Original Article

Cent Asian J Med Sci. 2016 May;2(1):54-60.

CENTRAL ASIAN JOURNAL of MEDICAL SCIENCES
CAJMS

Elevated Ammonia Level as a Diagnostic Marker of Hepatic Encephalopathy

Bayarmaa Ochirkhuree[1], Bira Namdag[2], Sarangerel Jambal[3], Batbaatar Gunchin[4]

[1]Gastroenterological Center, First Central Hospital, Ulaanbaatar, Mongolia; [2]Department of Internal Medicine, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [3]Neurological Clinic, Reflex Hospital, Ulaanbaatar, Mongolia; [4]School of Pharmacy and Biomedicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

Submitted: January 29, 2016
Revised: March 25, 2016
Accepted: April 5, 2016

Corresponding Author
Bayarmaa Ochirkhuree, MD
Gastroenterological Center, First Central Hospital, S. Zorig Street 2, Ulaanbaatar 210548, Mongolia
Tel: +976-9906-9964
Fax: +976-1132-3857
E-mail: baydak_o@yahoo.com

Objectives: Hepatic encephalopathy (HE) is a common and prognostic complication of cirrhosis. It may reflect either a reversible metabolic encephalopathy, brain atrophy, edema or any combination of these conditions. The mechanisms causing brain dysfunction in liver failure are still unknown. Ammonia is the best-characterized neurotoxin that precipitates HE. The purpose of this study was to ascertain the role of ammonia in HE. **Methods:** A hospital-based prospective study on HE was carried out at the First Central Hospital of Mongolia and the Chingeltei-Uul District Hospital in 2011-2013. Patients with hepatic failure were subdivided into the three following groups: (1) patients without HE, (2) patients with grade I-II HE, (3) patients with grade III-IV HE. We took liver function tests, Model for End-Stage Liver Disease (MELD) score and blood ammonia and correlated them with the severity of encephalopathy. The mean variables ±SD, p-values, and Pearson coefficients were calculated by SPSS 17.0. **Results:** The total sample size was 120 and the mean age was 36.8 ±15.4 years. Elevated ammonia level was observed in every stage of HE and increased by stage ($p < 0.0001$). MELD score and elevated ammonia level had a strong positive correlation ($r = 0.54$, $p = 0.0001$). In patients with any infection, the ammonia level was higher ($p < 0.0001$) than other groups. **Conclusion:** Ammonia is one of the diagnostic biomarkers of HE.

Keywords: Hepatic Encephalopathy, Oxidative Stress, Precipitating Factors, Hyperammonemia, Infection

Introduction

The prevalence of liver cirrhosis is 34.62 cases per 10,000 Mongolians [1]. Hepatic encephalopathy (HE) is a "brain dysfunction caused by liver insufficiency and/or portosystemic shunt, manifesting as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma" [2]. It is a common and prognostic complication of cirrhosis. However, HE is not a single clinical entity. It may reflect a reversible metabolic encephalopathy, brain atrophy, brain edema or any combination of these conditions.

The mechanisms causing brain dysfunction in liver failure are still unknown. Pathophysiology of HE is complex and probably involves the association of several different factors [3]. HE is subdivided into episodic, recurrent and persistent according to its time course [4]. Subtle signs of HE are observed in nearly 70% of patients with cirrhosis [5]. Symptoms may be debilitating

in a significant number of patients, and are observed in 24-53% of patients who undergo portosystemic shunt surgery [5]. Approximately 30% of patients dying with end-stage liver disease experience significant encephalopathy, approaching coma [6]. Mongolian researchers have found that hepatic coma at 41.3% and varices bleeding at 58.6% are the most common causes of mortality of HE [7].

