COEXISTENCE OF HYPERAMMONEMIA AND METABOLIC ENCEPHALOPATHY IN NONCIRRHOTIC PATIENTS

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ABSTRACT

Introduction*: Most of the time hyperammonemia is seen in hepatic encephalopathy, but it can coexist with various other conditions. In this study, we investigated the causes of hyperammonemia in noncirrhotic patients with encephalopathy. The aims of this study were identifying risk groups of patients who can present with hyperammonemic metabolic encephalophaty.*

Materials and methods*: This retrospective, observational, descriptive, sectional clinic study was conducted in a tertiary level training and research hospital between July 2013 and October 2015. Blood ammonia levels were analyzed in metabolic encephalopathy patients who have presented to the emergency department (ED).*

Results*: Among 135 patients (54 patients had cirrhosis and 81 patients did not have cirrhosis) enrolled in this study Mean age was 57 years (range 18-88 years). 67 % of the patients were male (n= 90) and 33% of the patients were female (n= 45). In cirrhotic group although mean values of ammonia got higher as Child-Pugh class raised from A to C (164.2, 202 and 248 µg/dl respectively) the difference was not statistically significant. In noncirrhotic group we found remarkable increased ammonia level in the patients with epilepsy or patients who have seizure (n:37, ammonia level: 110,49 (18-687)), patients with urinary problems (n:27, ammonia level: 135,88 (18-687)), patients with sepsis (n:28, ammonia level: 133,09 (29-687)), and patients who have starvation or oral intake difficulty (n:24, 133,7 (20,90-687))*

Conclusion*: Blood ammonia levels are useful in differential diagnosis of adult patients who present to ED with new or acute mental status changes of unknown cause. Ammonia levels may be elevated in noncirrhotic patients. Urinary problems, epilepsy or seizure, starvation or oral intake difficulty can be the cause of hyperammonemia. In clinical practice when evalutating patients with hyperammonemia emergency physicians should be familiar with causes other than cirrhosis.*

Keywords*: Hyperammonemia, ammonemia, ammonia, emergency medicine, Noncirrhotic hyperammonemia, cirrhotic hyperammonemia.*

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Introduction

Ammonia is one of the products of protein catabolism and toxic to cells when its blood level is elevated. Prior to excretion in urine it is converted to urea, which is less toxic than ammonia. Most of the time hyperammonemia is seen in hepatic encephalopathy, but hyperammonemia coexist with various other conditions. In high concentrations ammonia is toxic to cells and exerts its toxic activity mostly on the brain and causes to encephalopathy[(1)].

Mechanism of acute brain dysfunction is multifactorial. Changes in blood flow, failures of energy metabolism, disturbances in neurotransmitter function and inappropriate cellular depolarization contribute to encephalopathy.

Acute encephalopathy is a relatively common problem and metabolic disorders are one of its causes. A detailed history, physical examination, laboratory tests and imaging studies are needed to identify the cause of encephalopathy during acute illness.

In this study, we retrospectively analyzed blood ammonia levels in 135 patients after acute mental status changes had investigated and the diagnosis of metabolic encephalopathy had been done and we overviewed the coexistence of hyperammonemia and metabolic encephalopathy in non-cirrhotic patients.

Materials and methods

Setting

This retrospective, observational, descriptive, sectional clinic study was conducted between July 2013 and October 2015 in an urban training and research hospital with an affiliated emergency department (ED) residency program that has approximately 150,000 ED visits per year. A standardized medical record sheet was used.

Patients

We retrospectively included all adult patients who presented to ED with new or acute mental status changes (confusional state, acute organic brain syndrome, encephalopathy). The patients were included in the study if their blood ammonia level was measured in emergency room.

The patients were excluded from the study if the patient's age was <18 years, or had at least one of the following: intracranial bleeding, ischemic cerebrovascular event, intracranial mass lesion (primary or metastatic), central nervous system infections (meningitis, encephalitis), other primary central nervous system disease (multiple sclerosis etc).

