

ASSOCIATION OF SERUM AMMONIA LEVELS WITH GRADES OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH DECOMPENSATED CHRONIC LIVER DISEASE

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ABSTRACT

Objective: To examine the association of serum ammonia with hepatic encephalopathy.

Material and Methods: This descriptive study was accomplished at Medical Unit A of Khyber Teaching Hospital, Peshawar from July to December, 2016. The study included 100 patients with viral hepatic encephalopathy. Serum ammonia levels were checked for every patient. SPSS version 23 was used for data analysis while taking P value of less than 0.05 as significant. The Spearman's correlation test was run to assess any association of serum ammonia with the grade of hepatic coma.

Results: Out of 100 total patients, 12 (12%) presented in grade 1 hepatic encephalopathy, 39 (39%) in grade 2 hepatic encephalopathy, 34 (34%) in grade 3 encephalopathy and 15 (15%) in grade 4 encephalopathy. The serum ammonia levels of these patients widely ranged between 14 and 178 mcg/dl, at the mean values of 74.17 mcg/dl in grade I, 57.79 mcg/dl in grade II, 71.88 mcg/dl in grade III, and 81.13 mcg/dl in grade IV hepatic encephalopathy. The spearman correlation was 0.097.

Conclusion: Increasing serum ammonia levels were not related to higher grades of hepatic encephalopathy.

Key Words: Serum ammonia, hepatic encephalopathy, cirrhosis.

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INTRODUCTION

Hepatic encephalopathy is a sequel of decompensated chronic liver disease. There are various parameters to ascertain the grades of hepatic encephalopathy; serum ammonia level is one of them. The serum ammonia levels have been considered directly related to the gravity of hepatic encephalopathy, but it is very usual to find normal levels in patients with higher grades of encephalopathy and vice versa. In view of this, we proceeded with a study to examine the association of serum ammonia with hepatic encephalopathy. Decompensated cirrhosis complicates into hepatic encephalopathy in a majority of its affectees. It manifests in the form of neuropsychiatric abnormalities like changes in personality, behavior, sensorium, cognition

and so forth.¹ Hepatic encephalopathy is diagnosed when other potential causes of similar presentation are excluded.²⁻⁴ The toxins nominated in the pathogenesis of hepatic coma include; ammonia, manganese, short-chain fatty acids, mercaptans, gamma amino-butyric acid and many others.⁵⁻⁸ Liver is the usual and chief site of removing excess ammonia from the body through its conversion into urea. In the setting of acute or chronic liver failure, this role is taken over by astrocytes of the brain, which in return get swollen, causing cerebral edema and altered mental status.^{9,10}

Although, the link between hepatic encephalopathy and hyperammonemia has been studied previously, the statistics were controversial. Moreover, there is a relative scarcity of such studies at the national level. As chronic liver disease is one of the leading causes of hospitalization in Pakistan, this study will focus on surfacing the true link between hepatic encephalopathy and serum ammonia in patients with chronically failed liver.

MATERIAL AND METHODS

This cross-sectional study was conducted in Medical Unit A of Khyber Teaching Hospital from July

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2016 to December 2016. Approval was taken from the Hospital Ethical Committee before recruiting patients into the study. The study comprised of adult patients of either gender admitted with hepatic encephalopathy secondary to viral Hepatitis B or C. Informed written consent was obtained from every participant. Moreover, patients who had encephalopathy due to other medical conditions e.g. uremia / toxic metabolites, hypertension, hypoxia, stroke, encephalitis, brain trauma, Wernicke's encephalopathy, Hashimoto's encephalopathy and psychiatric disturbances were excluded from the study.

Hepatic encephalopathy was diagnosed on the basis of direct or collateral history followed by clinical examination and assessment. Patients were stratified into different grades of hepatic coma by using West-Haven Classification System of hepatic encephalopathy. Each such participant had his/her serum ammonia level measured on admission. Normal serum ammonia levels were taken as 15-42 mcg/dl.

