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CLINICAL SPECTRUM OF HEPATIC ENCEPHALOPATHY IN PATIENTS OF ALCOHOLIC LIVER CIRRHOSIS

General Medicine

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ABSTRACT

Hepatic encephalopathy is the term used to describe the complex and variable changes in neuropsychiatric status which complicate liver disease.It is a complex, potentially reversible neuropsychiatric condition that occurs as a consequence of acute or chronic liver disease. Hepatic encephalopathy is a well recognized clinical complication of cirrhosis of liver and the presence and prompt identification of well defined precipitating factors is extremely important in diagnosis and treatment of this fatal condition. An acute episode of Hepatic encephalopathy typically manifests as a combination of impaired mental status and neuromuscular dysfunction occurring over a period of hours to days. Altered consciousness includes a variety of symptoms ranging from changes in personality and sleep disturbance to disorientation, stupor and coma.Nearly one third to one half of hospitalizations for cirrhosis are related to hepatic encephalopathy. The frequency of hospitalization for hepatic encephalopathy has nearly doubled over the last decade.

KEYWORDS

Hepatic encephalopathy, alcoholic liver cirrhosis, West Haven grading,Serum Ammonia

INTRODUCTION

The classic papers of Adams and Foley in 1949 and 1953 herald our present perception of the syndrome of Hepatic encephalopathy in chronic liver disease**(1,2)**. Walsh should be credited with the first clear distinction of the different neurological changes in acute versus chronic liver failure**(3).** Frerichs, the father of modern hepatology, described the terminal mental changes in patients with liver disease.**(4,5)**

From the pathophysiologic perspective, data from recent studies indicate that ammonia remains the central player in the pathogenesis of Hepatic encephalopathy. However, systemic and neuroinflammation, as well as oxidative stress and cellular senescence, are known to be implicated. In addition, blood-brain barrier (BBB) permeability/ function, cerebrospinal fluid composition, lymphatic flow, cerebral energy metabolism, neurotransmission and cell-cell communication are all deranged, causing neurological impairment and providing potential therapeutic targets.

Cirrhosis is defined as a diffuse disruption of the normal architecture of the liver with fibrosis and nodule formation. It is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening. Cirrhosis of liver due to alcoholism as the prime cause is very common in our day to day clinical practice. Bright's 1836 prescription of '2 grains of calomel every 2 hours and the ammonia julep every 4 hours' for delirium in patients with acute yellow atrophy, treatment of hepatic encephalopathy has evolved greatly**(6).**Crofton in 1908 recommended 'meat and egg protein should also be reduced because they furnish the bulk of the most toxic intestinal products' **(7).** He even advocated saline laxatives and enemas. High carbohydrate diets with supplemental intravenous glucose were advocated by Jones in the 1930s. Sherlock popularized the treatment, suggesting its efficacy arose from suppression of enteric floral production of ammonia. Lactulose was introduced by Bircher in 1966 and soon became the mainstay of therapy .In the management of patients of Hepatic encephalopathy with alcoholic liver cirrhosis it is important to stage the encephalopathy and then try to identify and treat the precipitating factors. In the presence of the precipitating factors the neurological deficits are usually reversible upon their correction and the prognosis is better if the precipitant can be identified & treated. Numerous studies have demonstrated that neuroinflammation and neuronal cell death are features of Hepatic Encephalopathy and episodes of overt Hepatic Encephalopathy can lead to irreversibility. These manifest as persisting neurological complications post-Liver Transplant. This fundamentally changes our understanding of Hepatic Encephalopathy as a reversible syndrome. More importantly, it has been demonstrated that Hepatic Encephalopathy is associated with high rates of mortality, irrespective of the severity of liver disease, indicating that Hepatic Encephalopathy is not merely a symptom of liver failure, but that it may have independent pathophysiological and prognostic implications This study aims at studying the clinical spectrum of hepatic encephalopathy in patients of alcoholic liver cirrhosis, including the study of precipitating factors of hepatic encephalopathy, staging of hepatic encephalopathy and mortality associated with it.

AIMS & OBJECTIVES -

The aims & Objectives of this study were,

1) To study the clinical features of Hepatic encephalopathy in patients of alcoholic liver cirrhosis.
2) To study the precipitating factors of Hepatic encephalopathy in patients of alcoholic liver cirrhosis.
3) To study the complications and outcome of Hepatic encephalopathy in patients of alcoholic liver cirrhosis.

MATERIALS & METHODS-

Study Design:
An Observational Study

Source Of Data:
Patients admitted in Dr. VMGMC Solapur ,in the Department of Medicine.

Sample Size :
The sample size is - 100

Selection Of Cases:
Inclusion Criteria

1) Patients with age equal to or more than 18 years.
2) Patients presenting with clinical signs and symptoms of Hepatic Encephalopathy.