Blood samples

Initial blood samples were taken within 24 hours of presentation to emergency room. Sampling time varied based on the patients' presentation times to the ED and it included day, night, weekday, and weekend shifts. Standardized venous blood was obtained without stasis through an antecubital vein for complete blood count (CBC), biochemical parameters and ammonia determination. Standardized arterial blood sample for arterial blood gas analysis was obtained through the radial artery. Venous blood samples were collected in iced tubes and the ammonia determination was performed immediately using the Ammonia Checker. Plasma was obtained by centrifugation at 1500 g, +4 centigrade degree, 10 minutes. Analysis was performed with commercially available chemical assay kits (Roche diagnostic, Germany) on a Roche / Cobas C 8000 auto-analyzer. In our laboratory; normal reference range for ammonia is 18,7-86,9 μg/dl.

Clinical and laboratory information

Clinical information recorded included age, sex, in hospital mortality, presenting symptom (seizure or trauma), history of malignancy, recent chemotherapy, organ transplantation, steroid usage, starvation or oral intake difficulty, urea–cycle disorder, supply of urea-cycle substrates, dialysis, hepatitis b, hepatitis c, alcohol addiction, biliary cirrhosis, diarrhea, constipation, gastrointestinal hemorrhage, urinary problems (stasis, infection, deformities of urinary tract), the etiology of encephalopathy, endotracheal intubation, the need of cranial tomography, Child-Pugh class, antibiotics usage for treatment, parenteral nutrition, prophylactic use of anti-epileptic agents, mannitol usage, hepatic vascular pathology, lactulose use. (See table 1).

Characteristic	Number	(%)
Outcome		
Discharged (from ED, ward or ICU)	112	(82,9)
Dead	21	(15,5)
Leaving the hospital before treatment was complete	3	(2,2)
Cirrhotic	54	(40)
Noncirrhotic	81	(60)
Endotracheal intubation	41	(30)
Sepsis	50	(37)
Antibiotics usage for treatment	65	(48)
Malignancy	23	(17)
Resent chemotherapy	10	(7,4)
Organ transplantation	2;4-suggested	(0,14;0,3-suggested)
Steroid usage for any purpose	12	(8)
Parenteral nutrition in any period	49	(36,2)
Starvation or oral intake difficulty	49	(36,2)
Trauma prior to admission	6	(4)
Urinary stasis	32	(23,7)
Urogenital deformities	2	(0,14)
Urinary infection	37	(27,4)
Dialysis	24	(17,7)
History of seizures	42	(31,1)
Prophylactic use of anti-epileptic agents	37	(27,4)
Use of mannitol for diuresis	19	(14)
Cranial tomography for any purpose	95	(70,3)
Drug-induced hepatic encephalopathy	1	(0,72)

Table 1: Patients' characteristics of 135 patients.

Laboratory data included ammonia, pH of blood, calcium (Ca), sodium (Na), blood urine nitrogen (BUN), creatinine, platelets, mean platelet volume (MPV), white blood cell (WBC), hemoglo-

bin, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Lactate dehydrogenase (LDH), albumin, total bilurubin and the international normalized ratio (INR) of the prothrombin time.

Statistical analysis

Variance of homogeneity test was used, to see if the groups were paired or unpaired. To compare paired data between various groups One-way analysis of variance (ANOVA) - F test was used (pH, WBC, CRP, MPV, Albumin, bilirubin, INR, creatinine, Na, Ca). To compare unpaired data between various groups, Mann Whitney U test was done (Sex, ammonia, hemoglobin (Hb), Platelets (Plt), AST, ALT, LDH and BUN). All data were processed with the software package Statistical Package for the Social Sciences (SPSS) Version 15.0 (SPSS Inc., Chicago, IL) and 2-sided P values < 0.05 were considered significant.

Results

Patients' characteristics

One hundred ninety-six eligible patients were enrolled. Sixty-one patients were subsequently excluded before analysis due to incomplete ammonia level records. Ammonia levels could not be studied in 61 patients due to inappropriate sampling or transportation of blood [ice containers were not used for transport in 48 patients (78,6%), blood samples were hemolyzed in 7 patients (11,4%), blood was drawn to a wrong tube in 6 patients (9,8%)].

Patient characteristics of 135 patients were shown in table 1. Mean age was 57 years (range 18-88 years). 67% of the patients were male (n= 90) and 33% of the patients were female (n= 45). 54 patients had cirrhosis and 81 patients did not have cirrhosis.

