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Study of blood ammonia levels in hepatic encephalopathy patients

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Abstract: *Background:* Hepatic encephalopathy is a complex neuropsychiatric syndrome occurring in patients with significant liver disease. It is characterized by personality changes intellectual impairment and a depressed level of consciousness. The ranges from subtle cerebral dysfunction to deep coma. There are few studies available on the blood ammonia levels in patients with hepatic encephalopathy and there are very few studies on blood ammonia levels among Indian patients. *Aims and Objective:* 1) To study the grades of consciousness and blood ammonia levels in hepatic encephalopathy. 2) To study the blood ammonium levels in hepatic encephalopathy patients during the disease and after recovery. 3) To study the significance of blood ammonia levels as diagnostic and prognostic tool. *Design and Methods:* A total of 100 patients comprised of 22 patients with grade 1 hepatic encephalopathy 40 patients with grade 2, 32 with grade 3 and 6 patients with grade 4 hepatic encephalopathy were studied. *Results:* The mean blood ammonia level (µmol/L) ± SD during hepatic encephalopathy was as follows. In grade-1 hepatic encephalopathy 129.56 ± 28.11; in grade-2 161.26± 42.0; in grade-3 194.8±42.1; and in grade-4 264.0±34.7. The mean ± SD of blood ammonia level after recovery was in grade-1 53.4 ± 20.9; in grade-2 46.57 ± 15.40; in grade-3 51.6 ± 9.9. Between grade-1 and grade-2 $t=2.79$ $p<0.01$, between grade-2 and grade-3 $t=2.12$, $p<0.05$, between grade-3 and grade-4 $t=3.05$ and $p<0.01$ and the co-relation between the grades of hepatic encephalopathy and mortality $r=0.98$,$t=6.9$ and $p<0.001$. *Conclusion:* Raised blood ammonia levels appears to be an important laboratory abnormality seen in patients with hepatic encephalopathy and there is a significant co-relation between severity of hepatic encephalopathy and blood ammonia levels in these patients.

Keywords: Hepatic Encephalopathy, Blood Ammonia.

Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome occurring in patients with significant liver disease. Hepatic encephalopathy is characterized by personality changes intellectual impairment and a depressed level of consciousness [1]. The spectrum ranges from subtle cerebral dysfunction to deep coma. Hepatic encephalopathy results from impaired hepatic function [2] and or disordered hepatic perfusion leading to accumulation of putative neuroactive gut derived toxins. A significant liver dysfunction encompasses 3 main types.

1. Acute liver failure syndrome.
2. Major portosystemic bypass of liver
3. Chronic liver disease/ cirrhosis.

Cirrhosis of the liver is the commonest condition leading to hepatic encephalopathy [3]. Viral hepatitis is next in frequency in causing hepatic encephalopathy. Eclampsia, acute poisoning with chemicals, drugs, metals, certain type of mushrooms, Wilson's disease, haemochromatosis, obstructive jaundice and hepatic vein occlusion are other conditions, which may lead to development of hepatic encephalopathy. The exact pathogenesis of this syndrome is not known, but a metabolic cause is suggested and studied. Ammonia one of the principle products of nitrogen metabolism is normally converted into urea in the liver by a series of enzymatic reactions. Liver disease and congenital or acquired defects in the urea cycle may cause elevations in the blood ammonia concentration. Ammonia is a highly neurotoxic and along with other factors contributes to the development of encephalopathy [4] and finally coma that is often a terminal event in

patients with severe liver disease. Under normal circumstances most of the blood ammonia is of dietary in origin. Normal digestive processes generate ammonia from ingested proteins. Bacteria in the gastrointestinal tract generate ammonia from ingested proteins by metabolizing protein, products of dietary protein digestion and urea.

