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Is measuring serum ammonia helpful in patients with liver cirrhosis?

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ABSTRACT

Background. Ammonia has been traditionally viewed as one of the main culprits for the development of hepatic encephalopathy. In the setting of liver cirrhosis or portal-systemic shunting, hepatocytes fail to metabolize ammonia, and thus excess ammonia reaches the systemic circulation, and from there, the brain.

Material and methods. We performed a descriptive study involving 28 adult patients with liver cirrhosis. None of the patients had overt hepatic encephalopathy at the time of assessment, as judged by the West Haven criteria. Severity of liver cirrhosis was measured through the Child-Pugh and MELD scores. Serum ammonia was measured by venous sampling.

Results. Mean age of the patients was 50±10 years-old. There were 68% males (n=19). Mean MELD score was 17±5 points. Mean Child-Pugh score was 8±2 points. Mean serum ammonia level was 76±37 µmol/L (range: 34-204 µmol/L). Serum ammonia levels correlated significantly with both scores of liver disease severity, more so with MELD (R=0.61, p=0.0005), than with the Child-Pugh score (R=0.38, p=0.04)

Conclusions. We reaffirm the importance of measuring blood ammonia in patients with liver cirrhosis, since it is a helpful biomarker which correlates with liver disease severity and hepatic encephalopathy.

Keywords: serum ammonia, hepatic encephalopathy, liver cirrhosis, venous ammonia

Abbreviations (in alphabetical order):

CT – Computer Tomography
HBV – Hepatitis B Virus
HCV – Hepatitis C Virus
HDV – Hepatitis D Virus
HE – Hepatic Encephalopathy
INR – International Normalized Ratio
MELD – Model for End-stage Liver Disease
MRI – Magnetic Resonance Imaging

INTRODUCTION

Ammonia (NH3) is a colorless irritant gas produced in the human body (during several metabolic reactions which involve nitrogen-containing amino-acids), and also in the human gut (by the actions of urease-containing bacteria on dietary proteins) [1-3]. The normal serum ammonia level in a normal adult is between 15-45 micrograms per deciliter. Other authors have given an interval between 11-50 µM [4]. Normally, ammonia produced in the human gut is absorbed into the portal blood and reaches the liver, where it is converted into urea by the urea cycle. Urea (which is hydro-soluble) can then be excreted by the kidneys [5]. However, in the setting of liver disease or portal-systemic shunting, hepatocytes fail to metabolize ammonia to urea, and thus excess ammonia reaches the systemic circulation, and from there, the brain [3].

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MATERIAL AND METHODS

We performed a descriptive study involving 28 adult patients with liver cirrhosis at the Gastroenterology and Hepatology Department of Fundeni Clinical Institute. None of the patients had overt hepatic encephalopathy at the time of assessment, as judged by the West Haven criteria for hepatic encephalopathy. All patients were evaluated through abdominal ultrasound plus either abdominal CT scan or abdominal MRI. Laboratory workup included serum albumin, total serum proteins, fibrinogen, INR, prothrombin time, aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, conjugated bilirubin, urea, creatinine, uric acid, sodium, potassium, serum glucose, total cholesterol, serum triglycerides, complete blood count and, of course, serum ammonia (measured in venous blood). Severity of liver cirrhosis was measured through the Child-Pugh and MELD scores. All available data (laboratory results, discharge papers) were collected through the hospital's medical database Hipocrate. Collection and processing of the data was achieved by using Microsoft Office 2016. Statistical analysis was done with MedCalc statistical software version 20.218.

RESULTS

Mean age of the patients was 50±10 years-old. There were 68% males (n=19). Mean MELD score was 17±5 points (range: 7-30 points). Mean Child-Pugh score was 8±2 points (range: 5-12 points). The most common etiology for liver cirrhosis was HCV (n=11), followed by HBV ± HDV (n=9) and alcoholic liver disease (n=5). The remaining three patients had: primary biliary cirrhosis (n=1), autoimmune hepatitis (n=1) and drug-induced hepatitis (n=1). Mean disease duration between diagnosis and current assessment was 5±5 years (range: 0-18 years). Obviously, there was a strong correlation between both scores of liver disease severity (R=0.76, p<0.0001). Mean serum ammonia level was 76±37 µmol/L (range: 34-204 µmol/L). Serum ammonia levels correlated significantly with both scores of liver disease severity, more so with MELD (R=0.61, p=0.0005), than with the Child-Pugh score (R=0.38, p=0.04) (see Figure 1 and Figure 2).

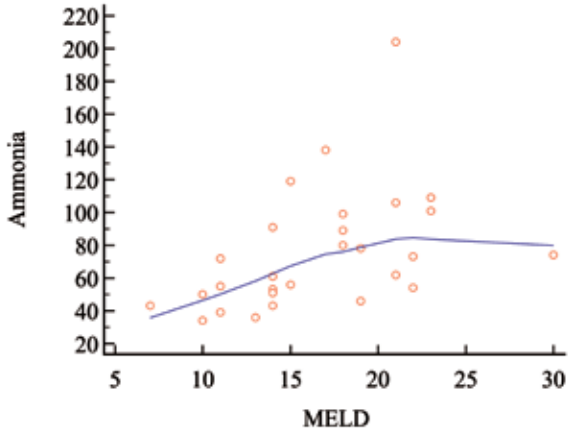

FIGURE 1. Positive correlation between serum ammonia concentrations and MELD scores in our patients