Diagnosis of cirrhosis was based on clinical, biochemical, ultrasonographic and liver histopathology findings from patients' hospital medical records and computer database. The clinical features of patients who had cirrhosis and hepatic encephalopathy at the time of admission are seen in table 2. In our study; chronic viral hepatitis (B and C) was the leading cause of cirrhosis. Starvation or oral intake difficulty followed by sepsis was the leading cause of hepatic encephalopathy in cirrhotic patients (Table 2).

Etiology of cirrhosis for cirrhotic 54 patients'	number of patients	% of patients
#Hepatitis B	36	(48,6-cirrhotic)
#Hepatitis C	16	(21,6-cirrhotic)
#Alcohol	7	(9,4-cirrhotic)
#Primary biliary cirrhosis	4	(5,4-cirrhotic)
#Cryptogenic	7	(9,4-cirrhotic)
#Other (3 cardiopulmonary, 1 haemochromatosis)	4	(5,4-cirrhotic)
Child-Pugh class of cirrhotic 54 patients		
#A	14	(19-cirrhotic)
#B	30	(40,5-cirrhotic)
#C	30	(40,5-cirrhotic)
Cause of activation of hepatic encephalopathy in cirrhotic 54 patients*		
#Starvation or oral intake difficulty	25	(46,2)
#Sepsis	20	(37)
#Urinary infection	14	(25,9)
#Diarrhea	18	(24)
#Urinary Stasis	15	(27,7)
#Gastrointestinal hemorrhage	6	(8,1)
#Variceal bleeding	3	(4)
#Constipation	2	(2,7)
Hepatic vascular pathology		
#Prior porto-systemic shunt	4	(5,4)
#Portal vein thrombosis	3	(4)
#Hepatic vein thrombosis	3	(4)

Table 2: Clinical Features of patients who had cirrhosis. **There is more than one etiology causing hepatic encephalopathy in some of the cirrhotic patients.*

	Child-Pugh class A (n:12)	Child-Pugh class B (n:22)	Child-Pugh class C (n:20)	p value
Mean Age (years)	66,25 (57-74)	63,23 (52-79)	62,6 (49-84)	0,3
Sex (male)	9 (%75)	18 ((%81,8)	15 (%75)	0,842
Ammonia (µg/dl)	164,23 (38-403)	202 (36-398)	248 (56,9-563)	0,245
pH	7,39 (7,32-7,51)	7,38 (7,25-7,48)	7,36 (7,22-7,49)	0,518
Hemoglobin (g/dl)	12,52 (10-16,3)	11,3 (6,3-17,2)	10,2 (5-13,4)	0,013*
Platelets ×1000	136,16 (23-297)	111,8 (46-425)	106,1 (20-216)	0,181
MPV (fL)	10,24(8-9-13,8)	9,77 (7,5-13,4)	10,38 (8,2-13,5)	0,339
WBC (K/uL)	6,5 (2-14,3)	8,19 (1,3-18,8)	10,0 (3,7-39,4)	0,15
CRP (mg/dl)	1,96 (0,2-9,9)	3,1 (0,49-14)	7,91 (0,2-50,0)	0,018*
AST (U/L)	45 (13-121)	122 (26-834)	99,3 (32-243)	0,014*
ALT (U/L)	32 (12-119)	94 (15-1060)	44,45 (13-128)	0,233
LDH (U/L)	283 (85-735)	345 (100-1147)	388 (161-1903)	0,183
Albumin (g/dl)	3,47 (2,1-4,5)	2,76 (1,93-3,66)	2,23 (1,36-2,97)	<0,001*
Bilirubin (mg/dl)	1,77 (0,4-3,97)	3,36 (0,4-10)	6,89 (1,44-29,30)	<0,001*
INR	1,16 (0,9-1,93)	1,56 (1-3,59)	1,68 (1,2-3,19)	<0,001*
S.creatinine (mg/dl)	1,27 (0,69-3,6)	1,40 (0,4-4,11)	2,20 (0,5-9,3)	0,065
S. BUN (mg/dl)	67 (29-141)	80,6 (12-230)	103,8 (24-251)	0,126
S.sodium (mEq/L)	136,1 (126-150)	134,9 (123-144)	132,5 (121-142)	0,164
S.calcium (mg/dl)	8,8 (7,8-10,2)	8,2 (7-10,4)	7,74 (7-8,6)	<0,001*

Table 3: Laboratory test results of cirrhotic patients compared between Child-Pugh class A, B and C.