Blood ammonia levels reflect the difference between the rates of addition to the circulation and the rate removal, and so indirectly reflect the tissue levels. The pH difference between blood and tissue also affect blood ammonia levels, the more acidic the blood relative to tissue the more ammonia remains in the circulation. In patients with liver disease there is a tendency for blood ammonia levels to rise [5]. The main reason for this is presumably the failure of the liver, due to portal-systemic shunting and hepatocellular dysfunction, to remove ammonia from the portal venous blood, in which the concentration is always much higher than in other parts of the circulation. The most commonly used grading system based on mental state and clinical findings was proposed by parsons and smith.

Clinical grades of hepatic encephalopathy:

Grade-1

- Mild confusion, Euphoria, Anxiety (or) depression
- Shortened attention span
- Slowing of ability to perform mental tasks (Addition/Subtraction)
- Reversal of sleep rhythm
- Asterixis can be detected.

Grade-2

- Drowsiness, Lethargy, gross deficits in ability to perform mental tasks
- Obvious personality changes
- Inappropriate behaviour
- Intermittent disorientation of time and place, Lack of sphincter control

Grade-3

- Somnolent but a rousable
- Persistent disorientation of time and place
- Pronounced confusion
- Unable to perform mental tasks
- Occasional fits of rage, Amnesia

Grade-4 Coma with

- Response to painful stimuli
- No response to painful stimuli

Minimal Hepatic encephalopathy. Lack of detectable changes in personality or behaviors. Minimal changes in memory, concentration, intellectual function and co-ordination. Asterixis is absent [6]. The present study was undertaken to assess blood ammonia levels in patients with hepatic encephalopathy. To study the relationship between blood ammonia levels and the grades of hepatic encephalopathy which helps in monitoring the clinical status of the patients.

Material and Methods

The present study includes 100 cases of diagnosed, investigated cases of hepatic encephalopathy, admitted to medical wards during the period of NOV 2017 to APRIL 2019 in Basaveshwar Teaching & General Hospital, attached to M.R.Medical College, Gulbarga. Minimum criteria for diagnosis of hepatic encephalopathy and hence for case selection as follows:

A detailed history of all patients was taken at the time of admission from patients or relatives or colleagues. The points regarding present complaints, their onset, duration and progress were noted, particular stress was laid to detect etiology like consumption of alcohol, history suggestive of hepatitis, history of exposure to chemical or drugs which are hepatotoxic. History suggestive of cirrhosis was searched by old discharge cards and papers etc.

In the past history, any history of jaundice ascites and edema are noted. History of previous hospitalization and its details were noted. In personal history, emphasis was laid on drinking habits, other relevant, history like drug consumption, etc. was also noted. Patients in our study were graded based on mental state and clinical findings into four grades.

Sample Size: 100

Sampling Procedure: Simple random sampling

Inclusion Criteria: Patients with hepatic encephalopathy confirmed by abnormal liver function tests and raised blood ammonia levels.

Exclusion Criteria:

- Rheumatic heart disease
- Ischemic heart disease
- Diabetes
- Cerebrovascular stroke
- Meningitis

Study Design: Prospective study

Data Analysis: Data will be analyzed by using SPSS 18.0 software for qualitative data analysis chi-square test. Fisher exact will applied from quantitative data T-test will applied.

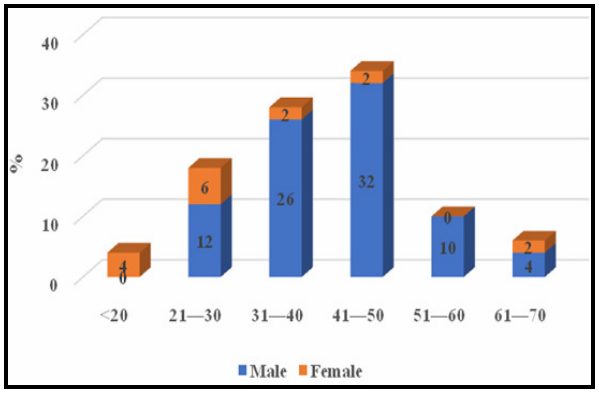
Results

Age and Sex distribution: 100 patients are evaluated in this study. The youngest patient was 16 years old and older was 70 years. Maximum numbers of patients were in the age group 41-50 years.

