Original Article

Pediatric Education and Research
Volume 5 Number 2, May - August 2017
DOI: https://dx.doi.org/10.21088/per.2321.1644.5217.15

Etiological and Laboratory Parameters in Children with Hepatic Encephalopathy: A Tertiary Care Study

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Abstract

Introduction: Hepatic encephalopathy is a common neuropsychiatric syndrome seen in patients with significant hepatic dysfunction and liver failure, in the absence of neurological disorders. Common causes of hepatic encephalopathy includes, viral hepatitis, Wilson disease, autoimmune hepatitis and idiopathic. Very few studies have been conducted in India on causes and prognostic factors of hepatic encephalopathy. *Methods:* The present observational study was done in children aged 1 to 18 years of age, of either sex admitted in pediatric ward as a case of hepatic encephalopathy. Fifty two children, who fulfilled the inclusion criteria were enrolled and subjected to detailed laboratory investigations to find out the etiology. All enrolled children were managed as per standard hospital protocol. Basic parameters, investigations and outcome were recorded in pretested proforma. Children were further divided into two groups: Group I-those who improved and discharged and Group II- children who died to find out prognostic factors in such children. *Results:* The mean age of the study population was 81.54 ± 42.4 months with a range of 1 - 18 years. Male to female ratio in study was 2.5:1.Wilson's disease was found to be the most common cause of hepatic encephalopathy (42.3%) followed by Idiopathic (26.9%), Hepatitis A (21.1%), Hepatitis B (7.6%) and autoimmune hepatitis (5.7%). Out of 52 patients, 35 improved and were discharged and 17 had died. All the patients in group II had INR more than 4 while the corresponding figure was 34 % in the group I. *Conclusion:* Wilson disease was the most common cause of hepatic encephalopathy and INR and stage of encephalopathy were major determinant of outcome. Children in hyper-acute liver failure and acute liver failure had also poor outcome.

Keywords: Hepatic Encephalopathy; Wilson Disease; Hepatitis; INR.

Introduction

Hepatic encephalopathy,a serious but often reversible neurologic abnormalities that arise when the liver cannot detoxify the portal venous blood. Hepatic encephalopathy (HE) is a common neuropsychiatric syndrome seen in patients with significant hepatic dysfunction in the absence of neurological disorders. It is seen in up to 30-45% of patients with cirrhosis and its latent or sub clinical form (minimal hepatic encephalopathy can affect up to 60% of patients with liver disease [1]. The classification of hepatic encephalopathy done on basis of grading done by Blei At et al. 2001 [2]. Brain dysfunction, an important component in the diagnosis of acute liver failure and chronic liver disease results from an effect of hepatocyte failure on the function of the brain [3].

The etiologies of hepatic encephalopathy in children are varied and include viral hepatitis, autoimmune hepatitis, metabolic diseases and inborn errors of metabolism. Although controversy about the exact pathogenic mechanism exists, certain factors like hyper-ammonia and increased blood-brain permeability to ammonia, increased brain concentration of manganese and inhibitory

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Received on 14.06.2017, **Accepted on** 28.06.2017

neurosteroids (allopregnanolone) have been documented [4]. The precipitating factors of hepatic encephalopathy are sepsis, gastrointestinal bleeding, constipation, and diuretic use in pre-existing liver disease. Identification of these precipitants and other prognostic indices would enable clinicians rationale measures in the management of this condition, which has been associated with poor outcome [5,6]. The prognosis and outcome of child presented with hepatic encephalopathy depends on stage of presentation, classification, cause of encephalopathy and baseline bilirubin.There are very few studies regarding its etiology in northern India in children.The present study was carried out with aim to find the cause and prognostic factors in children with hepatic encephalopathy.

Methods

The present study was conducted in Department of Pediatrics, Institute of Medical Sciences, B.H.U, Varanasi (U.P.). It was a prospective observational study from December 2014 to August 2016. Ethical committee of Institute approved the study protocol. Informed consent was taken from parent or legal caretaker of patient.

Inclusion Criteria

Any children aged 1month and 18years of either sex admitted in pediatric ward from pediatric emergency or OPD with jaundice, abnormal behavior, irritability, altered sleep-wake cycle and/or altered mental state (Glasgow coma score< 15) was included in the study.

Exclusion Criteria

Patients in whom persistent altered mental attributed by inflammatory brain disease, intracranial space occupying lesion, uremic encephalopathy, respiratory failure, severe malaria, sepsis will be excluded from the study.