Precipitating factors are critically important in the diagnosis and management of HE. They are responsible for most episodes of HE. As explained by Cordoba, "HE episodes have been traditionally related to the occurrence of a precipitating factor, which can be defined as a clinical event that does not cause direct injury to the liver or portal-systemic circulation and is responsible for the acute change in mental status. Precipitating factors appear to act by increasing the generation of putative toxins or enhancing the effects of toxins on the central nervous system. They are temporally related to the development of HE, and their correction to re-establishment of consciousness. Several factors are commonly considered under this category (gastrointestinal bleeding, constipation, excessive protein intake, dehydration, electrolyte disturbances, renal failure, and infection), and are thought to explain the majority of HE episodes." [8]. Cirrhosis complicated by gastroesophagealvariceal hemorrhage is characterized by high mortality and rebleeding rates. Gastrointestinal (GI) bleeding is associated with bacterial infection in up to 66% of patients with cirrhosis who are vulnerable to infection because of the disruption of the intestinal mucosal barrier and the frequent invasive manipulations during hemorrhage [9]. Patients with cirrhosis and ascites show a higher susceptibility to bacterial infections, mainly because of inadequate defense mechanisms. In these patients, the most frequent infectious complication was spontaneous bacterial peritonitis (SBP) followed by urinary infections (about 20%), pneumonia (about 15%) and bacteremia (12%) [10].

Ammonia is the best-characterized neurotoxin that precipitates HE. The primary source of ammonia is the GI tract and another source may be urea digested by Helicobacter pylori in the stomach, although the role of H. pylori in HE is unclear [11]. The liver converts ammonia into glutamine. However, glutamine is metabolized in mitochondria yielding glutamate and ammonia, and glutamine-derived ammonia may interfere with mitochondrial function leading to astrocyte dysfunction [12]. The arterial concentration of ammonia is increased in about 90% of patients with HE [13]. Hyperammonemia may increase the cerebral uptake of neutral amino acids [14], oxidative stress and changes in mitochondrial permeability [15], intracellular osmolarity in astrocytes [16], synthesis of nitric oxide (NO) [17] and alterations in neural membranes, such as the changes in the uptake of neurotransmitters.

It is well accepted that high ammonia levels are a dominant explanation of the pathogenesis of hepatic encephalopathy. The normal range of blood ammonia is 11-51 μmol/L in females and 16-60 μmol/L in males. In clinical practice several methods are used to detect total ammonia level and partial pressure of ammonia in the veins, arterial blood, serum or cerebrospinal fluid for the diagnosis of HE. These tests are especially important to conduct after ammonia lowering treatment to determine if the treatment is effective.

There have not been any clinical trials in Mongolia, nor do any standards or guidelines for hepatic encephalopathy exist in this country. Therefore, we purposed to study the timing of the first bout of overt (O-) HE, common precipitating factors, key biomarkers of HE and their correlations with the severity of OHE. This article is meant to provide an opportunity to identify a role of ammonia in the pathogenesis of HE and establish it as a significant biomarker for the severity of HE.

Materials and Methods

1. Study population

A total of 120 cirrhotic patients with hepatic failure and encephalopathy (45 female and 75 male), aged 20-70 were involved in the study. Patients with hepatic failure were divided into three subgroups as follows: (1) patients with clinical evidence of hepatic failure but no HE, (2) patients with grade I-II HE and (3) patients with grade III-IV HE. The West-Haven scale was used to grade HE. Patients were hospitalized at the Gastroenterological Center of the First Central Hospital and the Chingeltei-Uul District Hospital in Mongolia from January 2011 to December 2013.

2. Data collection

Patients with cirrhosis were diagnosed on the basis of clinical, laboratory and instrumental examinations. For data collection, a questionnaire was developed that included a detailed clinical history of the patient's present and past illnesses. Clinical

findings on examination including jaundice, pallor, fever, asterixis and ascites were recorded. Patients with acute fulminant failure, uremia, and other metabolic and septic encephalopathy by the clinical signs and laboratorial indices were excluded from the study. The liver function tests, clinical features, Model for End-Stage Liver Disease (MELD) score and blood ammonia level were entered into the COBAS INTEGRA quantitative system as the main predictive factors of the chronic hepatic failure and HE. All blood tests were performed in the laboratory of the First Central Hospital of Mongolia. Duration of the first episode of OHE after diagnosis of cirrhosis, precipitating factors, MELD score and blood biomarkers of infection, varices bleeding and encephalopathy were analyzed.

