

# FREQUENCY OF PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY AMONG PATIENTS WITH LIVER CIRRHOSIS IN GASTROENTEROLOGY DEPARTMENT OF NISHTAR HOSPITAL MULTAN

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## ABSTRACT

**Objective;** To determine Frequency of Precipitating Factors of Hepatic Encephalopathy Among Patients with Liver Cirrhosis.

**Patients and Methods:** The study is hospital based, cross sectional and prospective study, conducted in Nishtar Hospital Multan from March 2021 to March 2022. It includes already labelled of two hundred and ten (n=210) liver cirrhotic adults. Hepatic encephalopathy was clinically diagnosed on the basis of history from patients' attendants, physical examination and relevant laboratory and radiological investigations. Other Biochemical and hematological tests like Complete blood count, Serum urea, creatinine, Prothrombin Time, INR, Liver function tests, Serum Albumin, Serum protein, with A:G ratio hepatitis B and C serology by ELISA technique was requested. Data was analyzed using SPSS version 23 for descriptive analysis of the study variables. **Results;** During the study period a total of 210 patients with underlying HE was included. Mean age was 48 years, 128 were males and 82 were female. Regarding etiology of liver cirrhosis, 150 of cases had Hepatitis C, 10 had hepatitis B, 3 cases had Autoimmune Hepatitis, 4 had Wilsons diseases 4 cases had Alcoholic liver disease and Non-Alcoholic liver disease and cryptogenic cirrhosis counts for 39 cases.

**Conclusion;** The results of this study conclude that constipation was the most common precipitating factor of hepatic encephalopathy followed by infection, serum electrolyte derangement and upper gastrointestinal bleeding in our population subset which are potentially preventable and reversible in majority of cases. There is a definite need for health education and proper counseling in patients who were diagnosed as liver cirrhosis in relation to hepatic encephalopathy. Finally hoping this will be the Beginning for further general health education aiming to improve the community awareness about precipitating factors of hepatic Encephalopathy

## INTRODUCTION

More than 30,000 deaths results annually in United States due to liver cirrhosis <sup>(1)</sup>, and worldwide endstage liver disease accounts for one in forty deaths<sup>(2)</sup>. Patient who are having liver cirrhosis and portal hypertension will develops complication sooner or later in their life and Hepatic encephalopathy (HE) is one of the leading complication in such patients. 35-50% of patients with liver cirrhosis have Over hepatic encephalopathy as indicated in the Studies <sup>(4,5)</sup>. Hepatic encephalopathy is serious complication of liver cirrhosis with high morbidity and 30% of mortality rate<sup>(6 & 7)</sup>.

Patient with Hepatic encephalopathy have neuropsychiatric symptoms in the background of liver disease with no neurological deficit. Mortality rate is 30% in Hepatic encephalopathy. As the ratio of hepatitis B and C patients is rising in Pakistan, so the pool of liver cirrhotic patients in Pakistan is also in rising trend. Liver has the role to detoxify and neutralize toxic chemical that are absorbed from the gastrointestinal tract and other by-products of normal metabolism. The toxic substances are detoxified efficiently by the hepatocytes after they reaches there through portal circulation. Portosystemic shunts formed as the liver fibrosis advances and hepatic resistance increased, thus forcing the blood to bypass the liver. This result in the entry of various toxins in to the systemic circulation, then to the vital organs of the body including brain though the blood <sup>(8)</sup>.

Building up of nitrogenous waste product in systemic circulation due to the inability of the liver to detoxify those toxins or due to collateral circulation is the main pathogenesis of Hepatic encephalopathy. Ammonia being important waste product, is absorbed by Brain astrocytes after it crosses the Blood brain barrier, lead to swelling to astrocytes (Brain Edema), Defective hepatic clearance of

GABA inhibitory neurotransmitter, decrease level of glutamate also plays important role in pathogenesis of Hepatic encephalopathy <sup>(9)</sup>.

Usage of certain drugs like diuretics, analgesics, tranquilizers, infection, Variceal bleed and large volume paracentesis are other important precipitating risk factors for Hepatic encephalopathy.