Exclusion Criteria

1) Patients with an age less than 18 years.
2) Patients presenting with Hepatic Encephalopathy with causes other than alcoholic liver cirrhosis.

OBSERVATION & RESULTS-

(Table No. 1) Distribution Of Patients According To Age.

SR. NO.	AGE GROUP	NO. OF PATIENTS	%
1	18-20	0	0
2	21-30	14	14
3	31-40	20	20
4	41-50	35	35
5	51-60	25	25

6	61 & above	6	6
	TOTAL	100	100

(Table No. 2) Distribution Of Patients According To Sex

SR. NO.	SEX	NO. OF PATIENTS	%
1	MALE	95	95
2	FEMALE	5	5
	TOTAL	100	100

(Table No. 3) Distribution Of Patients According To Child Pugh Score.

SR NO.	CPS-CLASS	NO. OF PATIENTS	%
1	A	25	25
2	B	22	22
3	C	53	53
	TOTAL	100	100

(Table No. 4) Distribution Of Patients According To West Haven Classification.

WHC GRADE	NO. OF PATIENTS	%
1	12	12
2	27	27
3	28	28
4	33	33
TOTAL	100	100

(Table No. 5) Presenting Symptoms

SR NO.	SYMPTOMS	NO. OF PATIENTS
1	FEVER	20
2	VOMITING	18
3	DIARRHEA	10
4	CONSTIPATION	55
5	HEMATEMESIS	31
6	MALENA	34
7	SLEEP DISTURBANCES	65
8	DISORIENTATION	35
9	CONFUSION	52
10	COMA	33
11	ABDOMINAL PAIN	45

(Table No. 6) Precipitating Factors Of Hepatic Encephalopathy

SR NO.	PRECIPITATING FACTORS	NO. OF PATIENTS
1	INFECTIONS	17
2	HEMATEMESIS	11
3	MALENA	34
4	CONSTIPATION	55
5	NA+ <135	25
6	K+ <3.5	8
7	SEDATIVES	8
8	DIURETICS OVERUSE	6
9	EXCESS PROTEIN	11

(Table N0. 7) Number Of Precipitating Factors

NO. OF PRECIPITATING FACTORS	NO. OF PATIENTS	%
1	31	31
2	47	47
3 OR MORE	22	22

(Table No. 8) Anemia (grades Of Anemia)

GRADES	NO. OF PATIENTS
NORMAL HB	15
MILD ANEMIA	13
MODERATE ANEMIA	42
SEVERE ANEMIA	30
TOTAL	100

(Table No. 9) Peripheral Smear Examination

SR NO.	PERIPHERAL SMEAR	NO. OF PATIENTS	%
1	NORMOCYTIC NORMOCHROMIC	35	35
2	MICROCYTIC HYPOCHROMIC	32	32
3	MACROCYTIC	24	24
4	DIMORPHIC	9	9

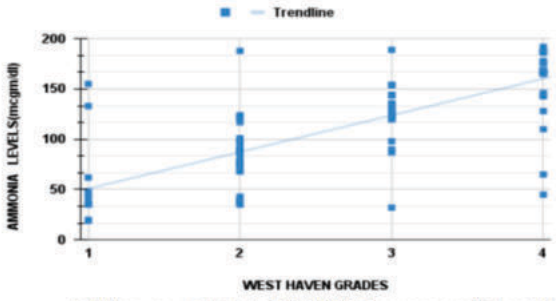
(Table No. 10) Prothrombin Time & Inr

INR	NO. OF PATIENTS
<1.2	11
1.3 TO 1.5	13
1.6 TO 2	23
2.1 TO 2.5	27
>2.5	26

(Table No. 11) Serum Ammonia Levels In Comparison With Severity Of Hepatic Encephalopathy.

SR NO.	SERUM AMMONIA	WHC G-1	WHC G-2	WHC G-3	WHC G-4
1	0-50	9	6	1	1
2	51-100	1	19	4	1
3	101-150	1	1	19	6
4	151-200	1	1	4	25
	TOTAL	12	27	28	33

(WHC- WEST HAVEN CLASSIFICATION)
(G- GRADES)



(Chi square statistic is 119.7231, Pearson coefficient-0.75, p value is <0.00001.The result is significant at p<0.05).