3. Statistical analysis

Data were initially analyzed using descriptive statistics. Groups of patients were compared using a paired t-test and one-way ANOVA. Correlation analysis was performed between ammonia level and blood biomarkers of precipitating factors and MELD score by the Pearson correlation coefficient. Findings with $p < 0.05$ were considered significant. Statistical analyses were performed using SPSS 17.0 program.

4. Ethical statement

Ethical approval was obtained from the Ethical Committee of the School of Medicine, Mongolian National University of Medical Sciences. Each patient signed a consent form before being involved in the study.

5. Hypothesis

The study hypotheses are as follows: (1) the timing of first episode of OHE occurs within five years after diagnosis of liver cirrhosis, (2) infection and varices bleeding are the most common precipitating factors of HE, (3) elevated ammonia level is one of the diagnostic biomarkers of HE.

Results

Characteristics of the study population are shown in Table 1. Of 120 cirrhotic patients with hepatic failure and encephalopathy,

Table 1. Study population characteristics

Characteristic	Total (n = 120) n (%)	HE Stage		
		0-I (n = 40) n (%)	I-II (n = 40) n (%)	III-IV (n = 40) n (%)
Area of residence				
Urban	61 (50.8)	11 (27.5)	29 (72.5)	21 (52.5)
Rural	59 (49.2)	29 (72.5)	11 (27.5)	19 (47.5)
Sex				
Male	43 (35.8)	15 (37.5)	16 (40.0)	12 (30.0)
Female	77 (64.2)	25 (62.5)	24 (60.0)	28 (70.0)
Age (years)				
20-29	9 (7.5)	4 (10.0)	2 (5.0)	3 (7.5)
30-39	19 (15.8)	6 (15.0)	10 (25.0)	3 (7.5)
40-49	33 (27.5)	6 (15.0)	14 (35.0)	13 (32.5)
50-59	37 (30.8)	14 (35.0)	9 (22.5)	14 (35.0)
60-69	17 (14.2)	7 (17.5)	5 (12.5)	5 (12.5)
≥70	5 (4.2)	3 (7.5)	0 (0.0)	2 (5.0)
Education				
University	30 (25.4)	12 (30.8)	8 (20.0)	10 (25.6)
Secondary	83 (70.3)	25 (64.1)	30 (75.0)	28 (71.8)
Primary	5 (4.2)	2 (5.1)	2 (5.0)	1 (2.6)
Not educated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body mass index				
Underweight	21 (17.5)	3 (7.5)	10 (25.0)	8 (20.0)
Normal	70 (58.3)	27 (67.5)	20 (50.0)	23 (57.5)
Overweight	21 (17.5)	10 (25.0)	8 (20.0)	3 (7.5)
Obese	8 (6.7)	0 (0.0)	2 (5.0)	6 (15.0)

77 (64.2%) were male and 43 (35.8%) were female. Males suffered from cirrhosis 1.6 times more than females. The mean age of participants was 36.8 ±15.4 years. A total of 58.3% were between the ages of 40-59 years. The majority of participants had a secondary education (70.3%), exhibited normal weight (58.3%, body mass index <25) and were found to be in class "C" by the Child-Pugh classification of cirrhosis (51.6%). By the etiology of cirrhosis we found HBsAgat at 29%, anti-HCV at 36%, co-infection (B+C) or (B+D) at 10%, alcohol at 12%, mixed (alcohol+virus) at 12%, and autoimmune at 1%.

