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Original Research

Hyperammonemia and Hepatic Encephalopathy in Pediatric and Adult Liver Intensive Care Unit

Ilhan Ocak,[1] Mustafa Colak,[1] Muharrem Battal[2]

[1]Liver Transplant Intensive Care Unit, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye
[2]Department of Surgery, Yeni Yüzyıl University Medical Faculty, İstanbul, Türkiye

Abstract

Objectives: The exact mechanism that causes the neurotoxicity of hepatic encephalopathy (HE) is still unknown. In this retrospective study, we aimed to define the frequency of hyperammonemia and its relationship with HE.

Methods: The records of 190 patients who were followed up in the Organ transplantation and Hepato-pancreato-biliary surgery intensive care unit (ICU) between August 2021 and August 2022 were reviewed retrospectively. 111 adults and children whose ammonia levels were examined during their stay in the ICU were included in the study He was evaluated with West Haven Criteria. HE had grades 0–4 in the groups.

Results: The median age (range) was 5 (0–16) children and 60 (20–104) adults. The median ammonia value (range) was 42,2 (16–314). Hyperammonemia was present in 39 patients (35%) of all patients. Patients with hyperammonemia and grade 0 encephalopathy were 16 (14%), grade 1–2 patients were 11(10%), and grade 3 patients were 12 (11%).

Conclusion: While our findings and literature evidence strongly support the view that ammonia is the primary factor responsible for, HE development, it shows that factors other than ammonia can only exacerbate HE. In addition, we think that the increased ammonia value in patients with acute liver failure and acute on chronic liver failure is correlated with the increase in the degree of encephalopathy.

Keywords: Ammonia, hepatic encephalopathy, inflammation, liver failure

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Hyperammonemia is a metabolic condition characterized by elevated levels of ammonia, a nitrogen-containing compound. Ammonia is a potent neurotoxin. Hyperammonemia is most manifested by neurological signs and symptoms, which may be acute or chronic depending on the underlying abnormality. Acute hepatic encephalopathy presents alcoholism or exposure to other hepatotoxins.[1] It presents acutely with cerebral edema, increased intracranial pressure, and cerebral herniation resulting in a high mortality rate (55–70%).[2-5] Chronic hepatic encephalopathy is usually the result of liver cirrhosis due to chronic liver disease. It is usually caused by Viral Hepatitis B and C infection (HBV, HCV), Autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency and is associated with alcoholism. It manifests with neuropsychiatric symptoms that deeply affect the socio-economic aspects of the patient's life.[6-10] In this retrospective study, we aimed to define the frequency of hyperammonemia and its relationship with HE.

Address for correspondence: Ilhan Ocak, MD. Karaciger Nakli Yogun Bakim Unitesi, Basaksehir Cam ve Sakura Sehir Hastanesi, İstanbul, Türkiye
Phone: +90 532 452 10 52 **E-mail:** ilhanocak.md@gmail.com

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Methods

The study was conducted in the tertiary intensive care unit (ICU), where pediatric and adult patients have been admitted to the organ transplantation and hepato-pancreato-biliary surgery ICU. The records of patients who were followed between August 2021 and August 2022 were reviewed retrospectively. Patients whose ammonia levels were examined during their stay in the ICU were included in the study.

The selected adult and child groups had HE grades 0–4. According to the laboratory results and the degree of encephalopathy in the tables, ECLST was started for the patients.

Acute physiology and chronic health evaluation, and pediatric risk of mortality scores were performed at the time of admission. West Haven classification and Glasgow coma score (GCS) scoring were used to determine the grade of encephalopathy. The study was performed by the Declaration of Helsinki. The study was approved by the Institutional review board (Date: November 01, 2022; Approval No. 3014).

Statistical Analysis

SPSS Statistics 20 (IBM, Armonk, NY) was used for all statistical analyses. Kolmogorov–Smirnoff analysis was used to analyze the normality of study data. In encephalopathy groups; While Kruskal–Wallis was used to comparing ammonia values, a one-way ANOVA test was used to compare AST, ALT, total bilirubin, and INR values. P<0.05 was considered significant in the study.

Results

The records of 190 patients admitted to the ICU between August 2021 and August 2022 were reviewed retrospectively. 111 adults and children whose ammonia levels were examined during their stay in the ICU were included in the study. The median age (range) was 5 (0–16) children and 60 (20–104) adults. The median ammonia value (range) was 42, 2 (16–314).