(Table No. 12) Grades Of Ascites

GRADES OF ASCITES	NO. OF PATIENTS
GRADE 1	26
GRADE 2	17
GRADE3	57
TOTAL	100

(Table No. 13) Spontaneous Bacterial Peritonitis(sbp)

SR NO.	TYPE OF SBP	NO. OF PATIENTS	%
1	CLASSIC SPONTANEOUS BACTERIAL PERITONITIS	4	23
2	CULTURE NEGATIVE NEUTROCYTIC ASCITES	10	59
3	MONO BACTERIAL BACTERASCITES	3	18
	TOTAL	17	100

(Table No. 14) Prognosis And Outcome

PROGNOSIS	PATIENTS
DISCHARGE	80
DEATH	20

(Table No. 15) Child Pugh Score(cps) & Mortality

CPS	NO. OF PATIENTS	DEATHS	% DEATHS
A	25	0	0
B	22	4	20
C	53	16	80
	TOTAL	20	

(Table No.-15) Mortality According To Precipitating Factors

SR NO.	PRECIPITATING FACTORS	NO. OF PATIENTS	DEATHS	% DEATHS
1	INFECTIONS	17	7	41
2	HEMATEMESIS	31	8	26
3	MALENA	34	8	24
4	CONSTIPATION	55	10	18

5	NA + <135	25	2	8
6	K + <3.5	8	2	25
7	DIURETIC OVERUSE	6	0	0
8	SEDATIVE	7	2	29
9	EXCESSIVE PROTEIN INTAKE	11	2	18

(Table No. 17) West Haven Criteria & Mortality

WHC GRADE	NO. OF PATIENTS	DEATHS	% DEATHS
1	12	0	0
2	27	0	0
3	28	6	30
4	33	14	70
TOTAL	100	20	

DISCUSSION-

In this study the majority of the patients were males, constituting about 95% of cases compared to 5% females. Majority of patients were in the age bracket of 41- 50 years (35 patients), followed by the age bracket of 51- 60 years(25 patients). Similar findings were seen in **Saira Afzal et al. , Alam et al.(8,9).** .Males are easily accessible to alcohol,hence affecting more men than females. The male preponderance is explained by the patterns of alcohol consumption in males. Similar male dominance was also reported by **Iqbal J et al and Kumar SKK et al.(10,11).**

In the present study 100 patients of alcoholic liver cirrhosis presenting with hepatic encephalopathy were studied for their precipitating factors. Constipation & Gastrointestinal bleeding(hematemesis & malena) were the most common precipitating factors in this study. Electrolyte imbalance (Hyponatremia, hypokalemia) & infections were the other common precipitating factors .

Mortality when studied according to the precipitating factors, infections accounted for the highest mortality(41%) followed by gastrointestinal bleeding (hematemesis, malena) and electrolyte imbalances(hyponatremia, hypokalemia). Constipation, being the most common precipitating factor in the study, had a mortality percentage of 18 %.Patients with electrolyte imbalance had a history of diarrhea or vomiting or were already on diuretic therapy amongst the presenting symptoms, Most of the patients in this study had neuropsychiatric manifestations as their primary presenting symptoms ranging from altered sleep pattern(most common in this study),disorientation, confusion to coma. Constipation was the second most common presenting symptom of patients in this study, followed by abdominal pain & Gastrointestinal bleeding manifestations (Hematemesis & Malena).

Anemia may be seen in 66%-75% of patients with liver cirrhosis **(12,13)**. Iron deficiency, which is the commonest type of anemia, has been observed in 22% of patients with compensated cirrhosis and 78% in those with decompensated disease.In this study 85% percent of the patients had anemia ,while the remaining 15% of patients had normal hemoglobin levels. Anemia was seen in 85% of cases by **Jadumani Nayak et al**,which is similar to our study.**(14)**.

The INR measures the function of a limited number of clotting factors (fibrinogen, II, VII, IX, X). The INR does reflect hepatic synthetic failure – so it is a useful prognostic factor regarding the severity of the liver disease.The Asian Pacific Association for the Study of the Liver(APASL) considers that an INR ≥ 1.5 and a total bilirubin (TB) ≥ 5 mg/dL in patients with cirrhosis and noncirrhotic chronic liver disease were important indicators for the diagnosis of ACLF.)In this study,11 patients had a normal INR of less than 1.2, while the remaining 89 patients had deranged INR values. 13 patients had an INR between 1.3 to 1.5 , 23 patients had an INR In the range of 1.6 to 2.0, 27 patients had INR value In the range of 2.1 to 2.5.Remaining 26 patients had an INR Value greater than 2.5.