Laboratory results of cirrhotic patients that are classified according to Child-Pugh class are pre-

sented in Table 3. Kruskall-Wallis one-way analysis of variance test was used to compare median values between groups. There was statistically significant difference between Child-pugh class A, B and C groups with regard to Hb, CRP, AST, albumin, bilirubin, INR, Ca results. Although mean values of ammonia got higher as Child-Pugh class raised from A to C (164.2, 202 and 248 μg/dl respectively for A, B and C) the difference was not statistically significant. Similarly as the Child-Pugh score raised from A to C mean blood pH, Plt count and serum Na values were lower; LDH, serum creatinine, BUN values were higher but no statistically significant difference was found between groups.

Laboratory test results were compared between cirrhotic (n: 54) and noncirrhotic (n: 81) patients. (Table 4) Mean age of cirrhotic patients was statistically older than non-cirrhotic patients and the ratio of man to woman was higher in cirrhotic group. In the cirrhotic group ammonia, bilirubin, BUN levels were significantly higher compared to non-cirrhotic group. Hb, Plt, ALT, AST, LDH, Alb, Na, Ca levels were significantly lower in cirrhotic patients.

	Non-cirrhotic (n: 81)	Cirrhotic (n: 54)	p value
Age (years)	52,56(18-88)	63,67(49-84)	*ANOVA <0,0001
Sex (male)	48(%59,25)	42 (%77)	*Mann Whitney U <0,0001
Ammonia (µg/dl)	106,35(18-687)	210,36(36-563)	*Mann Whitney U <0,0001
pH	7,37(7,19-7,54)	7,38(7,22-7,51)	ANOVA 0,802
Hemoglobin (g/dl)	11,7(5,5-17,1)	11,16(5-17,20)	*Mann Whitney U <0,0001
Platelets ×1000	223,39(33-655)	115,14(20-425)	*Mann Whitney U <0,0001
MPV (fL)	10,49(6,9-13,2)	10,10(7,5-13,80)	ANOVA 0,101
WBC (K/uL)	9,57(2-33,60)	8,51(1,30-39,40)	ANOVA 0,309
CRP (mg/dl)	4,32(0,2-22,5)	4,63(0,20-50)	ANOVA 0,787
AST (U/L)	198,40(5-4108)	96,79(13-834)	*Mann Whitney U <0,0001
ALT (U/L)	177,80(2-5256)	62,44(12-1060)	*Mann Whitney U <0,0001
LDH (U/L)	355,12(90-3311)	347,81(85-1903)	*Mann Whitney U <0,0001
Albumin (g/dl)	3,43(1,53-4,8)	2,72(1,36-4,50)	*ANOVA <0,0001
Bilirubin (mg/dl)	2,6(0,1-25,20)	4,32(0,4-29,30)	*ANOVA <0,043
INR	1,46(0,7-10)	1,522(0,9-3,59)	ANOVA 0,745
S. creatinine (mg/dl)	1,29(0,3-5,4)	1,67(0,4-9,3)	ANOVA 0,92
S. BUN (mg/dl)	52,77(11-222)	86,28(12-251)	*Mann Whitney U <0,0001
S. sodium (mEq/L)	137,95(114-174)	134,29(121-150)	*ANOVA <0,002
S. calcium (mg/dl)	8,63(5-10,20)	8,20(7-10,40)	*ANOVA <0,006

Table 4: Compared laboratory test results of cirrhotic and noncirrhotic patients.

When noncirrhotic patients (n=81) were grouped separately, 4 pathologies were seen more than others. Those were patients with epilepsy or seizures, patients with urinary problems, patients with sepsis and patients with starvation or oral intake difficulty. Laboratory results of these patients are reported in table 4. Since some of the patients had more than one pathology and was evaluated in more than one group no comparison between groups was done.