Hyperammonemia was present in 39 patients (35%) of all patients. Demographic data, etiology, and scoring of the patients are in Table 1. Patients with hyperammonemia and Grade 0 encephalopathy were 16 (14%), Grade 1–2 patients were 11 (10%), and Grade 3 patients were 12 (11%). Ammonia values according to encephalopathy degrees are shown in Table 2. In all patients, the encephalopathy grade 0 group had an increase above normal in INR and liver function tests (AST/ALT/T. Bil). But encephalopathy did not develop. In all patients, the mean INR of the Grade 3–4 group was significantly higher than the mean INR of the grade 1–2 group (Table 3 and 4). In pediatric patients, the mean liver function tests (AST/ALT) of the grade 1–2 group were significantly higher than the mean liver function tests (AST/ALT) of the grade 3–4 group. However, the total bilirubin was significantly lower (Table 3). In adult patients, the mean liver function tests (AST/ALT/T. Bil) of the grade 3–4 group were significantly higher than the mean liver function tests (AST/ALT/T. Bil) of the grade 1–2 group (Table 4). In all patients, although there was an increase in C-reactive protein (CRP) and procalcitonin, the increase in encephalopathy grade was not significantly correlated (Table 3 and 4). In all patients, ammonia level and grade of encephalopathy were correlated (Table 5 and 6).

Table 1. Demography, etiology, and intensive care scoring values

Child (n)	15
*Age	5 (0–16)
*PRISM Score	26 (20–36)
Adult (n)	96
*Age	60 (20–104)
*APACHE II Score	22 (20–28)
Post-surgery	
Child	7
Adult	72
Acute liver failure	
Child	5
Adult	13
Acute on chronic liver failure	
Child	3
Adult	4
Septic Shock	
Child	0
Adult	7
Gender	
Male	42
Female	69

*Median values (range); APACHE: Acute physiology and chronic health evaluation; PRISM: Pediatric risk of mortality; n: Number.

Table 2. Ammonia values by grade of encephalopathy

Encephalopathy	Ammonia (µmol /L) [Medain CI%95]	p
Grade 0		<0.001
Child	64 (61–72)	
Adult	70 (63–83)	
Grade 1–2		
Child	133 (82–218)	
Adult	97 (84–108)	
Grade 3–4		
Child	197 (90–314)	
Adult	167 (115–290)	

Table 3. Laboratory values by grade of encephalopathy (Child)

	Grade 0	Grade 1–2	Grade 3–4	p
AST (u/L)	326 (±205)	4843 (±2267)	2500 (±1555)	0.05
ALT (u/L)	282 (±177)	4239 (±2327)	2327 (±1465)	<0.01
T.Bil (mg/dL)	2.9 (±1.7)	3.2 (±0.8)	39 (±12.1)	<0.01
INR	1.53 (±0.31)	2.22 (±0.35)	3.16 (±0.55)	<0.01
Procalcitonin (ng/ml)	2.12 (±2.7)	9.2 (±13.6)	17.9 (±15.1)	0.15
CRP (mg/L)	154 (±84)	102 (±64)	134 (±47.5)	0.32

Mean values (±Std Deviation); AST: Aspartat aminotransferaz; ALT: Alanin aminotransferaz; T.Bil: Total bilirubin; INR: International normalized ratio; CRP: C-Reactive protein.

Table 4. Laboratory values by grade of encephalopathy (Adult)

	Grade 0	Grade 1–2	Grade 3–4	p
AST (U/L)	1162 (±2840)	2580 (±2267)	6609 (±3960)	<0.01
ALT (U/L)	1191 (±1956)	1913 (±2515)	6113 (±4847)	<0.01
T.Bil (mg/dL)	2.6 (±1.7)	3.8 (±1.7)	23 (±13.6)	<0.01
INR	1.57 (±0.5)	1.92 (±0.55)	4 (±0.1.4)	<0.01
Procalcitonin (ng/ml)	6.5 (±14.4)	4.5 (±5.54)	9 (±16.6)	0.79
CRP (mg/L)	226 (±99)	155 (±55)	128 (±33.2)	0.42

Mean values (±Std Deviation), AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz, T.Bil: Total bilirubin, INR: International normalized ratio, CRP: C-Reactive protein.

Supportive treatment was not applied to the grade 0 patient group. Grade 1–2 patient group recovered with ECLST. Although ECLST was given, 12 patients who were grade 3 became encephalopathy grade 4 in a median of 73 h. Liver transplantation was performed on 4 patients from this group. Encephalopathy resolved. Six patients of this group, who could not be transplanted or had no indication for transplantation, entered the period of irreversible encephalopathy as GCS 3 in the range of 4–8 days. He became an ex-patient. Brain death occurred in the remaining two patients.