Table-1: Age and Sex Distribution

Age group (years)	Sex		Total	Percentage
	Male	Female		
<20	-	4	4	4.00
21 - 30	12	6	18	18.00
31- 40	26	2	28	28.00
41 - 50	32	2	34	34.00
51 - 60	10	-	10	10.00
61 - 70	4	2	6	6.00
Total	84	16	100	

Fig-1: Age and Gender

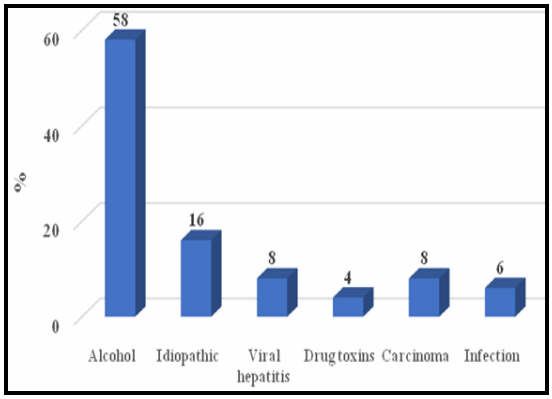


Maximum female patients were in the age group 21-30 years. Mean age of presentation for males in present study is 42.9 years. Mean age of presentation for females in present study is 33.12 years. The peak incidence of hepatic encephalopathy was in the 4th decade (34%) followed by 31(1st decade (18%), 18% in 2nd decade, 10% in fifth decade, 6% in 6th decade.

Table-2: Etiology

Etiology	No. of cases	Percentage
Alcohol	58	58.00
Idiopathic	16	16.00
Viral hepatitis	8	8.00
Drug toxins	4	4.00
Carcinoma	8	8.00
Infection	6	6.00

Fig-2: Etiology



Of the 100 patients in our study 58 (58%) were alcoholics which consisted the majority, followed by viral hepatitis 8 (8%), carcinoma in 8% of patients, drug induced hepatitis was in 4 (4%) patients and infection in 6% of patients. The cause could not be found in 16 (16%) patients and were labeled as idiopathic.

Table-3: Precipitating Factors

Precipitating factors	No. of cases	%
Infection	28	28.00
Drugs (diuretics, sedatives)	4	4.00
Electrolyte imbalance	8	8.00
Gastrointestinal bleed	12	12.00
Paracentesis	4	4.00

In our study the major precipitating factor was infection in 28 (28%) followed by gastrointestinal bleeding in 12 (12%), drugs (diuretics, sedatives) in 4 (4%), electrolyte imbalance in 8 (8%) and lastly paracentesis in 4 (4%) patients.

Fig-3: Precipitating Factors

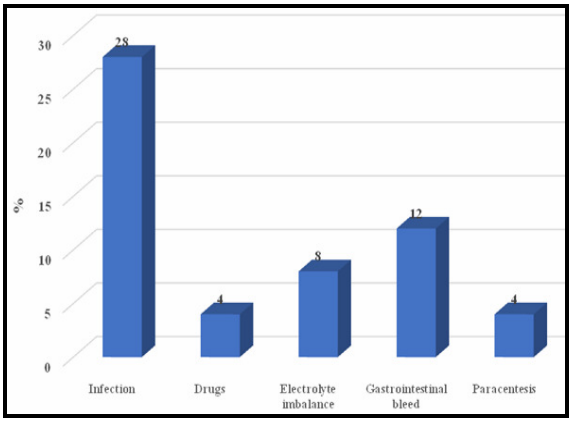
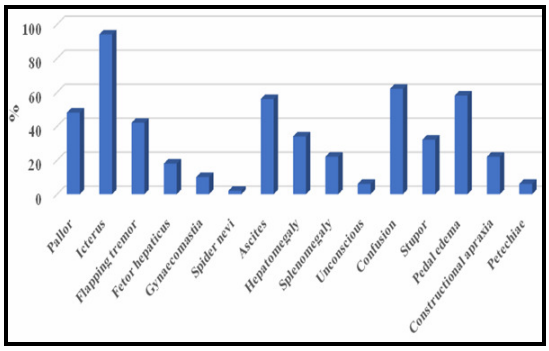