In this study it was observed that the serum ammonia levels had a high level of correlation with the severity of hepatic encephalopathy. Chi square statistic is 119.7231, Pearson coefficient is 0.75 suggestive of high correlation with a p value of < 0.00001 , thus making the study & correlation statistically significant. A study done by **Ong JP, Aggarwal A et al** also tried to find the correlation between serum ammonia levels and severity of hepatic encephalopathy. The 121 patients who were enrolled in **Ong JP, Aggarwal A et al** study had the following West Haven Criteria grades: 30 patients (25 percent) had grade zero encephalopathy; 27 patients (22 percent) had grade 1; 23 patients (19 percent) had grade 2; 28 patients (23 percent) had grade 3; and 13 patients (11 percent) had grade 4. All four measurements.of ammonia increased with the severity of hepatic encephalopathy. The arterial total ammonia level had the highest correlation, but it was not statistically significant. Other variables that had a correlation to the severity of hepatic encephalopathy included International Normalized Ratio (INR) values, serum creatinine levels, bilirubin levels, and lactulose use. A multivariable ordered logistic regression analysis revealed that only serum ammonia levels and INR values were independently associated with the severity of hepatic encephalopathy**. (15).** A study done by **Clemmenson JO et al** on 22 patients of liver failure retrospectively and 22 patients prospectively concluded that vast amounts of ammonia escape hepatic metabolism in liver failure leading to high ammonia concentrations in blood, which in turn is associated with increased cerebral ammonia uptake and cerebral herniation. **(16)** A study done by **Tarantino G et al** on 153 consecutive patients of liver failure concluded that identifying patients with high blood ammonia concentrations could be clinically useful, as high levels would lead to suspicion of being in presence of portosystemic collaterals and its complications.**(17)** In a similar study by **Brar R, Gupta PK, Virmani SK, Sarkar G,** it was found that there is a strong correlation between serum ammonia level and severity of liver disease. Higher serum ammonia was found in severe liver disease.It was found that High grade i.e. grade III and IV patients were having significantly raised ammonia levels. So, serum ammonia can be used to assess severity of hepatic encephalopathy and can also be an important predictor of clinical outcome in severe liver disease patients.**(18)**

In this study 17 out of 100 patients had SBP. This was consistent with a study conducted by Caly et al (144) that revealed a prevalence of 10 to 30% of SBP in cirrhotic patients with ascites admitted to hospitals.In a study conducted by Fieguereda et al(147), SBP was prevalent in 20% of cirrhotic patients with ascites. A similar study by Ajitpal et al (145) out of 100 patients of alcoholic cirrhosis , SBP was diagnosed in 24 patients.Out of 17 patients of SBP, 4 patients (23%) were of classic SBP type, 10 patients (59%) were of Culture negative neutrocytic ascites (CNNA) type and 3 patients (18%) were of mono bacterial bacterascites. This was earlier proven in a study conducted by **Runyon et al(19)** that the incidence of Culture negative neutrocytic ascites (CNNA) variant of SBP ranges from 7 to 44% of total SBP patients. In a study conducted by Figueiredo et al (147) classic SBP, Culture negative neutrocytic ascites (CNNA) and mono bacterial bacterascites (MNB) were present in 24 %, 66 % and 10% of alcoholic cirrhotic patients respectively.

According to Child Pugh classification of patients in this study 53% were in class C, 22% in class B and 25% in class A.Mortality was seen higher in patients of Class C (80%) followed by Class B (20%). No mortality was seen in patients of Class A. In accordance with our study higher mortality was seen in Group C by **Fakhar Ali Qazi Arisar et al.(20)** Majority of the patients in this study had higher grades of encephalopathy with 33% of patients in grade 4, 28% in grade 3, 27% in grade 2, while 12% had grade 1 HE.Mortality was higher in patients of grade 4 HE (70%) followed by in patients of grade 3 HE (30%)No mortality was seen in patients of grade 1 & grade 2 HE in this study.Similar findings were seen in **Alam et al. and Bikha Ram Devrajani et al.(21,22)**. The mortality rate of HE is high as shown by the study of **Sargent and Fullwood(23)**, while in this study the mortality rate was 20%.Patients who did expire were mostly in class C of Child Pugh classification and grade III and IV of Hepatic Encephalopathy.

CONCLUSION-

From this study it was concluded that Hepatic encephalopathy in patients of alcoholic liver cirrhosis is usually precipitated by underlying factors like Upper GI bleed, Infections, Diuretics, Electrolyte imbalance and Constipation. There is a definite need for health education in people regarding ill effects of alcohol abuse and diseases caused by it.Abstinence of alcohol is important.There is a definite need for health education in patients who are diagnosed with cirrhosis of liver regarding the risk of hepatic encephalopathy and its precipitating factors. The early detection and treatment of precipitating factors of hepatic encephalopathy helps in reducing the mortality of this fatal condition. It can be concluded that serum ammonia levels correlate with severity of hepatic encephalopathy and can also be an important predictor of clinical outcome in severe liver disease patients.

Prompt control of infections, routine upper GI endoscopy , prevention of constipation & correction of electrolyte imbalances is very important in patients of hepatic encephalopathy.

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