Data was analyzed by using SPSS version 23. Frequencies and percentages were calculated for categorical variables like gender, age groups, and causes of liver cirrhosis and grades of hepatic encephalopathy. Median and inter-quartile range were determined for the continuous variables such as ammonia level and

disease duration etc. Finally, the Spearman's correlation was run to identify the link between ammonia levels and the level of hepatic encephalopathy. A p-value of <0.05 was taken as criterion standard.

RESULTS

Out of 100 total patients, 63 (63%) were males and 37 (37%) were females. A total of 13% were aged ≤ 40 years, 31% aged between 41-50 years, 42% between 51-60 years, and 14% aged > 60 years with a mean age of 51.62 ± 8.60 . Demographic characteristics with grades of hepatic encephalopathy is shown in Table 1. Among patients recruited in the study, 28% had duration of liver cirrhosis less than or equal to 2 years, 39% had cirrhosis ranging from 3 to 4 years and 33% had cirrhosis for greater than 4 years with a mean duration of liver cirrhosis of 3.69 ± 1.77 . 12% (12%) patients presented in grade 1 hepatic encephalopathy, 39 (39%) in grade 2 hepatic encephalopathy, 34 (34%) in grade 3 encephalopathy and 15 (15%) in grade 4 encephalopathy. Nine (9.0%) patients were Hepatitis B positive and 91 (91%) patients were hepatitis C positive. The serum ammonia levels of these patients widely ranged between 14 and 178 mcg/dl with a mean \pm SD of 68.05 ± 38.64 . However no association of increasing encephalopathy grades was seen with rising serum ammonia levels, as

Table 1: A comparison of the clinical characteristics of the patients and hepatic encephalopathy

Characteristics	Grade of Hepatic Encephalopathy			
	Grade-I n (%)	Grade-II n (%)	Grade-III n (%)	Grade-IV n (%)
Gender				
Male	4 (4.0%)	26 (26.0%)	23 (23.0%)	10 (10.0%)
Female	8 (8.0%)	13 (13.0%)	11 (11.0%)	5 (5.0%)
Age (years)				
≤ 40	1 (1.0%)	3 (3.0%)	7 (7.0%)	2 (2.0%)
41-50	4 (4.0%)	15 (15.0%)	10 (10.0%)	2 (2.0%)
51-60	6 (6.0%)	14 (14.0%)	12 (12.0%)	10 (10.0%)
> 60	1 (1.0%)	7 (7.0%)	5 (5.0%)	1 (1.0%)
Duration of Liver Cirrhosis (years)				
≤ 2	4 (4.0%)	11 (11.0%)	10 (10.0%)	3 (3.0%)
3-4	4 (4.0%)	15 (15.0%)	13 (13.0%)	7 (7.0%)
> 4	4 (4.0%)	13 (13.0%)	11 (11.0%)	5 (5.0%)

Table 2: An overview of the serum ammonia levels, grade of hepatic coma and the Spearman's correlation statistics

Grade/Correlation	Result		
Grade	Ammonia level, mcg/dl (Median)	Interquartile Range	Mean Ammonia levels \pm SD
Grade I	70.5	63.3	74.17 \pm 42.23
Grade II	55	39	57.79 \pm 29.75
Grade III	65	52	71.88 \pm 39.37
Grade IV	68	74	81.13 \pm 50.55
	Correlation Coefficient (r_s)	P-value	
Spearman correlation	0.097	0.338	

evidenced from the following tables. Results of Spearman's correlation showed that there was no significant connection between ammonia levels and grades of hepatic encephalopathy ($r_s = 0.097$, $P = 0.338$), as evident in Table 2.

