

Is There a Correlation Between Glasgow Coma Scale Score and Simultaneous Arterial Blood Ammonia Level in Hepatic Encephalopathy?

Hepatik Ensefalopatide Glasgow Koma Skala Skoru ve Eş Zamanlı Arterial Kan Amonyak Düzeyi Arasında Bir Korelasyon Var mı?

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ABSTRACT Objective: It has been reported that there is a good correlation between the degree of the hyperammonemia and the depth of coma in hepatic encephalopathy (HE), a neurobehavioral disorder. The Glasgow coma scale (GCS) has been used widely to evaluate brain dysfunction due to structural and metabolic disorders. We would like to determine whether there is an inverse correlation between the GCS score and simultaneous blood ammonia level in patients presenting with HE. **Material and Methods:** This retrospective clinical study includes 27 patients presenting with HE in emergency department (ED). On admission, all patients had a full neurological examination including the GCS, followed with obtaining simultaneous arterial blood ammonia level. **Results:** Mean GCS score was 10.1±3.7. Mean level of arterial blood ammonium was 291±175 µg/dL. There was a negative correlation between the GCS scores and blood ammonium levels ($r = -0.641$; $p < 0.001$). **Conclusion:** Our results have shown that the GCS may be used to estimate arterial blood ammonia levels in patients with HE (Regression coefficient of -0,956).

Key Words: Hepatic encephalopathy; Glasgow coma scale; ammonia

ÖZET Amaç: Biz hepatik ensefalopati (HE) ile başvuran hastalarda Glasgow koma skala (GKS) skoru ile eş zamanlı olarak elde edilen kan amonyak düzeyi arasında ters (negatif) bir korelasyon olup olmadığını belirlemek istedik. **Gereç ve Yöntemler:** Bu geriye dönük klinik çalışma acil poliklinikte tanı almış HE'li 27 hastayı içermektedir. Başvuru sırasında hastaların GKS'ını da içeren tam bir nörolojik muayenesi yapıldı ve hemen takiben amonyak düzeyini belirlemek için arterial kan örneği alındı. **Bulgular:** Ortalama GKS skoru 10.1±3.7 idi. Ortalama arterial kan amonyak düzeyi 291±175 µg/dL idi. Glasgow koma skala skorları ile eş zamanlı olarak elde edilmiş arterial kan amonyak düzeyleri arasında istatistiksel olarak anlamlı negatif bir korelasyon vardı ($r = -0.641$; $p < 0.001$). **Sonuç:** Bulgularımız acil poliklinikteki HE'li hastalarda GKS skorunun arterial kan amonyak düzeylerini tahmin etmede kullanılabileceğini göstermektedir (Regression coefficient of -0,956).

Anahtar Kelimeler: Hepatik ensefalopati; Glasgow koma skalası; amonyak

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Hepatic encephalopathy (HE) is a neurobehavioral problem characterized by depressed level of consciousness, cognitive impairment, and personality changes induced by circulating neurotoxic substances that have bypassed normal hepatic detoxification because of diversion of portal blood flow into the systemic circulation.^{1,2} In the patients with HE, clinical manifestations range from subtle abnormalities to coma.^{1,3}

Hepatic encephalopathy most commonly occurs in the setting of liver cirrhosis or in those who have undergone portocaval shunt surgery.² In pathogenesis of HE, ammonia has an essential role and influence on the brain functions with several different mechanisms such as causing a depletion of ATP and astrocyte swelling resulted in edema in the brain.^{1,4-8} In the patients with HE, developed brain edema has also a risk of cerebral herniation.⁹ It has been reported that arterial ammonia of >150 mmol/L in patients with stage III/IV encephalopathy places the patient at risk of cerebral herniation, a risk that is considerably higher with values >200 mmol/L.⁹

Although the Glasgow coma scale (GCS) has not been rigorously evaluated in patients with HE, its widespread use in structural and metabolic disorders of brain function justifies its application in acute and chronic liver disease.⁶ It has been known that the level of consciousness is an essential part of staging classifications used in patients with HE and it is consistent with the steps of clinical stage.^{10,11} It has been reported that although the 'West Haven criteria' is a specific staging classification of altered mental state in liver injury, the GCS is a useful staging system as well.¹² Although, it has been reported that there is no linear correlation between blood ammonia level and HE grade¹², it has also been reported that blood ammonia levels correlate with the severity of HE.^{4,5,13} Therefore, this relationship is still controversial.^{1,4-6,12-14} In the literature, there are few studies regarding that the scores of the GCS may be increased by a therapy decreasing serum ammonia level of patients with HE.^{15,16} Therefore, it may be useful to use the GCS score in estimating blood ammonia level and in determining the degree of coma in HE. To our knowledge, in the literature, there are not any studies investigating whether there is a correlation between the GCS score and simultaneous blood ammonia level.

In this study, we would like to determine whether in patients presenting with HE, the GCS can be used to estimate arterial blood ammonia levels, hence, there is an inverse correlation between the GCS score and simultaneous blood ammonium level.