The hepatic encephalopathy is a diagnosis of exclusion <sup>(10)</sup>. The symptoms range from subtle personality changes to deep coma <sup>(11)</sup>. The present paper focus to determine the precipitating factors of hepatic encephalopathy (HE) in patients with liver cirrhosis.

| Child-Turcotte-Pugh Classification for Severity of Cirrhosis                          |         |                                           |                                 |
|---------------------------------------------------------------------------------------|---------|-------------------------------------------|---------------------------------|
|                                                                                       | Points* |                                           |                                 |
|                                                                                       | 1       | 2                                         | 3                               |
| Encephalopathy                                                                        | None    | Grade 1-2<br>(or precipitant induced)     | Grade 3-4<br>(or chronic)       |
| Ascites                                                                               | None    | Mild to moderate<br>(diuretic responsive) | Severe<br>(diuretic refractory) |
| Bilirubin (mg/dL)                                                                     | < 2     | 2-3                                       | >3                              |
| Albumin (g/dL)                                                                        | > 3.5   | 2.8-3.5                                   | <2.8                            |
| INR                                                                                   | <1.7    | 1.7-2.3                                   | >2.3                            |
| *Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) |         |                                           |                                 |
| Class A = 5 to 6 points (least severe liver disease)                                  |         |                                           |                                 |
| Class B = 7 to 9 points (moderately severe liver disease)                             |         |                                           |                                 |
| Class C = 10 to 15 points (most severe liver disease)                                 |         |                                           |                                 |

| <b>West Haven Criteria for HE      TABLE B</b> |                         |                                                            |                                                               |
|------------------------------------------------|-------------------------|------------------------------------------------------------|---------------------------------------------------------------|
| Stage                                          | Consciousness           | Intellect and behaviour                                    | Neurological findings                                         |
| 0                                              | Normal                  | Normal                                                     | Normal examination; if impaired psychomotor testing, then MHE |
| 1                                              | Mild lack of awareness  | Shortened attention span; impaired addition or subtraction | Mild asterixis or tremor                                      |
| 2                                              | lethargic               | Disoriented; inappropriate behaviour                       | Obvious asterixis; slurred speech                             |
| 3                                              | Somnolent but arousable | Gross disorientation; bizarre behaviour                    | Muscular rigidity and clonus; Hyper-reflexia                  |
| 4                                              | Coma                    | Coma                                                       | Decerebrate posturing                                         |

## PATIENTS AND METHODS

The study is hospital based, cross sectional and prospective study, conducted in Nishtar Hospital Multan from March 2021 to March 2022. It includes already labelled of two hundred and ten (n=210) liver cirrhotic adults. Hepatic encephalopathy was clinically diagnosed on the basis of history from patients' attendants, physical examination and relevant laboratory and radiological investigations. Other Biochemical and hematological tests like Complete blood count, Serum urea, creatinine, Prothrombin Time, INR, Liver function tests, Serum Albumin, Serum protein, with A:G ratio hepatitis B and C serology by ELISA technique was requested. Data was analyzed using SPSS version 23 for descriptive analysis of the study variables.

## RESULTS

During the study period a total of 210 patients with underlying HE was included. Mean age was 48 years, 128 were males and 82 were female. Regarding etiology of liver cirrhosis, 150 of cases had Hepatitis C, 10 had hepatitis B, 3 cases had Autoimmune Hepatitis, 4 had Wilsons diseases 4 cases had Alcoholic liver disease and Non-Alcoholic liver disease and cryptogenic cirrhosis counts for 39 cases (Table 1)

|                          |     |
|--------------------------|-----|
| Total number of Patients | 210 |
| Male                     | 128 |
| Female                   | 82  |

|                                    |             |               |              |
|------------------------------------|-------------|---------------|--------------|
| Age Arrange                        | 16-80yrs    |               |              |
| Mean Age                           | 48 Yrs      |               |              |
| <b>Table 1</b>                     |             |               |              |
| <b>Etiology of Disease</b>         |             |               |              |
|                                    | <b>Male</b> | <b>Female</b> | <b>Total</b> |
| <b>Hepatitis C</b>                 | 88          | 62            | 150          |
| <b>Hepatitis B</b>                 | 07          | 03            | 10           |
| <b>Autoimmune hepatitis</b>        | 03          | 00            | 03           |
| <b>Wilson's Disease</b>            | 03          | 01            | 04           |
| <b>NAFLD/Cryptogenic cirrhosis</b> | 23          | 16            | 39           |
| <b>Alcoholic Liver disease</b>     | 04          | 0             | 04           |
|                                    | 128         | 82            | 210          |

Majority of the patients had advanced liver disease according to Child Pugh score as 26 patient in score A, 85 Patients in score B and 99 of cases in score C. **(Table 2).**

| <b><u>TABLE 2</u></b> |             |               |              |
|-----------------------|-------------|---------------|--------------|
| <b>CTP Class</b>      |             |               |              |
|                       | <b>Male</b> | <b>Female</b> | <b>Total</b> |
| <b>Child class A</b>  | 19          | 07            | 26           |
| <b>Child Class B</b>  | 52          | 33            | 85           |
| <b>Child Class C</b>  | 57          | 42            | 99           |
|                       | 128         | 82            | 210          |