Laboratory test results of noncirrhotic patients are presented in Table 5. Since some patients had more than one condition some patients' values were taken into calculation in more than one group. Mean ammonia levels were higher compared to reference values in all 4 noncirrhotic patient groups. Mean liver enzyme levels were higher than normal limits in noncirrhotic patient groups who had urinary problems, who had sepsis, who had starvation or oral intake difficulty.

	Epilepsy or patients who have seizure (n=37)	Patients with urinary problems (n=27)	Patients with sepsis (n=28)	Patients who have starvation or oral intake difficulty (n=24)
Age (years)	49,89(18-82)	66,74(20-88)	64,36(24-88)	64,62(24-87)
Sex (Male)	18(%48,6)	17(%62,96)	19(%67,85)	13(%54,16)
Ammonia (µg/dl)	110,49(18-687)	135,88(18-687)	133,09(29-687)	133,7(20,90-687)
pH	7,38(7,21-7,54)	7,37(7,19-7,54)	7,36(7,19-7,54)	7,36(7,21-7,54)
Hemoglobin (g/dl)	11,7(7,1-17,1)	10,4(5,5-16,3)	10,1(5,5-16,5)	9,8(5,5-13,9)
Platelets ×1000	265(43-655)	197(33-523)	240(33-655)	192(33-523)
MPV (fL)	10,4(7,7-13,2)	10,2(7,7-13,2)	10,3(6,9-13,2)	10,7(6,9-13,2)
WBC (K/uL)	8,5(3,7-21)	11,2(2-33,6)	12,7(3,7-33,6)	14,1(4,26-33,6)
CRP (mg/dl)	3,56(0,2-19,6)	7,4(0,2-22,5)	7,5(0,2-20,7)	8,71(0,20-22,50)
AST (U/L)	41,5(5-688)	372(7-4108)	143,8(8-1224)	207(8-1224)
ALT (U/L)	30,3(2-352)	356(6-5256)	76(2-352)	111(2-998)
LDH (U/L)	187,5(90-784)	593,9(125-3311)	503(100-3311)	581(177-3311)
Albumin (g/dl)	3,68(2,5-4,8)	2,9(1,5-4)	2,68(1,53-3,63)	2,69(1,53-4)
Bilirubin (mg/dl)	0,73(0,1-1,73)	4(0,2-25,2)	3,1(0,1-14,2)	5,34(0,1-25,2)
INR	1,06(0,7-2,5)	1,99(0,9-10)	1,59(0,9-5,3)	1,57(0,9-3,4)
S. creatinine (mg/dl)	1,04(0,35-4,94)	1,9(0,3-5,4)	1,5(0,3-5,4)	1,68(0,3-5,4)
S. Urea (mg/dl)	39,4(13-191)	85,8(16-222)	77,3(11-222)	72,08(11-191)
S. sodium (mEq/L)	140,8(132-174)	137(125-155)	137,7(125-155)	136(114-155)
S. calcium (mg/dl)	8,7(5-9,9)	8,4(6,4-10,2)	8,3(6,4-10,2)	8,2(6,4-10,2)

Table 5: Laboratory test results of noncirrhotic patients.

In our study 23 patients had oncologic disease. In this subgroup of oncologic patients (n=23), 12 patients also had cirrhosis (8 primary hepatic cancer, 1 metastatic colon cancer, 1 metastatic over cancer, 1 non metastatic gall bladder cancer, 1 non-metastatic myxoma). The rest of oncologic patients (n=11) had no cirrhosis; on the other hand 7 of

these patients had either liver metastasis or primary liver cancer (2 primary hepatic cancer, 1 metastatic breast cancer with liver metastasis, 1 metastatic colon cancer with liver metastasis, 1 metastatic renal cancer with liver metastasis, 2 metastatic cancer of unknown origin with liver metastasis, 1 nasopharynx cancer, 1 stomach cancer, 1 prostatic cancer, 1 ovarian cancer).

Mean ammonia level was 276,04 (86-563) μg/dl in oncologic patients who also had cirrhosis. 8 of these patients died during hospitalization after ER visit. (Mortality rate 66, 6 %). Mean ammonia level was 110, 47 (21-252) μg/dl in oncologic patients who did not have cirrhosis. 3 of these patients died during hospitalization after ED visit. (Mortality rate 27, 27 %)

In our study 10 of the 23 oncologic patients recently undergone chemotherapy, their mean value of ammonia was 116,25 (20,9-178) μg/dl. Of those 10 patients only 3 had neither cirrhosis nor liver neoplasm (primary or metastatic).