Detailed history and clinical examination was done in all children aged <18 years of age, who presents with jaundice, abnormal behavior, irritability, altered sleep-wake cycle and/or altered mental state (Glasgow coma score< 15) and subjected for investigations. Complete blood count, liver function tests(ALT, AST, TB, DB, TP, ALB, Alkaline phosphatase), viral markers(HBsAg, HCV, HEV, HAV), serum ceruloplasmin, 24 hrs urinary copper, autoimmune profile[antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver-kidney microsome (LKM)], coagulation profile (PT, APTT) and ultrasonography of abdomen were done in all cases.

Categorization of Cases

1. Viral hepatitis: If any of the viral markers positive
2. Wilson Disease: if ceruoplasmin< 20mg/dL and or 24 hour urinary copper > 100μg/day and presence of KF ring in cornea.
3. Autoimmune hepatitis: if any of the antibody positive (ANA, SMA, or LKM)
4. Idiopathic: if all tests were negative

Cases were also categorized based on duration of illness as hyperacute liver failure(<1week), acute liver failure(1week -4week), subacute liver failure(1month-6month) and chronic liver failure(>6months). Children were also classified into different stages I to IV on the basis of Ferenci P et al classification [7].

Data Analysis

Data was analyzed using SPSS 16.0 software. The quantitative data has been presented in the form of Mean ± S.D. Statistical analysis included Student's paired t-test and Mann-Whitney U- test to test differences between continuous variables and the chi-squared test to test differences between categorical data.

Results

Fifty two children were enrolled as they satisfied the inclusion criterion and willing to participate in the study. Mean age of the studied population was 81.54 ± 42.4 months. The male constituted 37 out of 52 (71.2%) with male to female ratio was 2.5:1. Out of 52 patients, 35 improved and were discharged (Group I) and 17 died (Group II). 90.5% of children did not receive Hepatitis A & B vaccine. Only 2 children (3.8%) were immunized with both hepatitis A & B. one child (3.8%) had received only Hepatitis B vaccine. The mean hemoglobin was decreased in both the groups. Total leucocyte count was increased in majority of the patients. None had severe thrombocytopenia (platelet count below 50,000) (Table 1).

The hepatic enzyme levels were significantly higher in the group II at admission. At 96 hours, the levels showed decreasing trend in group I while the levels increased in Group II.Total bilirubin at admission was comparable. However, at 96 hours the mean

bilirubin increased to significant high level in the groupII. Though the total protein levels in both groups were comparable at admission, it decreased significantly at 96 hours in Group II. INR was comparable in both groups at admission. At 96 hour INR decreased in the group who were discharged while it increased in the other group. INR was >4 in 29 patients (55.7%) during the hospital stay. All the patients in group II had INR more than 4 while the corresponding figure was 34% in the group I (Table 2).

In hyper acute liver failure (<1week), 3 out of 7 children improved and while 4 expired. In Acute liver failure (1-4 week), 25 out of 34 children improved and 9 expired. In sub-acute liver failure (1mo-6

Tables 1: Demographic profile and base line investigation

Age in (Months)	**Group I 81.88±44.54**	**Group II 80.82±39.00**	
Gender			Ratio- 2.5: 1
Male	23	14	
Female	12	03	
Parameters (CBC)	Group I (n-35)	Group II (n-17)	Significance
Hb g/dl	9.61 ± 2.32	9.34 ± 2.10	p=0.686
TLC /µL	13953 ± 9209	13298 ± 7335	p=0.799
Platelet count (×10^9/L)	2.76 ± 2.02	2.95 ± 2.28	p=0.762

Table 2: Liver function test, INR & Severity, on basis of INR

Parameters	**Group I (n-35)**	**Group II (n-17)**	**Significance**
ALT (0hr)	358.60±213.25	599.18±601.81	p=0.039*
ALT (96hr)	201.11±101.86	851.82±687.22	p=0.000*
AST (0hr)	353.51±205.03	593.59±258.28	p=0.001*
AST (96hr)	202.26±128.43	786.94±416.69	p=0.000*
TB (0hr)	17.88±10.67	18.04±8.91	p=0.961
TB (96hr)	12.02±7.29	23.78±9.02	p=0.000*
DB (0hr)	12.06±7.30	11.68±6.32	p=0.855
DB (96hr)	11.46±20.03	15.26±6.18	p=0.450
TP (0hr)	6.29±1.24	6.00±1.10	p=0.417
TP (96hr)	7.07±1.27	5.45±1.11	p=0.000*
Albumin (0hr)	3.50±3.27	3.65±5.00	p=0.891
Albumin (96hr)	3.42±0.62	3.10±4.12	p=0.652
Alkaline P (0hr)	358.63±267.55	514.13±408.53	p=0.427
Alkaline P (96hr)	227.63±181.83	655.71±449.15	p=0.000*
INR (At admission)	3.59 ± 1.58	4.13 ± 1.69	p=0.272
INR (At 96 hours)	1.9 1± 1.02	6.42 ± 1.15	p=0.000*
Severe (INR>4)	12 (34.4%)	17 (100.0%)	χ2=20.032 p=0.000*