Table-4: Physical Findings at Presentation		
Signs	**No. of cases**	**Percentage**
Pallor	48	48.00
Icterus	94	94.00
Flapping tremor	42	42.00
Fetor hepaticus	18	18.00
Gynecomastia	10	10.00
Spider nevi	2	2.00
Ascites	56	56.00
Hepatomegaly	34	34.00
Splenomegaly	22	22.00
Unconscious	6	6.00
Confusion	62	62.00
Stupor	32	32.00
Pedal edema	58	58.00
Constructional apraxia	22	22.00
Petechiae	6	6.00

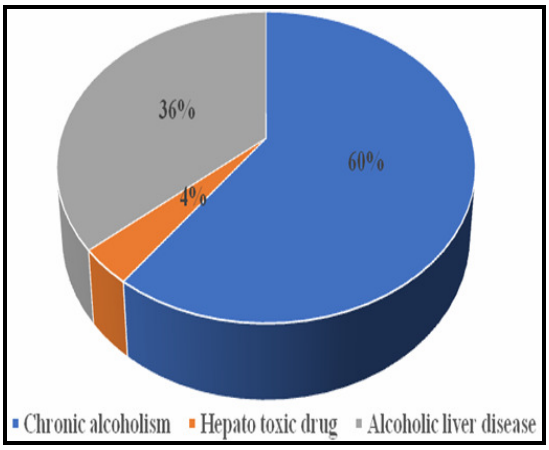
Fig-4: Physical Findings at Presentation



The physical findings at presentation and during the hospital stay of the study group are - icterus was the commonest finding seen in 94(94%) of patients followed by confusion in 62(62%), pedal edema in 58(58%) and ascites in56 (56%) patients. Patients with flapping tremor are 42(42%), hepatomegaly was present in 34 (34%) patients, patients presenting with stupor are 32 (32%), splenomegaly and constructional apraxia present in 22(22%) patients. Gynecomastia in 10 (10%) and spider nevi in one patients. Testicular atrophy was found in one patient and petechiae in 6 (6%) patients.

Table-5: Important relevant history		
	No. of cases	**%**
Chronic alcoholism	66	66.00
Hepatotoxic drug	4	4.00
Alcoholic liver disease	40	40.00

Fig-5: Important relevant history

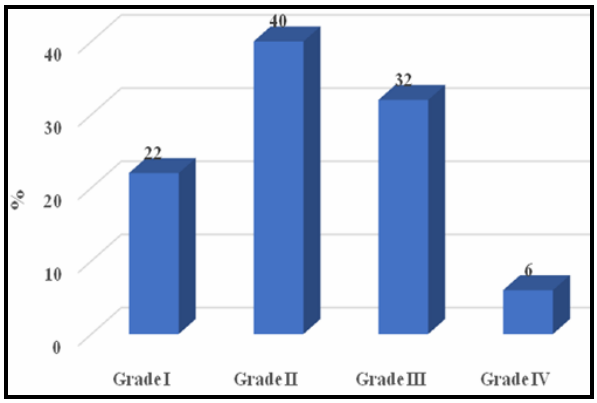


History of cirrhosis is considered on basis of old discharge cards or physicians referral chits about patient already investigated and diagnosed.

Table-6: Types of grading of hepatic Encephalopathy		
Grade	**No. of cases**	**Percentage**
Grade I	22	22.00
Grade II	40	40.00
Grade III	32	32.00
Grade IV	6	6.00

Highest patients are seen in grade-Il hepatic encephalopathy i.e., 40 and grade-Ill are 32. 22 patients are seen in grade-I hepatic encephalopathy and the lowest is seen in grade-IV i.e., 6patients.