Discussion

In this study, we aimed to define the frequency of hyperammonemia and its relationship with Encephalopathy in a special ICU for Organ transplantation and Hepato-pancreato-biliary surgery. The exact mechanism underlying HE neurotoxicity associated with acute and chronic liver failure remains unclear. The accepted view has been that gut-derived ammonia is not eliminated by the diseased liver and thus enters the CNS. Thus, blood, spinal fluid, and brain ammonia levels increase, which results in HE.[11-13]

Many studies have shown that the major neuropatho-

Table 5. Correlation between the ammonia level and liver function tests andthe grade of encephalopathy (Child)

	Pearson's r	Spearman's rho	p
Grade of encephalopathy			
AST (U/L)	0.470		0.12
ALT (U/L)	0.478		0.11
T.Bil (mg/dL)	0.842		<0.01
INR	0.886		<0.01
Procalcitonin (ng/ml)	0.579		<0.01
CRP (mg/L)	0.496		0.19
Ammonia (µmol/L)		0.887	<0.01

AST: Aspartat aminotransferaz; ALT: Alanin aminotransferaz; T.Bil: Total bilirubin; INR: International normalized ratio; CRP: C-Reactive protein.

Table 6. Correlation between the ammonia level and liver function tests andthe grade of encephalopathy (Adult)

	Pearson's r	Spearman's rho	p
Grade of encephalopathy			
AST (U/L)	0.529		<0.01
ALT (U/L)	0.534		<0.01
T.Bil (mg/dL)	0.741		<0.01
INR	0.727		<0.01
Procalcitonin (ng/ml)	0.071		0.72
CRP (mg/L)	0.576		0.17
Ammonia (µmol/L)		0.862	<0.01

AST: Aspartat aminotransferaz; ALT: Alanin aminotransferaz; T.Bil: Total bilirubin; INR: International normalized ratio; CRP: C-Reactive protein.

logical finding in acute liver failure (ALF) is swollen astrocytes, which contribute to the development of increased intracranial pressure, coma, and death. There is acceptable evidence that ammonia plays a significant role in the development of astrocyte swelling/brain edema in HE in ALF. This occurs between hours and a few days, depending on precipitating factors (e.g., infection and alcohol consumption).[12,13] HE who develops CLF, on the other hand, presents with a wide variety of neurological symptoms, including mood swings, impaired sleep-wake cycles, changes in muscle tone, and severe cognitive deficits.[14,15] Just as in the presence of sepsis and inflammation, blood levels of inflammation mediators such as tumor necrosis factor-alpha, Interleukin (IL)-1β, and IL-6 have been found to increase in patients with HE. Moreover, the development of astrocyte swelling-brain edema by these mediators suggests the possibility of exacerbation in HE.[14,15] Despite all the studies in the literature, it is suggested that these inflammatory factors other than ammonia, including infection, cytokines, and other blood and brain immune factors, play a potential role in the pathogenesis of HE, but the data on these factors are basic.[15,16]

However, the role of ammonia is of most interest, as events that cause increased blood or brain ammonia levels have been shown to cause HE, whereas lowering blood ammonia levels has been shown to improve HE. In addition, the clinical, pathological, and biochemical changes observed in HE can be reproduced by increasing blood or brain ammonia levels in experimental animals or by exposing cultured astrocytes to ammonium salts. As a result, ammonia contributes to the occurrence or progression of neurological complications in ALF and CLF.[17,18] In this retrospective study, grade of HE was found to be correlated with increased ammonia value in 39 patients with acute or acute on chronic liver failure (ACLF).[17-19] In addition, it was determined that the grade of encephalopathy was correlated with the elevation of INR and liver functional tests (ALT, AST, T.Bil) in adult patients. We think that this indicates the degree of damage to the liver, which is so impaired that it cannot metabolize ammonia. We observed that only ALT and AST elevations in pediatric patients were not correlated with encephalopathy grade. This group was the ACLF pediatric patient group. This showed us that the CLF group has a different mechanism. Although there was an increase in the inflammatory mediators CRP and procalcitonin, the increase in encephalopathy grade was not significantly correlated. This situation was evaluated as inflammatory mediators "aggravate encephalopathy" as in the literature. Procalcitonin elevation also supports the thesis that procalcitonin may be elevated in liver diseases.

While our findings and literature evidence strongly support the view that ammonia is the primary factor responsible for, HE development, it shows that factors other than ammonia can only exacerbate HE. In addition, we think that the increased ammonia value in patients with ALF and ACLF is correlated with the increase in the degree of encephalopathy.

However, due to the retrospective nature of our study and the lack of a control group, randomized controlled studies on the subject are needed.

Disclosures

Ethics Committee Approval: The Ethics Committee Number: 2022.11.371 and subject No: KAEK/2022.11.371.

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Conflict of Interest: None declared.

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