The first bout of OHE was observed at the time of cirrhosis diagnosis for 15% of the patients and within five years after cirrhosis diagnosis for 62% of the patients (Figure 1). The most common precipitants identified were infection at 44.2% (p <0.037) and GI bleeding at 40.6% (p < 0.0024). Infectious complications were SBP for eight patients (30.7%), urinary tract infection for five patients (19.2%), pneumonia for six patients (23.0%) and other complications for seven patients (27.0%). A total of 26 patients (43.3%) had two precipitating factors such as GI bleeding + urinary tract infection, GI bleeding + electrolyte disturbances and SBP + pneumonia. Among those with GI bleeding, 40 patients (81.6%) had esophageal varices and 9 patients (18.4%) had gastric varices hemorrhage.

Elevated ammonia level was observed in every stage of HE and increased by stage (p <0.0001) as shown in Table 2. Comparison of HE stages by the blood ammonia level in the post-hoc Tukey test showed significant differences between stages 0-I and I-II (p <0.0001), I-II and III-IV (p <0.0001), 0-I and III-IV (p <0.0001) before the treatment of HE and stages 0-I and I-II (p <0.006), I-II and III-IV (p <0.0001), 0-I and III-IV (p <0.0001) after the treatment of HE. There are significant differences between the stages of HE especially in the 0-I and III-IV stages before and after the ammonia lowering treatment.

Blood ammonia level was much higher for the group with precipitating factors of HE (p <0.0001), compared to the group with no precipitants (Table 3). Also shown is that ammonia lowering treatment is more effective for the group with precipitating factors. In the patients with infection that precipitated HE, the blood ammonia level was higher (p <0.0001) than other groups (Table 4). Ammonia level has a positive, weak correlation (r = 0.37) with the infection biomarker (WBC, Table 5) and a very strong, negative correlation (r = -0.81) with the bleeding biomarker (RBC, Table 5). There was a moderate, positive correlation (r = 0.54, p = 0.0001), as shown in Figure 2, between ammonia level and MELD score which identifies the surveillance of patient with the end stage of liver disease.

Table 2. Blood ammonia level (μmol/L) in the hepatic encephalopathy stages

Timing	HE Stage						p-value
	0-I (n = 40)		I-II (n = 40)		III-IV (n = 40)		
	Mean	SD	Mean	SD	Mean	SD	
Before treatment	29.27	8.73	70.93[a]	47.63	142.90[a]	35.65	0.0001
After treatment	33.19	20.33	47.36	24.59	121.76	42.90	0.0001

[a]p <0.001 by paired sample t-test

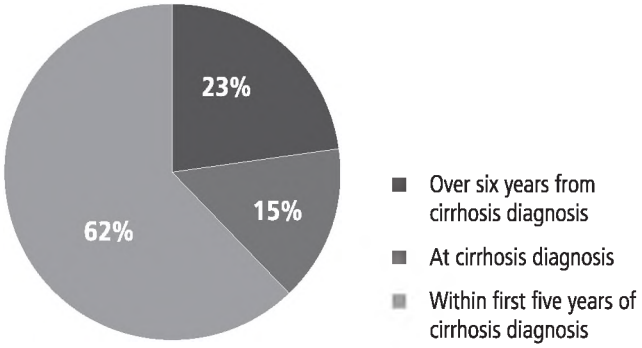

Figure 1. Timing of the first bout of HE in study patients.