MATERIAL AND METHODS

This retrospective study was approved by the Local Ethics Committee of our University, as appropriate to the ethical principles in the Declaration of Helsinki.

This clinical study consists of 27 patients admitted with HE in ED.

Inclusion criteria included: (1) the patients having a history of chronic hepatic failure; (2) the patients aged 18 years or older; and (3) the patients with no history of other causes of altered mental status.

Exclusion criteria were as follow: (1) the patients with any focal neurological deficits; (2) the patients who had any abnormal biochemical findings (e.g. increased creatinine, uremia, hyponatremia, hypernatremia, hypoglycemia, hyperglycemia, hypocalcemia, hypothyroid etc.) other than elevated ammonia level, contribute to altered mental status; (3) the patients who were observed any abnormal cranial computed tomography (CT) findings (except for brain edema due to elevated ammonia); (4) the patients exhibiting the signs of infection (increased body temperature with elevated blood leukocyte count), and (5) all kind of acute liver failure. In the study, the cut-off values of routine biochemical parameters which may produce neurological symptoms included: sodium <130 mEq/L and >150 mEq/L; calcium <7 mg/dL and >12 mg/dL; creatinine >3 mg/dL; blood urea nitrogen >30 mg/dL; and glucose <45 mg/dl and >350 mg/dL.

Of the patients, admission diagnosis (main complaint) was altered mental status, and hospital discharge diagnosis was hepatic encephalopathy. The patients presenting with an altered mental status were evaluated by clinical and laboratory examinations for the differential diagnosis of HE.

The diagnosis of HE was based on the presence of altered mental status, with depressed level of consciousness in a setting of chronic hepatic failure.^{1,5}

On admission, all HE patients had a full neurological examination followed by a taking blood for the simultaneous measurement of arterial am-

monia. The Glasgow Coma Scale was used in the neurological evaluation of cerebral dysfunctions in the patients.¹⁷

All patients received an effective therapy to decrease elevated blood ammonia, immediately after obtaining blood samples for the determination of ammonia level.

In our laboratory, Cobas Integra® 800 systems automatically calculate the ammonia concentration of each sample. Measurement of total ammonia levels was performed by using a Cobas Integra ammonia kit for blood (Cobas Integra® 800) with a normal 19-88 µg/dL in female; 25-94 µg/dL in male.

The clinical and laboratory examinations and treatments of the patients were written on the specific cards. At the end of the study, all data were reevaluated to statistical analysis.

Spearman correlation analysis was applied to determine whether or not there is a correlation between the GCS scores and arterial blood ammonia levels obtained from patients on admission. Additionally, the linear regression method was used to estimate ammonia levels from GCS after logarithmic transformation.

The results were analyzed using the computer software (SPSS, version 15.0). A $p < 0.05$ was considered statistically significant.

RESULTS

During a period between December 2001 and May 2006, about 50 patients presented to the hospital with a hepatic failure associated with altered mental status. Of these, about 35 were with chronic hepatic failure; however, only 27 met the criteria of our study mentioned above.

Mean age was 55.8 ± 16.3 years (range, 24 to 78).

Of 27 HE patients, 15 were male and 12 were female.

All of the patients had a history of liver cirrhosis and their clinical findings were consistent with liver cirrhosis such as vascular spiders, ascites, clubbing, abdominal wall vascular collaterals, gynecomastia, hepatomegaly, jaundice, nail changes, palmar erythema, and scleral icterus.

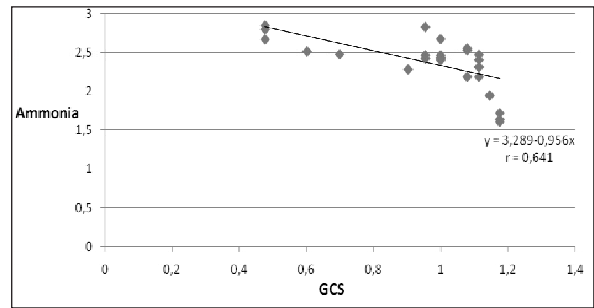


FIGURE 1: The correlation between the GCS scores and arterial blood ammonia levels obtained on admission.

Mean GCS score was 10.1 ± 3.7 , with a range of 3 to 15.

Mean level of arterial blood ammonia was 291 ± 175 µg/dL, with a range of 40 to 706 (N: 19-88 µg/dL in female; 25-94 µg/dL in male).

There was a negative correlation between the GCS scores and blood ammonium levels obtained on admission ($r = -0.641$; $p < 0.0001$) (Figure 1).

Regression analysis revealed a linear relation between the GCS scores and blood ammonium levels (the regression coefficient = -0.956 ; $p < 0.0001$).