DISCUSSION

Serum ammonia is primarily the end-product of protein degradation in the body. The bulk of such degradation of proteins takes place in the small intestine in the presence of an enzyme called 'urease'.¹¹⁻¹³ The ureases which are secreted by the gut microbiota, are responsible for the protein catabolism into ammonia and carbon dioxide. The resultant ammonia is circulated into the liver via the portal venous system where it is rapidly detoxified by the hepatocytes. The hepatocytes do this by converting more toxic ammonia into non-toxic urea, which is readily excreted by the kidneys.¹⁴⁻¹⁷

As is understandable that, liver is the chief organ of scavenging ammonia from the body, hyperammonemia will quickly develop, when liver fails.⁷ However, high ammonia in circulation can be a result of high protein diet, parental nutrition, congenital defects in the urea cycle or drugs like sodium valproate.^{6,18-20} Ammonia can readily diffuse across the blood-brain barrier so most of the times, serum ammonia correlates well with its level in the cerebrospinal fluid (CSF). Hence, in any situation where there is high ammonia level in the blood, a similar higher value for ammonia is expected in the brain. However, unfortunately the brain is very sensitive to the toxic effects of ammonia and as a result, cerebral edema may rapidly develop. When this happens, the affected patient manifests in the form of irritability, slurring of speech, reversal of sleep-awake cycle, flapping tremor, confusion, stupor or even deep coma.²¹⁻²³

In the context of a suitable clinical scenario, measuring serum ammonia level is of little value. However, if any doubts exist, serum ammonia assay is recommended by different authorities.⁶⁻⁸ It is noteworthy that, despite the popularity of serum ammonia as a diagnostic or prognostic indicator, recent studies questioned its usefulness. This is because serum ammonia is not always higher in patients with hepatic coma and may cause unnecessary confusion and may affect patient's management plan.⁷⁻⁸ As can be seen, our study did not show a significant correlation between serum ammonia and the severity of hepatic encephalopathy in chronic decompensated liver failure. Nevertheless, the efficacy of serum ammonia level as a marker of diagnosis in acute fulminant liver failure was found to be more than acute-on-chronic or chronic liver failure.⁹⁻¹¹ Ong JP concluded that, as much as 69% of patients had high ammonia levels, but in the absence of any clinical evidence of hepatic coma.¹² These data consolidate our observations further.

It must be noted that, in patients with high ammonia levels but in the absence of relevant clinical evidence of liver disease, alternative diagnoses must

always be considered. One such example is that of Wernicke encephalopathy, which can be a potential alternative diagnosis in alcoholic patients, irrespective of whether they do or do not have an accompanying liver disease.^{13-14,24} Similar recommendations were made in another study where serum ammonia level was not found to be associated with the worsening grade of hepatic coma.²⁵

Considering the limitations of the usefulness of serum ammonia as a marker of diagnosis or prognosis in patients with chronically failed or failing liver; Ong JP recommended a comprehensive laboratory panel including both venous and arterial ammonia along-with other parameters like international normalized ratio (INR), serum creatinine and serum bilirubin. Ong JP emphasized on the interpretation of all the parameters together, rather than using serum ammonia alone as a guide to diagnosis or treatment.¹²

It is worth mentioning that our study demonstrated no association between serum ammonia and the severity of hepatic encephalopathy. This adds further to the pre-existing controversy regarding the utility of blood ammonia assay in the diagnosis or prognosis of hepatic coma.

Despite the useful information produced by our study, there are few shortcomings. One of the limitations of our study was a smaller sample size. Secondly, patients with acute fulminant liver failure were not studied. Thirdly, we relied on a single ammonia level on admission rather than serial readings throughout the hospital stay of the patients. Furthermore, being a simple descriptive study is another limitation and randomized controlled trials are needed to verify/negate these findings. Therefore, in order to arrive at more comprehensive conclusion, we would recommend further studies in future and would suggest bigger sample size, randomized controlled trials and serial ammonia assays rather than a single reading.

CONCLUSION

We conclude that, there is enough evidence of declaring no association between serum ammonia, and the severity of hepatic encephalopathy in patients with end-stage liver disease. However, for our better understanding, we would recommend further studies incorporating bigger sample sizes and randomized control trials in future

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

- Khan WM:** Idea of article abstract.
Badshah A: Data collection results discussion writing.
Haider I: Discussions writing ,
Khan A: Literate Search.
Ajmal F: Literate Search.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.