Fig-6: Grading of hepatic encephalopathy



Discussion

Age and Sex: Maximum number of patients found in this study was in the age group of 4l-50 years. In males highest prevalence is in the age group of 4l-50 years, which may be because of addiction of alcohol leading to alcoholic liver disease. Mean age of presentation for males is 42.9 years and for females is 33.12 years in this study. The present study shows male to female ratio of 5.2:1. In the study of Sheila Sherlock et al, this ratio was 1.64:1. In a study conducted by Jonus P. Onget a1 [7], the male to female ratio was 2:1.

The difference in the male to female ratio is less in the study conducted by Janus P. Ong et al [7] in West, could be due to alcoholic habits of female population, which is comparatively more than in our country. The peak incidence of age for hepatic encephalopathy in our study group was in 4th decade. The mean age was 53.8 years in a study conducted by Janus P. Ong et al [7]. The incidence in our country is much earlier, which could be due to the low economic states and availability of cheap liquor, which is more injurious and has more harmful effects.

Etiology: In the present study, the main cause of hepatic encephalopathy was alcohol 58 (58%) patients. In comparison to the study conducted by Janus P Ong Ct a1 [7] where the most common etiology was cirrhosis of liver due .to alcohol in 86 patients. In a study by Sherlock et a1 [8], 47 out of ó6cases i.e., 71.2% of cases of hepatic encephalopathy were due to liver cirrhosis. Most of the patients in our set up whose hepatic encephalopathy is due to alcoholic cirrhosis of liver are from low socioeconomic status, poor nutrition during and after alcohol intake, repeated infections due to poor living conditions, which may play a major role. Viral hepatitis being the next common cause of hepatic encephalopathy in our study group 4 (8%). All these patients were HbsAg positive, presented with jaundice and altered sensorium. Among 4, 2 patients expired.

Carcinoma of the liver either primary (or) metastasis in the liver caused hepatic encephalopathy in 8 (8%) patients. In our study 4 (4%) patients had drug induced hepatic encephalopathy. One patient was an antitubercular therapy, patient improved after stopping the antitubercular therapy and with treatment of hepatic encephalopathy. Sheila Sherlock et al in 1995 had described isoniazid when combined with rifampicin has an hepatotoxic effect and is the second most common cause of acute fulminant hepatic failure. In our study 9 (9%) patients developed hepatic encephalopathy due to infection leading to septicemia and acute liver failure. In our study 16 (16%) patients, the cause of hepatic encephalopathy was not detectable and were labelled as idiopathic.

Precipitating Factors: In our study the main precipitating factor was infection in 28 (28%) patients. In a study conducted by Fessel JM et al [3] infection was the precipitating factor in 3% of patients. Infection, the main precipitating factor of hepatic encephalopathy in our study is disproportionately high in our study because of low socioeconomic status, poor living conditions, poor dietary habits, which leads to repeated infection and hepatic encephalopathy in cirrhotic patients. Infection precipitates coma by increasing tissue catabolism, leading to increased endogenous nitrogenous load and increased ammonia production.

The other precipitating factors such as electrolyte imbalance and gastrointestinal bleed in our study are in accord with the study done by Fessel JM et al [3]. In our study

drugs, as a precipitating factor was found in 4 (4%) patients, whereas 24% in the study done by Fessel JM et al. [3] In our study, no precipitating factor was detected in 44 (44%) of patients.

	Infection	Electrolyte imbalance	GI bleed	Drugs	Percentage
Fessel JM et al [3]	3%	11%	18%	24%	-
Present study	28%	8%	12%	4%	4%

Chronic Alcoholism: In our study, history of chronic alcoholism was present in 66 (66%) patients. Rama Lingaswami et al [9] from India considered alcohol as significant factor in causation of cirrhosis linked with HLA-BW-8, it enhances rate of development of liver damage in those who drink potentially hepatotoxic amount of alcohol.