INR: International normalized ratio

Table 3: Diagnosis, Stage & Classification of Children with Hepatic Encephalopathy

Diagnosis	**Total N (%)**	**Group I N (%)**	**Group II N (%)**
Wilson disease	21(40.3)	18 (51.42)	3 (17.64)
Hepatitis B with Wilson's disease	1 (1.9)	1 (2.85)	0 (0)
Viral Hepatitis A	10 (19.2)	5 (14.28)	5 (29.41)
Viral Hepatitis B	2 (3.8)	2 (5.71)	0 (0)
Viral Hepatitis A and B	1 (1.9)	1 (2.85)	0 (0)
Autoimmune disease	3 (5.7)	2 (5.71)	1 (5.88)
Idiopathic	14 (26.9)	6 (17.14)	8 (47.05)
Stage			
I	23 (44.2%)	23 (65.7%)	0 (0%)
II	6 (11.5%)	5 (14.2%)	1 (5.8%)
III	8 (15.3%)	4 (11.4%)	4 (23.5%)
IV	15 (28.8%)	3 (8.5%)	12 (70.5%)
Classification			
Hyper-acute liver failure<1week	7 (13.4%)	3 (8.6%)	4 (23.5%)
Acute liver failure 1-4 week	34 (65.4%)	25 (71.4%)	9 (52.9%)
Sub-acute liver failure 1mo-6months	9 (17.3%)	5 (14.3%)	4 (23.5%)
Chronic liver failure>6months	2 (3.8%)	2 (5.7%)	0 (0.0%)
Total	52 (100%)	35(100%)	17(100%)

Table 4: Comparison of etiology in different studies with present study

Study	Arora et al., (1996) N=44 India	Poddar et al., (2002) N= 67 India	Squires et al., (2006) N=348 USA	Kaur et al., (2012) N=58 India	Pandit et al., (2015) N=54 India	Present Study N=52 India
Patient category	Acute liver failure	Fulminant hepatic failure	Acute-liver failure	Acute liver failure	Acute liver failure	Hepatic Encephalopathy
Hepatitis A	6.3%	51%	1%	58%	36.3%	21.1%
Hepatitis B	11.3%	7.5%	-	4.6%	8.8%	7.6%
Hepatitis E	40.9%	25%	-	4.6%	-	-
Wilson disease	5%	-	3%	4.6%	Metabolic Including wilson 12.5%	42%
Autoimmune	-	-	6%	2.3%	-	5.7%
Idiopathic	11.3%	-	49%	9.2%	20%	28.8%
Paracetamol poisioning	-	-	14%	-	-	-