Majority of the patients were in stage II hepatic encephalopathy 85, while 79 stage III, 32 stage IV coma and 14 stage I. **(Table 3)**

| <b><u>TABLE 3</u></b> |             |               |              |
|-----------------------|-------------|---------------|--------------|
| <b>PSE Grades</b>     |             |               |              |
| <b>PSE</b>            | <b>Male</b> | <b>Female</b> | <b>Total</b> |
| <b>I</b>              | 10          | 04            | 14           |
| <b>II</b>             | 52          | 33            | 85           |
| <b>III</b>            | 48          | 31            | 79           |
| <b>IV</b>             | 18          | 14            | 32           |
| <b>TOTAL</b>          | 128         | 82            | 210          |

Amongst the precipitating factors, Constipation was found in 80 (38.90%), Infections in 69 (32.8%), G.I Bleed in 37 (17.6%), Paracentesis in 9 (2.8%), Diuretic overuse in 11 (5.2%), Diarrhea in 2 (0.90%), Medication use in 3 (1.42%) and electrolyte imbalance in 2 (0.90%).. **(Table 4)**

| <b><u>(TABLE 4)</u></b> |               |              |        |                 |           |              |                  |          |            |                       |
|-------------------------|---------------|--------------|--------|-----------------|-----------|--------------|------------------|----------|------------|-----------------------|
| ETIOLOGY                |               |              |        |                 |           |              |                  |          |            |                       |
|                         |               | Constipation | SBP    | Other Infection | G.I Bleed | Paracentesis | Diuretic Overuse | Diarrhea | Medication | Electrolyte Imbalance |
| Male                    | 128<br>60.95% | 45           | 30     | 12              | 24        | 5            | 7                | 0        | 3          | 2                     |
| Female                  | 82<br>39.05%  | 35           | 17     | 10              | 13        | 1            | 4                | 2        | 0          | 0                     |
| Total                   |               | 80           | 47     | 22              | 37        | 6            | 11               | 2        | 3          | 2                     |
| %age                    |               | 38.90%       | 32.80% |                 | 17.60%    | 2.80%        | 5.20%            | 0.90%    | 1.40%      | 0.90%                 |

## DISCUSSION

Patient with Hepatic encephalopathy have neuropsychiatric symptoms in the background of liver disease with no neurological deficit.<sup>(12)</sup>

Majority of such patient have a definitive precipitating factor that lead him to hepatic encephalopathy, treating that particular precipitating factor remains important part in the management.<sup>(13)</sup>

In our study, Hepatitis C virus remains the most common cause of liver cirrhosis in Pakistan and alcoholism remains the top cause in western countries with male pre-dominance<sup>(14)</sup>.

The current study showed male dominance (60.9%) The study revealed that most of the patients were between the ages of 40-70 years. Regarding factors precipitant for HE, 38.90% of patient with male dominance have Constipation as precipitating factor for Hepatic Encephalopathy. Infections was the second precipitating factor, found in

32.8%%. The type of infection were: SBP (68.1%), respiratory tract infection (20.6%), intestinal tract infection (6.7%), and Urinary tract infection (4.6%).

Infection, mainly Spontaneous Bacterial Peritonitis was found in 22.3% patients which predicts poor nutritional status of our patients. Improper dietary instructions by Patients relative and paramedics, undue water and protein restriction lead to worsening of patient's nutritional status, lowers their immunity and overall prognosis. <sup>(15)</sup> Patients with liver cirrhosis often present with upper or/and lower Gastrointestinal bleed. <sup>(18)</sup> 17.6% patients in our studies have GI bleed as precipitating factors for hepatic encephalopathy which agree with Bustamante et al., who reported a parallel result (23%) <sup>(19)</sup>. Electrolyte imbalance, mainly hyponatremia is also identified as precipitating factor in our study similar to the study by Hassanein et al. <sup>(20)</sup> In this study, 85 patients were in grade 2 HE, 70 patients in grade 3 HE, 32 in grade 4 and 14 patients in grade 1 Hepatic encephalopathy.

Hepatic encephalopathy is frequently reversible if it is precipitated by reversible precipitating factor. So our main concern should be to identify the precipitating factors and treat accordingly.