In our study 2 patients had Fluorouracil (5-FU) treatment according to patients' charts. One of those patients had stomach cancer and the other had colon cancer. The mean ammonia level was 67,5 μg/dl (stomach cancer-29 μg/dl, colon cancer-106 μg/dl respectively)

In our study 2 renal transplant patients had hyperammonemia (serum ammonia levels were 116 μg/dl and 127 μg/dl).

In our study 1 patient had hepatic encephalopathy and hyperammonemia (110 μg/dl) after high dose acetaminophen intake.

In our study 4 of the cirrhotic patients had prior portosystemic shunt. In those patients mean ammonia level was 158,5 (73-255) μg/dl and it was over the normal reference range for ammonia of our laboratory (18,7-86,9 μg/dl).

In our study 3 patients had hepatic vein thrombosis and 3 patients had portal vein thrombosis. All 6 patients had cirrhosis. Mean ammonia level was 150,83 (73-255) μg/dl and it was over the normal reference range for ammonia of our laboratory (18,7-86,9 μg/dl).

Discussion

Ammonia metabolism in the body involves five organs-the gut, kidney, muscles, liver, and the brain. Ammonia production is mostly in the gut, followed by the kidney and the muscles. Within the gastrointestinal (GI) tract, ammonia is a byproduct of protein digestion and bacterial metabolism. Ammonia is essential for the renal handling of acid in the kidneys. Lastly, skeletal muscle can also produce ammonia, especially during seizures or with intense exercise. Ammonia degradation primarily takes place in the liver[2].

Nitrogenous waste is a result of breakdown and catabolism of dietary and bodily proteins. In healthy individuals, amino acids that are not needed for protein synthesis are metabolized, and the nitrogen waste is converted to urea. In a healthy human, the main NH3 detoxification route is the synthesis of urea in the liver via urea-cycle enzymes. A second and alternative pathway, which becomes important in conditions of decreased urea synthesis in the liver or hepatic shunting, is synthesis of glutamine from NH3 and glutamate via glutamine synthetase[3].

In the brain, the secondary process and the activity of glutamate dehydrogenase mediate ammonia production. Generally the ammonia level remains low (<40 mmol/L) due to the fact that most ammonia produced in tissue is converted to glutamine and glutamine is excreted by the kidneys. Glutamine is also utilized for energy production by gut cells, which convert the nitrogen byproduct into alanine, citrulline, and ammonia. These are then transported to the liver via the bloodstream. Ammonia enters the urea cycle in hepatocytes and is ultimately converted to glutamine[3,4].

Ammonia levels are almost invariably high in patients with acute or chronic liver failure. In most of the studies correlation of ammonia levels with the presence or severity of hepatic encephalopathy is often variable and inaccurate. But in some previous studies there is a strong correlation between ammonia levels and the severity of hepatic encephalopathy. In our study although mean values of ammonia got higher as Child-Pugh class raised from A to C (164.2, 202 and 248 μg/dl respectively for A, B and C) the difference was not statistically significant. This is consistent with uncertain results in literature. We observed a strong correlation between venous total ammonia levels and severity of encephalopathy. Nevertheless these conflicting results may be explained by variability in ammonia levels throughout the day, or the possibility that compounds other than ammonia are also involved in the pathogenesis of hepatic encephalopathy.

In emergency settings, hyperammonemia is mostly seen in hepatic encephalopathy, but various other conditions can also cause hyperammonemia.

Urea cycle defects (UCD), organic acidemias, fatty acid oxidation defects, Reye syndrome can cause hyperammonemia especially in children. Post-chemotherapy or exposure to various toxins and drugs can also cause hyperammonemia. Laish et al classified the etiology noncirrhotic hyperammonaemia into two main groups; increased ammonia production and decreased ammonia elimination.

