encephalopathy. Higher grades of encephalopathy being associated with higher levels of ammonia. However, studies performed by Kundra A et al[37] in 2005 and Shawcross D.L. et al[38] in 2011 have found no correlation between the ammonia level and the severity of hepatic encephalopathy. But, similar findings have been reported by Ong JP et al in 2003,[35] F Nicolao et al in 2003,[39] L Kramer et al in 2000,[10] and M Mahmood et al in 2013.[36]

CONCLUSION: This study concludes that the arterial ammonia level corresponds to the severity of hepatic encephalopathy and neuropsychiatric manifestations in chronic liver disease and interventions directed at reducing the ammonia level leads to improvements in outcomes and prognosis. However, a larger multicentric study is required to confirm our findings.

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