Discussion

Hepatic viral infection is the most important cause (75%) of cirrhosis related to a limited availability of antiviral therapy and lack of surveillance system in Mongolia. There is an increasing concern regarding the development of a hepatitis C virus becoming an epidemic. Maqsood et al. also reported the same pattern in a study in Pakistan [18]. The majority of patients in our study were from rural areas which unfortunately meant that they reached tertiary hospital care late. The prevalence of OHE at the time of cirrhosis diagnosis has been shown to be 10-14%

Table 3. Test results by presence or absence of precipitating factors

Variable	No precipitating factor (n = 60)		With precipitating factor (n = 60)		p-value
	Mean	SD	Mean	SD	
Ammonia before treatment (μmol/L)	29.29	11.08	132.76[b]	36.11	0.0001
Ammonia after treatment (μmol/L)	31.68	17.59	103.16	45.29	0.0001
MELD score	19.97	6.18	29.52	7.67	0.0001
Hb before treatment (g/dL)	10.61	4.80	18.92[a]	15.74	0.0001
Hb after treatment (g/dL)	12.24	10.38	26.58	28.28	0.0001
RBC before treatment ($x10^{12}$/L)	3.43[a]	0.78	3.11	1.86	0.220
RBC after treatment ($x10^{12}$/L)	3.67	0.78	3.25	1.31	0.036
WBC before treatment ($x10^{9}$/L)	6.98	4.99	9.79	7.55	0.018
WBC after treatment ($x10^{9}$/L)	6.02	3.41	9.17	7.27	0.003

[a]p<0.001 [b]p<0.0001

Table 4. Blood ammonia level with respect to infection and varices bleeding

Condition	Before treatment		After treatment		p-value
	Mean ammonia level (μmol/L)	SD (μmol/L)	Mean ammonia level (μmol/L)	SD (μmol/L)	
Infection	105.14[a]	61.37	80.38	49.83	0.0001
No infection	72.50	55.04	63.30	49.40	0.013
No varices bleeding	90.22	57.77	78.36	51.64	0.056
Varices bleeding	75.40	58.18	61.49	48.08	0.0001

[a]p <0.001

Table 5. Correlation coefficients of the blood ammonia level and biomarkers of precipitating factors before and after ammonia lowering treatment

		Ammonia	Hb	RBC	WBC
Ammonia	before	1			
	after	1			
Hb	before	0.17	1		
	after	-0.14	1		
RBC	before	-0.05	-0.07	1	
	after	-0.81	-0.12	1	
WBC	before	0.30[a]	-0.13	0.08	1
	after	0.37[a]	-0.12	-0.08	1

[a]p <0.001

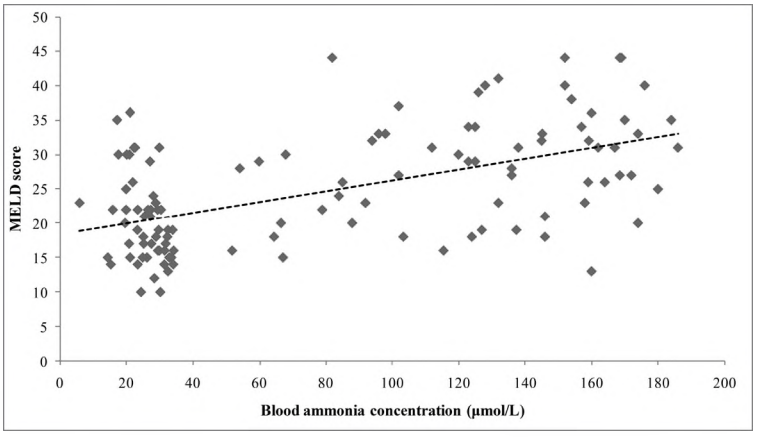

Figure 2. Correlation of MELD score and blood ammonia level (Pearson correlation coefficient r = 0.54, R^2 = 0.292, p = 0.0001).

in Italy and Denmark [19-20]. In Spain, the risk of the first bout of OHE was 5-25% within five years after cirrhosis depending on the presence of risk factors, such as other complications to cirrhosis [21]. In our study the prevalence of OHE was 77% at the time of first diagnosis and within the first five years after cirrhosis diagnosis, which is higher than other countries.