In increased ammonia production group, there are infections (especially by urea-producing bacteria: Proteus mirablis, Klebsiella species, Escherichia coli, Morganella morganii, Providencia rettgeri, diphtheroids, Mycobacterium genavense, herpes simplex), haemato-oncological disorders (multiple myeloma, acute leukemia, bone marrow transplantation, 5-FU), organ transplantation, protein load and increased catabolism (severe exercise, seizures, starvation or trauma, total parenteral nutrition, gastrointestinal bleeding, steroid use). In decreased ammonia elimination group; there are urinary problems (ureterosigmoidostomy etc), portosystemic shunts (congenital or acquired) and drug induced hyperammonemia[5].

In our study mean ammonia levels were higher compared to reference values in all 4 groups of noncirrhotic patient groups. Mean liver enzyme levels were higher than normal limits in noncirrhotic patient groups who had urinary problems, who had sepsis, who had starvarion or oral intake difficulty.

Infection

Infection is a cause of hyperammonemia in both cirrhotic and non-cirrhotic patient groups. In non-cirrhotic patient group, the infection is mostly of urinary tract origin. The venous drainage of the bladder flows directly into the systemic circulation; hence, the NH3 bypasses the liver and is not detoxified to urea. As NH3 is electrically neutral and lipidsoluble, it can readily cross cell membranes and diffuse into the urothelial cells, where the lower pH converts it to the less permeable ammonium ion, preventing its diffusion back into the urine[5,6]. In our study ammonia levels were high in noncirrhotic patients who had sepsis. This may be due to increased catabolism rate or liver bypass of NH3 by venous drainage.

Haemato-oncological disorders, chemotherapy and organ transplantation

Noncirrhotic hyperammonaemic encephalopathy in the absence of documented liver dysfunction may be a rare cause of altered sensorium in patients with some kind of cancer[7]. Hyperammonaemia usually occurs in advanced forms of multiple myeloma. It suggests a direct link between malignant plasma cells and NH3 level, supporting the role of NH3 in altered sensorium in this setting[8]. Lora-Tamayo J et found high mortality rate (44%) among myeloma patients in their study[9].

In our study 23 patients had oncologic disease. In this subgroup of oncologic patients (n=23), 12 patients also had cirrhosis (8 primary hepatic cancer, 1 metastatic colon cancer, 1 metastatic over cancer, 1 non metastatic gall bladder cancer, 1 non-metastatic myxoma). The rest of oncologic patients (n=11) had no cirrhosis; on the other hand 7 of these patients had either liver metastasis or primary liver cancer (2 primary hepatic cancer, 1 metastatic breast cancer with liver metastasis, 1 metastatic colon cancer with liver metastasis, 1 metastatic renal cancer with liver metastasis, 2 metastatic cancer of unknown origin with liver metastasis, 1 nasopharynx cancer, 1 stomach cancer, 1 prostatic cancer, 1 ovarian cancer). Mean ammonia level was 276,04 (86-563) μg/dl in oncologic patients who also had cirrhosis. Mean ammonia level was 110, 47 (21-252) μg/dl in oncologic patients who did not have cirrhosis.

In our study we found marked hyperammonemia associated with primary liver cancer and liver metastasis of other solid tumors.

Only 4 of oncological patients had neither cirrhosis nor liver neoplasm (primary or metastatic). One of those patients (ammonia lever 139 μg/dl) had prostate cancer and biliary stone disease. The other patient had nasopharinx cancer (ammonia lever 112 μg/dl) and urinary stasis. The remaining 2 oncological patients had normal ammonia levels. Thus we think that oncologic disease itself is not a cause for hyperammonia.

In our study 10 of the 23 oncologic patients recently undergone chemotherapy, their mean value of ammonia was 116,25 μg/dl (20,9-178). Of those 10 patients only 3 had neither cirrhosis nor liver neoplasm (primary or metastatic) and ammonia levels are 20,9- over cancer, 29-stomach cancer ve 112 μg/dl- nasopharinx cancer respectively. The patient who had nasopharinx cancer also had urinary stasis. Thus we think recent chemotheraphy itself is not a cause for hyperammonemia solely.

Hyperammonaemia induced by 5-FU is a distinct entity. The pathogenesis may be related to NH3 being a product of 5-FU metabolism, and possibly, to the direct inhibition of the Krebs cycle[10].

In our study 2 of the patients received 5-FU treatment according to patient files.