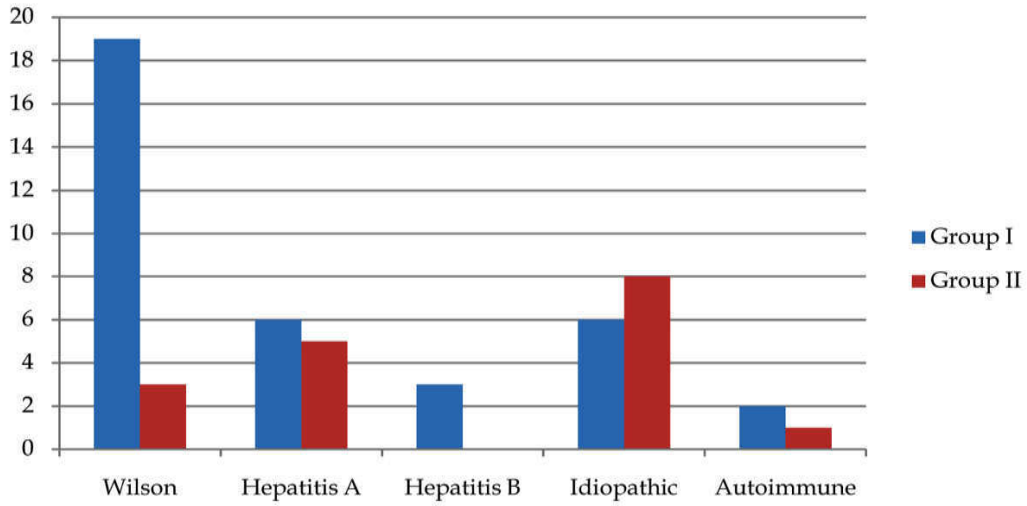

Fig. 1: Comparison of study groups in children with hepatic encephalopathy

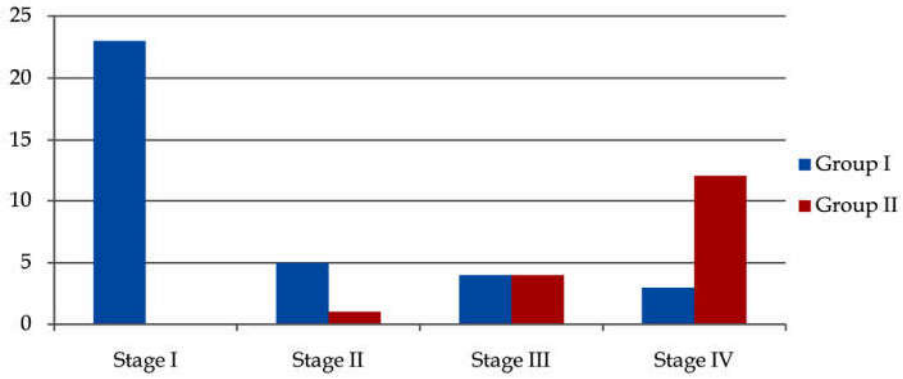

Fig. 2: Comparison of stages/grades of hepatic encephalopathy

months), 5 out of 9 children improved and 4 died. 2 children presented with chronic liver failure (>6months) and both improved (Table 3). Sleep wake cycle was altered in all the enrolled patients, suggesting diagnosis of hepatic encephalopathy.

Wilson's disease was the most common cause of hepatic encephalopathy (42.3%) followed by idiopathic (26.9%), hepatitis A (21.1%), hepatitis B (7.6%) and autoimmune hepatitis (5.7%). The causes of mortality in children with hepatic encephalopathy were Idiopathic 8 (47.05%) followed by viral hepatitis

5(29.4%), Wilson disease 17.6% and autoimmune 5.9%. The children who died presented with significantly higher states of encephalopathy as compared to who survived (Table 3).

Discussion

Fifty- two patients were enrolled in the present study, we could identify cause of hepatic encephalopathy in 73.1% cases. Male to female ratio in our study population was 2.5:1, which was similar to other study [8]. Only 9.5% (n=5) have received Hepatitis A &/or B vaccines. Low immunization coverage for Hepatitis has led to many case of viral hepatitis in the present study.

Most common cause of Hepatic encephalopathy in present study was Wilson's disease (42.3%), followed by Idiopathic (28.8%), Hepatitis A (21.1%), Hepatitis B (7.6%) and auto immune hepatitis (5.7%). Wilson disease was the most common cause of hepatic encephalopathy in present study. This is in contrast to the findings of previous workers (Table 4). This may be due to higher clinical suspicion and screening of all the patients for Wilson disease.

Most of the children in hepatic encephalopathy presented with acute liver failure (65.3%,) followed by sub-acute liver failure (17.3%), hyper acute liver failure (13.4%) and chronic liver failure (3.8%). Children presenting with stage I hepatic encephalopathy had good outcome, irrespective of etiology. Children (11.5%) presented in, has also good outcome. Out of the 6 children with stage II hepatic encephalopathy only 1 expired. Stage III and IV encephalopathy patients had poor outcome ($p<0.0001$). Similar was the observations of previous workers [910].

The children who died had progressive deterioration of liver function including INR. All patients, who died had INR more than 4. O' Grady et al., (1989) in their study of early indicators of prognosis in fulminant hepatic failure concluded that serum bilirubin greater than 300 µmol/L and prothrombin time greater than 50s had poor prognosis. Ciocca et al., (2008) in their study of prognostic factors in pediatric acute liver failure observed that Hepatitis A is the main cause of ALF in children in Argentina. Advanced encephalopathy and prolonged prothrombin time were significantly associated with death or need for Liver Transplantation. Dhawan et al., (2002) in their study of Acute liver failure observed that prognostic criteria for mortality are less well defined compared to the adult population, although a significantly elevated INR ≥4 carries a high chance of death, and liver transplantation should be considered at this stage. Srivastav et al., (1998) proposed that hypoglycemia (blood glucose< 45mg/dl) predicts mortality. In present study none of children was hypoglycemic.

Outcome of children with hepatic encephalopathy depends on duration, which child develops hepatic encephalopathy. In present study children presented as hyper-acute liver failure and acute liver failure had poor out-come than children with sub-acute and chronic liver failure. However, the difference was not statistically significant. Staging or grade of hepatic encephalopathy was a major parameter for prediction of out-come in present study. Children presenting in grade III or IV have poor outcome than children with grade I or II. In the present study, etiology could not be ascertained in14 (28.8%) cases. Previous workers also reported similar findings (Table 4). Many of the idiopathic cases could be due to some metabolic or infective cause for which screening has not been done. More than half (57.1 %) of the idiopathic group died suggesting some serious underlying cause.

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