Grades of Hepatic Encephalopathy: In our study, 22 patients (22%) at the time of admission were in grade I, 40 (40%) in grade-lI, 32 (32%) in grade-Ill and 6 (6%) were in grade-IV hepatic encephalopathy. Out of the 22 patients admitted with grade-I hepatic encephalopathy, 20 patients recovered and 2 patients expired. Out of the 40 patients admitted with grade-II hepatic encephalopathy, 10 (25%) patients expired. Out of 32 patients admitted with grade-III hepatic encephalopathy, 10 patients improved, 22(68.8%) patients expired. Out of 6 patients admitted with grade-IV hepatic encephalopathy, all the patients expired. Mortality is 100% in grade-IV hepatic encephalopathy. In our study, the total number of patients who have recovered were 60 (60%) and 40 (40%) patients expired.

Ammonia: In our study; venous blood ammonia levels are elevated in all the patients during hepatic encephalopathy. Venous blood ammonia levels were calculated during the hepatic encephalopathy and after the recovery. In patients with grade-I consciousness, the mean venous blood ammonia level was 129.56 ± 28.11 [µmol/ liter. Out of 22 patients admitted, 2 patient expired. 20 patients recovered. After recovery the mean venous blood ammonia level was 53.4±20.9 µmol/ liter. After recovery, out of 20 patients 10patients blood ammonia levels were mildly high and the remaining 10 patients ammonia levels reverted to normal. In patients with grade-Il consciousness, the mean venous blood ammonia level was 161.26±42.0 µmol/ liter.

Out of the 40 patients, 10 patients expired. 30 patients improved, the mean blood ammonia level after recovery was 46.57± 15.40 µmol/ liter. Out of 30 patients that are recovered, in 14 patients, the blood ammonia levels were mildly high and in the remaining 16 patients, the ammonia levels reverted back to normal. In patients with grade-Ill, the mean venous blood ammonia level was 194.8±42.1 µµmol/ liter. Out of 32 patients 22(68.8%) patients expired. 10 patients improved. The mean venous blood ammonia level after recovery was 51.6±9.9 µmol/liter. Out of 10 patients that recovered, in 4 patients the blood ammonia levels were mildly high and in the remaining 6 patients, the ammonia levels reverted back to normal. In patients with grade-IV, the mean venous blood ammonia level was 264±34.7 µmol/ liter. All the 6 patients who were admitted with grade-l are expired.

In a study conducted by Zenorolie ML et al [10], all the patients with hepatic encephalopathy showed elevated blood ammonia levels. In this study, venous blood ammonia levels reverted back to normal in 66.6% of patients and mild elevation present in 33.4% of patients even after recovery. In our study, venous blood ammonia levels reverted back to normal after recovery in 53.4% of patients and mild elevation present in 46.6% of patients. In study conducted by Janus P Ong et al [7] in 2000 in liver cell failure patients, there was significant elevation of blood ammonia levels in all the patients, concluding a definite correlation between blood ammonia and severity of hepatic encephalopathy.

Ong JP et al in 2000 [7] in their study in 121 patients concluded that venous total ammonia levels correlates with the severity of hepatic encephalopathy. In our study, the venous ammonia levels correlated with the severity of hepatic encephalopathy. In the study conducted by Kundra A et al [11] in 40 patients, concluded that raised blood ammonia

is an important laboratory abnormality seen in patients with acute liver failure and there is a significant correlation between the severity of encephalopathy and blood ammonia levels. Elevated venous blood ammonia levels in patients with hepatic encephalopathy is an important diagnostic tool. Ammonia level is used in the diagnosis of hepatic encephalopathy in cirrhotic patients with altered mental status and it is recommended to obtain venous blood ammonia levels when hepatic encephalopathy is suspected, both for diagnosis and as a guide to treatment.

Conclusion

1. Alcoholic liver disease was the most important causative factor for hepatic encephalopathy.
2. Mortality rate in patients with hepatic encephalopathy was 40%.
3. Blood ammonia levels are correlating with severity and grades of hepatic encephalopathy and hence it is a most useful diagnostic and prognostic tool in patients with hepatic encephalopathy.
4. These findings support the hypothesis of ammonia as a major neurotoxin precipitating encephalopathy in liver cell failure patients whether the cause being cirrhosis or fulminant hepatic failure.

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