In the literature transplantation is considered to be a cause of hyperammonemia especially in bone marrow, liver, heart-lung transplant patients. In our study 2 renal transplant patients had hyperammonemia with ammonia levels being 116, 127 μg/dl respectively.

Epilepsy or patients who have seizure

Recent studies have shown that epileptic seizure alone may lead to high ammonia levels. Nakamura et al mentioned that high ammonia levels can be due to recent generalized convulsion and ammonia levels can be helpful when the patients present with decreased level of consciousness with an unknown cause. However, the mechanism of ammonia level increase in seizures remains unclear. Some studies have discussed that ammonia may be produced in the muscles because of hypercontraction at the time of convulsion[11,12].

Glutamine is the most abundant of all amino acids, it has the highest plasma concentration, and constitutes approximately 50% of the whole body free amino acid pool[13]. Glutamine serves as an obligatory fuel for intestinal and other rapidly dividing cells and plays an important role in the regulation of acid/base balance by providing the most important substrate for renal ammoniagenesis in many mammals[14]. Brain contains appreciable amounts of both glutamine synthetase and glutaminase[15]. Olde Damink SW et al stated that 'the normal brain is generally viewed as an organ of ammonia uptake and glutamine release'[4]. Tracer studies using 13N-ammonia have demonstrated that in the normal brain ammonia is rapidly incorporated in glutamine suggesting that cerebral ammonia detoxification is by the glutamine synthetase reaction[16]. In our study non cirrhotic patients who had either epilepsy or seizures had high mean ammonia levels; this may be a result of glutamine related ammonia metabolism. On the other hand, glutamine may have been released from muscle cells during convulsions too. More studies are needed about this subject.

Urinary problems

The kidneys play a principal role in waste nitrogen excretion. Also, renal glutamine and ammonia metabolism plays a key role in acid-base regulation[14]. With respect to both nitrogen excretion and acid-base equilibrium, the kidneys and liver interact in a very sophisticated manner.

The kidneys contain both glutaminase and glutamine synthetase and therefore, the kidneys are capable of both synthesizing and degrading glutamine[4].

In normal human, kidneys excrete only minor amounts of ammonia in the urine: 30% of total renal ammonia production is released into the urine, the remainder is released into the renal vein. These figures illustrate that the normal kidney is an organ of net ammonia addition to the body[4]. In our study hyperammonemia was seen with urinary obstruction which supports the hypothesis that urinary obstruction will cause hyperammonemia by causing backflow.

Increased catabolism / Patients who have starvation or oral intake difficulty

Conditions that increase muscle catabolism can lead to hyperammonaemia. Patients who are in catabolic state usually have additional problems like renal failure, urinary stasis or sepsis hence it is not easy to evaluate the effect of catabolism alone. In our study the noncirrhotic patients also had elevated ammonia levels but all of those cirrhotic patients had secondary disease that can cause hyperammonemia. Thus in our opinion it is not useful alone.

Portosystemic shunts/ thrombosis of hepatic or portal vein

Portosystemic venous shunts in cirrhotic patients can lead to hyperammonaemia and hepatic encephalopathy. In literature, noncirrhotic congenital portosystemic shunts, extrahepatic or intrahepatic, may also be responsible for hyperammonemia[5]. In our study 4 patient had prior portosystemic shunt due to cirrhosis. 3 of the cirrhotic patients in our study had hepatic and 3 had portal vein thrombosis.

Drug-induced hepatic encephalopathy

In our study 1 patient had hepatic encephalopathy and hyperammonemia after high dose paracetamol intake. In literature there are case reports or drug induced hyperammonemia with valproic acid, glycine, carbamazepine, ribavirin, sulphadiazine with pyrimethamine and salicylate use[5].

Limitations

Due to retrospective study design there was data loss. Some patients were subsequently excluded from the study before analysis due to incomplete ammonia level records.

Conclusions

Blood ammonia levels are useful in differential diagnosis of adult patients who present to ED with new or acute mental status changes of unknown cause. Ammonia levels may be elevated in noncirrhotic patients.

Urinary problems, epilepsy or seizure, starvation or oral intake difficulty can be the cause of hyperammonemia. Emergency physicians should be familiar with hyperammonemia causes other than cirrhosis in clinical practice.

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