DISCUSSION

In the pathogenesis of HE, elevated ammonia plays a central role.^{1,4-6} The blood-brain barrier permeability to ammonia is increased in patients with HE.¹⁸ As a result, in these patients, brain edema may develop.⁶⁻⁸ The main causes of brain edema are increased intracellular osmolarity and glutamate levels during the change to glutamine of ammonia as a result of elevated brain ammonia.⁶⁻⁸ However, other mechanisms such as false neurotransmitters (e.g. octopamine), displacing nor-epinephrine and dopamine, after the metabolism of ammonia into astrocytes, and the excesses of neurotoxins other than ammonia such as mercaptans (e.g. methanethiol) and short-chain fatty acids, uncoupling oxidative phosphorylation, altering the mitochondrial respiratory state, and inhibiting the urea cycle that may lead to hyperammonemia have also been implicated in the pathogenesis of HE.^{4,5,19} Additionally, during the removal of brain ammonia depending on the formation of glutamine, a reacti-

on that is catalyzed by the ATP- dependent enzyme glutamine synthetase, which is localized in the astrocytes, increased brain ammonia leads to a depletion of ATP in the midbrain ARAS.^{4,5} It has been reported that cerebral blood flow and glucose metabolism reduced in the cingulate gyrus, an important element in the attentional system and frontal and parietal association cortices of patients with over grade 1 encephalopathy.⁵ Also hyperammonemia leads to an increase in the GABA activity in the cerebral cortex, with increased in expression of peripheral-type benzodiazepine receptors.^{1,4,5} Besides, there are significant alterations in cerebral serotonin and dopamine metabolism.⁵ It has been reported that there is also a reduction in postsynaptic glutamate receptors of the N-methyl-D-aspartate type.⁵

In the literature, the correlation of blood ammonia levels with the clinical severity of HE is still controversial.^{1,4-6,12-14,20} Blei et al. have reported that the correlation of blood ammonia levels with mental state in cirrhosis is inaccurate.⁶ Wright and Jalan have been reported that there is no linear correlation between arterial ammonia level and the clinical grade of HE.¹² However, other authors have suggested the presence of this correlation in HE.^{4,5,13,20} Kundra et al. have reported that in patients with acute liver failure, not in those chronic, there seems to be a significant correlation between the severity of encephalopathy and blood ammonia level.¹⁴ However, authors suggested that although different between the two groups was not significant statistically, in chronic liver failure patients with HE were found to have a higher plasma ammonia level, compared to those without HE.¹⁴ In their study, venous samples were used for the determination of plasma ammonia level in contrast to our study. Ong et al prospectively evaluated the correlation between blood ammonia levels and the clinical severity of HE in 121 patients with liver cirrhosis and found a strong correlation.²⁰ Authors obtained from patients with grade 3 or 4 encephalopathy the highest total ammonia levels.²⁰ On the other hand, it has been known that the scores of the GCS may be increased by a therapy decreasing

blood ammonia level of patients with HE. In the literature, there are a few studies regarding the use of the GCS in the neurological evaluation of the patients with HE.^{14,16} Hawkes et al. have reported three cases with HE.¹⁶ Authors observed that these cases had initially the elevated concentrations of ammonia and the lower scores of GCS; however after treatment, they displayed the normal levels of consciousness and ammonia.¹⁶ Huang et al. reported eight acute liver failure patients with HE who were administered liver dialysis treatment.¹⁵ Authors used the GCS score and cerebral blood flow to follow improving from HE of the patients with treatment.¹⁵ They demonstrated that after the initial treatment, consciousness levels measured by the GCS improved from a pre-treatment median of 5 (range 3 to 6) to a post-treatment median of 7 (range 5 to 9).¹⁵ On the other hand, elevated arterial levels of ammonia have been associated with an increased risk of cerebral herniation.⁹ This association may point to a parallelism between the degree of brain edema and blood ammonia level. Kundra et al. suggested that high blood ammonia levels in acute liver failure patients appeared to correlate with clinical features of cerebral edema and raised intracranial tension.¹⁴

In the present study, we found a negative correlation between the GCS scores and arterial blood ammonia levels obtained on admission. This result may point to that increased arterial ammonia level has a correlation with the GCS, in contrast to HE grade. This status may be attributed to effecting the level of consciousness rather than mental functions of the elevated blood ammonia. Additionally, we demonstrated the presence of different blood ammonia levels in the patients with similar GCS score. These results may associate with special status of the patient during drawing blood sample. For example, in hyperactive HE patients, muscle contractions can cause the release of ammonia in blood.²¹

Limitations of the present study include the lack of a control group without chronic hepatic failure, the relatively small number of cases, and its retrospective design.

CONCLUSION

Our results have shown that in patients with HE, there is a negative correlation between the GCS scores and blood ammonia levels. With this correlation, it can say that elevated blood ammonia is associated with lower GCS and the GCS may be used to estimate arterial blood ammonia levels, in con-

trast to clinical grading. Further prospective studies are needed to support these results. Additionally, we agree with Wright and Jalan that the GCS may be useful in evaluating the stages of HE.¹²

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