It is difficult to prove the correlation of the blood ammonia level and encephalopathy stages. The relation between plasma ammonia levels and cerebral dysfunction seems to be clear in patients with acute liver failure where plasma ammonia has a direct correlation with the presence of intracranial hypertension and death [22]. During the episode of HE, ammonia shows a huge interpersonal variability in cirrhosis. This may highlight the importance of additional factors that participate in the pathogenesis of HE [23]. Ammonia levels have been shown to be elevated in over 90% of patients with HE in France [24] and levels of glutamine in cerebrospinal fluid, which is the final by-product of ammonia detoxification, were correlated with the severity of HE [25]. Also Clemmesen et al. proved that when the arterial ammonia level is higher than 200 mg/dL there is risk for cerebral herniation in fulminant hepatic failure [25].

The precipitating factor is a clinical event that does not cause a direct injury to the liver or to the portal-systemic circulation but is responsible for the acute change in the mental state. Precipitating factors appear to act by increasing the generation of putative toxins on the central nervous system. They are temporally related to the development of HE and their correction to the re-establishment of consciousness. Infection is a well-known precipitant of HE, but the mechanisms involved are not completely understood. The systemic inflammatory response syndrome (SIRS) results from the release and circulation of proinflammatory cytokines and mediators. One study conducted in Italy found that the most frequent infectious complication that occurs is SBP followed by urinary infections (about 20%), pneumonia (about 15%) and bacteremia (12%) [26]. Our results of the infection complication were similar to this study. GI bleeding is associated with bacterial infection in up to 66% of patients with cirrhosis who are vulnerable to infection because of the disruption of the intestinal mucosal barrier and the frequent invasive manipulations during hemorrhage [9]. Pathogenic effects in the development of HE may result from decreased oxygen delivery, the effects of cytokines or compounds released from necrotic liver tissue [27]. In particular, it is known that proinflammatory cytokines may have a pivotal role in impairing several brain functions [28]. Additionally, the effects of hypotension on cerebral perfusion may be magnified in liver failure because of an associated impairment in the autoregulation of cerebral blood flow [29].

Limitations of this study should be noted. First, we could not measure the arterial ammonia level and partial pressure of ammonia due to the lack of facilities. Second, we determined the timing of the first episode of OHE only by anamnesis of patients due to the limited availability of a control system after diagnosis of cirrhosis in Mongolia.

Our results show the necessity of improving the control after cirrhosis diagnosis, having awareness of the patients and their caregivers, providing prevention and urgent diagnosis, and correcting the common precipitating factors such as infection and GI bleeding. Also the measuring of the blood ammonia level is a significant marker for the evaluation of HE.

Conflict of Interest

The authors state no conflict of interest.

References

1. Center for Health Development. Mongolian Health Indicators 2014. Ulaanbaatar, Mongolia: Center for Health Development; 2014. p 140.
2. Hendrik V, Piero A, Jasmohan B, Juan C, Peter F, Kevin D, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the study of liver disease and the European Association for the study of liver. J Hepatol 2014; 60: 715-735.
3. Papatheodoridis GV, Goulis J, Leandro G, Pacth D, Burroughs AK. TIPS compared with endoscopic treatment for prevention of variceal rebleeding: a meta-analysis. Hepatology 1999; 30: 612-622.
4. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716-721.
5. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic

encephalopathy in patients with cirrhosis. J Hepatol 1999; 30: 890-895.
6. Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther 2007; 25: 3-9.
7. Galtsog L, Undarmaa E, Ariunzul B, Narantsetseg M, Suvd B, Gerlee K. The mortality investigation of liver cirrhosis in Ulaanbaatar city hospitals. Current situation and perspective of diagnosis and treatment of the liver cirrhosis conference. Ulaanbaatar, Mongolia; 2004. p 50-52.
8. Juan Cordoba. New assessment of hepatic encephalopathy. J Hepatol 2011; 54: 1030-1040.
9. Pauwels A, Mostefa-Kara N, Debenes B, Degoutte E, Levy V. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk for infection. Hepatology 1996; 24: 802-806.
10. Garcia-Tsao G. Bacterial infections in cirrhosis: treatment and prophylaxis. J Hepatol 2005; 42: 585-592.
11. Blei AT. Helicobacter pylori, harmful to the brain? Gut 2001; 48: 590.
12. Albrecht J, Norenberg MD. Glutamine: a Trojan horse in ammonia neurotoxicity. Hepatology 2006; 44: 788-794.
13. Watson H, Jepsen P, Wong F, Gines P, Gordoba J, Vilstrup H. Satavaptan treatment for ascites in patients with cirrhosis: a meta-analysis of effect on hepatic encephalopathy development. Metab Brain Dis 2013; 28: 301-305.
14. Aldridge DR, Tranah EJ, Shawcross DL. Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. J Clin Exp Hepatol 2015; 5: S7-S20.
15. Moriyama M, Jayakumar AR, Tong XY, Norenberg MD. Role of mitogen-activated protein kinases in the mechanism of oxidant-induced cell swelling in cultured astrocytes. J Neurosci Res 2010; 88: 2450-2458.
16. Soria LR, Marrone J, Calamita G, Marinelli RA. Ammonia detoxification via ureagenesis in rat hepatocytes involves mitochondrial aquaporin-8 channels. Hepatology 2013; 57: 2061-2071.
17. Blei AT, Larsen FS. Pathophysiology of cerebral edema in fulminant hepatic failure. J Hepatol 1999; 31: 771-776.
18. MaqsoodS, SaleemS, Iqbal A, Butt JA. Precipitating factors of hepatic encephalopathy: experience at Pakistan Institute Of Medical Sciences Islamabad. JAyub Med Coll Abbottabad 2006; 18: 57-61.
19. Riggio O, Mannaioni G, Ridola L, Angeloni S, Merli M, Carla V et al. Peripheral and splanchnic indole and oxindole levels in cirrhotic patients: a study on the pathophysiology of hepatic encephalopathy. Am J Gastroenterol 2010; 105: 1374-1381.
20. Jepsen R, Ott P, Anderssen PK, Sorensen HT, Vilstrup H. The clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010; 51: 1675-1682.
21. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol 2001; 96: 2718-2723.
22. Gorg B, Qvartskhava N, Keitel V, Bidmon HJ, Selbach O, Schliess F, et al. Ammonia induces RNA oxidation in cultured astrocytes and brain in vivo. Hepatology 2008; 48: 567-579.
23. Allert N, Köller H, Siebler M. Ammonia-induced depolarization of cultured rat cortical astrocytes. Brain Res 1998; 782: 261-270.
24. Bismuth M, Funakoshi N, Cadranel J, Blanc P. Hepatic encephalopathy: from pathophysiology to therapeutic management. Eur J Gastroenterol Hepatol 2011; 23: 8-22.
25. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral hernation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999; 29: 648-653.
26. Saija A, Princi P, Lanza M, Scalese M, Aramnejad E, De Sarro A. Systemic cytokine administration can affect blood-brain barrier permeability in the rat. Life Sci 1995; 56: 775-784.
27. Cauli O, Rodrigo R, Piedrafita B, Biox J, Felipo V. Inflammation and hepatic encephalopathy: ibuprofen restores learning ability in rats with portacaval shunts. Hepatology 2007; 46: 514-519.
28. Strauss G, Hansen BA, Kirkegaard P, Rasmussen A, Hjortrup A, Larsen FS. Liver function, cerebral blood flow autoregulation, and hepatic encephalopathy in fulminant hepatic failure. Hepatology 1997; 25: 837-839.
29. Larsen FS, Knudsen GM, Hansen BA. Pathophysiological changes in cerebral circulation, oxidative metabolism and blood-brain barrier in patients with acute liver failure. Tailored cerebral oxygen utilization. J Hepatol 1997; 27: 231-238.