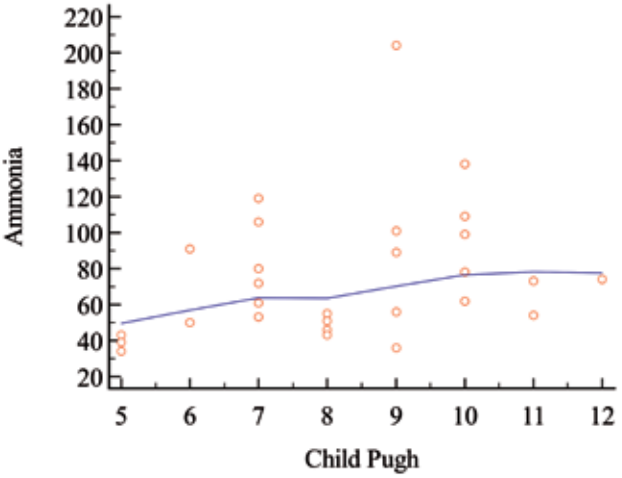

FIGURE 2. Positive correlation between serum ammonia concentrations and Child-Pugh scores in our patients

Mean platelet count was 82500 ± 42937 platelets/µL (range: 25000 – 165000 platelets/µL), with only three patients having a platelet count within normal range. Hence, most of the patients had thrombocytopenia due to hypersplenism. Serum ammonia did not correlate with platelet count (R=0.008, p=0.96). No correlation was found between levels of ammonia and other laboratory parameters, as judged by using the Spearman correlation coefficient, apart from the INR (Table 1). Serum ammonia did not correlate with disease duration (R=-0.369, p=0.053).

TABLE 1. Correlation between levels of serum ammonia and those of other laboratory parameters.

Blood parameter	Mean values in our patients	Correlation coefficient with ammonia	Significance level (p value)
Albumin	3 ± 0.6 g/dL	-0.33	0.08
Total bilirubin	3.5 ± 2.8 mg/dL	0.34	0.07
Creatinine	0.74 ± 0.24 mg/dL	0.24	0.22
Sodium	137 ± 5 mEq/L	-0.46	**0.01**
INR	1.55 ± 0.29	**0.56**	**0.001**

DISCUSSIONS

Ammonia has been traditionally viewed as one of the main culprits for the development of hepatic encephalopathy (HE). Indeed, the neuropathological changes seen in the brains of patients with hepatic encephalopathy (e.g., Alzheimer type II astrocytosis)

are similar to those seen in patients with inherited hyperammonemia [6]. Moreover, it is known that hepatic encephalopathy can develop (or worsen) in patients with liver cirrhosis after consuming an excess of dietary proteins or after an episode of gastrointestinal hemorrhage [3]. The traditional view is that ammonia should be measured from arterial blood. However, studies have shown that venous blood might suffice for measuring ammonia levels. In the study performed by Nicolao et al, both types of ammonia (arterial and venous), were higher in cirrhotic patients with HE than in both controls and cirrhotic patients without HE. Moreover, both types of serum ammonia correlated similarly with the severity of hepatic encephalopathy [7]. These results are consistent with those published by Ong et al, who also found that each type of serum ammonia (arterial and venous) increased with the degree of HE. Their conclusion was that venous sampling is adequate for ammonia measurement [8]. The fact that ammonia levels do not always reflect the severity of HE, can be explained by individual differences in ammonia metabolism and by differences in the accuracy of ammonia assays and interpretation of results in the laboratory [9]. Also, serum ammonia levels do not actually tell us how much ammonia enters the brain, since the blood-brain barrier is altered in patients with hepatic encephalopathy [10]. This would explain why patients with seemingly normal levels of ammonia develop hepatic encephalopathy. For example, in the study performed by Qureshi et al, most of the patients with normal ammonia levels were in HE grades I-II, but there were also a few with grade III and one patient was in grade IV. Conversely, the majority of patients with moderate or high hyperammonemia were in grades III-IV of HE, but a few had only grade I-II [11]. Measuring the partial pressure of ammonia in arterial blood (pNH3) was shown by Kramer et al to correlate better with the degree of clinical and electrophysiologic abnormalities seen in HE, as compared to serum ammonia [12]. Other papers however, such as the ones written by Nicolao et al and Ong et al, have failed to confirm this.

There is also the possibility of measuring ammonia levels in the cerebrospinal fluid (CSF), either through the indophenol direct method, or through the enzymatic method. If the indophenol direct method is used, the CSF can be stored in the refrigerator (at 4º C) and ammonia determinations can be performed within two days [13]. In healthy subjects there is no apreciable ammonia in the CSF, however in patients with liver cirrhosis, abnormal elevations of serum ammonia are accompanied by elevations of ammonia in the CSF [14]. Moore et al have found that the CSF ammonia is linearly related to arterial ammonia, irrespective of the pH gradient between the blood and CSF. They concluded that the distribution of ammonia between blood and CSF probably follows the nonionic diffusion theory [15].

In recent years, other potential biomarkers for HE have emerged, one example being 3-nitro-tyrosine which was studied in conjunction with minimal hepatic encephalopathy. In one study, the levels of 3-nitro-tyrosine at a cut-off value of 14 nM, correlated with the presence of minimal hepatic encephalopathy, with good sensitivity (89%) and specificity (93%) [16]. In another study, 3-nitro-tyrosine was increased in patients with minimal hepatic encephalopathy (as diagnosed by the Psychometric hepatic encephalopathy score) and correlated with impaired driving ability [17].

CONCLUSIONS

We acknowledge that the diagnosis of hepatic encephalopathy is mainly a clinical one, but reaffirm the importance of measuring blood ammonia in patients with liver cirrhosis, since it is a helpful biomarker which correlates with liver disease severity and hepatic encephalopathy.

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