## CONCLUSION

The results of this study conclude that constipation was the most common precipitating factor of hepatic encephalopathy followed by infection, serum electrolyte derangement and upper gastrointestinal bleeding in our population subset which are potentially preventable and reversible in majority of cases. There is a definite need for health education and proper counseling in patients who were diagnosed as liver cirrhosis in relation to hepatic encephalopathy. Finally hoping this will be the Beginning for further general health education aiming to improve

the community awareness about precipitating factors of hepatic Encephalopathy

## REFERENCES

- [1] Romero-Gomez M, Boza F, Garcia-Valdecasas MS, et al. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am J Gastroenterol* 2001; 96: 2718.
- [2] Joseph F. Perz, Gregory L. Armstrong, Leigh A. Farrington, Yvan J.F. Hutin, Beth P. Bell: The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer Worldwide: journal of hepatology Volume 45, October 2006, Pages 529–538.
- [3]. Sanyal AJ, Mullen KD, Bass NM. The treatment of hepatic encephalopathy in the cirrhotic patient. *Gastroenterol Hepatol (N Y)* 2010;6(4 Suppl 8):1–12. [PMC free article] [PubMed]
- [4]. Bismuth M, Funakoshi N, Cadranel JF, Blanc P. Hepatic encephalopathy: From pathophysiology to therapeutic management. *Eur J Gastroenterol Hepatol*. 2011;23:8–22. [PubMed]
- [5]. Butterworth RF. Editorial: Rifaximin and minimal hepatic encephalopathy. *Am J Gastroenterol*. 2011;106:317–8. [PubMed]
- [6]. Mehboob F. Frequency of risk factors for hepatic encephalopathy in patients of chronic liver disease. *Ann King edward Med Coll* 2003; 9:29-30
- [7]. Alam. I, Razaullah, Haider I, Humayun M, Taqweem MA, Nisar M, Intikhab et al. Spectrum of precipitating factors for hepatic encephalopathy in liver disease. *Pak J Med Res* 2005; 44:96-100
- [8]. Blauenfeldt RA, Olesen SS, Hansen JB, Graversen C, Drewes AM. Abnormal brain processing in hepatic encephalopathy: Evidence of cerebral reorganization? *Eur J Gastroenterol Hepatol*. 2010;22:1323–30.[PubMed]

[9] Ryan JM, Shawcross DL (2011). "Hepatic encephalopathy". *Medicine* 39 (10): 617–620.

[10] Rothenberg ME, Keefe EB. Antibiotics in the management of hepatic encephalopathy: an evidence-based review. *Rev Gastroenterol Disord* 2005; 5: s26-35.

[11] Haussinger, D. And G. kircheis, 2002. Hepatic encephalopathy. *Schweiz Rundsch Med Prax.*, 91:957-63.

[12]. Ferenci P.(1995): Hepatic Encephalopathy. In: Haubrich WS, Schaffner F, Berk JE, editors. *Gastroenterolgy*. 5th edition. Philadelphia: W.B. Saunders. 1988-2003

[13]. Mumtaz K, Umair S., Syed Ahmed, et al. (2010): Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis,. *Journal of the College of Physicians and Surgeons Pakistan*. Vol. 20 (8): 514 -18.

[14] Faloon WW, Evans GL. Precipitating factors in the genesis of hepatic coma. *N Y State J Med* 1970; 70: 2891-6.

[15] Charlton M. (2006): Branched-chain amino acid enriched supplements as therapy for liver disease. *J Nutr*. 136: 295S–98S.

[16] Blei AT. and Cordoba J.(2001): Hepatic encephalopathy. *Am J Gastroenterol*; 96: 1968–76.

[17] Blei AT. (2004): Infection, inflammation and hepatic encephalopathy, synergism redefined. *J Hepatol* ; 40:327–30.

[18] Tromn A., Griga T., Greving I., et al. (2000): Hepatic encephalopathy in patients with cirrhosis and upper GI bleeding. *Hepatology*; 47:473 –79.

[19] Bustamante J., Rimola A., Ventura PJ., et al. (1999): Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol*. 30: 890-95.

[20] Hassanein TI, Tofteng F, Brown RS Jr, McGuire B, Lynch P, Mehta R, et al. Randomized controlled study of extracorporeal albumin

dialysis for hepatic encephalopathy in advanced cirrhosis. *Hepatology* 2007; 46:1853-62

[21]. Rothenberg ME, Keefe EB. Antibiotics in the management of hepatic encephalopathy: an evidence-based review. *Rev Gastroenterol Disord* 2005; 5: S26-35.

[22]. Alam I, Razaullah, Haider I, Humayun M, Taqweem A, Nisar M. Spectrum of Precipitating factors of Hepatic encephalopathy in liver cirrhosis. *Pak J Med Res* 2005; 44: 96-100.

[23]. Hourmand-Ollivier I, Piquet MA, Toudic JP, Denise P, Dao T. Actigraphy: A new diagnostic tool for hepatic encephalopathy. *World J Gastroenterol* 2006; 12: 2243-4.