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Sodium and Calcium Levels as a Predictor for Hepatic Encephalopathy in Pediatric Patients with Chronic Liver Disease

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Abstract

Background: Chronic liver disease (CLD) in children is a growing health problem with significant morbidity and mortality. There is a specific susceptibility to electrolyte imbalance in chronic liver disease patients that can deteriorate their condition to hepatic encephalopathy. The aim of this study is to evaluate the electrolyte disturbance in CLD patients with and without hepatic encephalopathy.

Methods: This cross-sectional study was conducted in Ghaem Hospital, Mashhad University of Medical Sciences, Iran, during a six-year period. All patients below 14 years of age with chronic liver disease admitted to the pediatric gastroenterology department were included. Demographic data, laboratory tests, clinical manifestations and presence of hepatic encephalopathy were recorded in a checklist for each patient. Data was entered in SPSS software version 20. Qualitative data were analyzed using chi-square, and quantitative data were analyzed using independent t-tests. A P-value <0.05 was considered significant.

Results: Our study on 85 CLD patients showed that the serum sodium level and serum calcium level were significantly lower in patients with hepatic encephalopathy with P-Values of 0.001 and 0.02, respectively. Also, serum urea and bilirubinemia levels were significantly higher in the patients with hepatic encephalopathy with P-Values of 0.03 and 0.001 respectively.

Conclusion: It seems that reducing serum sodium and calcium level can be predictive of hepatic encephalopathy in pediatric patients with chronic liver disease.

Key Words: Calcium, Chronic Liver Disease, Pediatrics, Sodium.

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1- INTRODUCTION

Chronic liver disease (CLD) in children is a growing health problem with significant morbidity and mortality (1). CLD is defined as a clinical and laboratory disturbance of liver's function that lasts more than six months. There are different etiologies for CLD in children, including a broad spectrum of infections, developmental abnormalities, autoimmune hepatitis, and metabolic disorders, resulting in hepatic dysfunction and cirrhosis [2, 3). Patients with CLD suffer from various organ problems, such as cardiovascular, renal, respiratory, and neurological involvement (3-5). Thus, there is a specific susceptibility to electrolyte imbalance in CLD patients that can further deteriorate their condition.

This study aimed to ascertain the electrolyte disturbance in CLD patients with and without hepatic encephalopathy.

2- MATERIALS AND METHOD

This cross-sectional retrospective study was carried out in the pediatric gastroenterology department of the Ghaem Hospital, Mashhad University of medical sciences, Iran, in six years. All CLD patients below 14 years of age admitted to the pediatric gastroenterology department were included in the study. The presence or absence of hepatic encephalopathy was recorded for each patient. CLD was defined as a known history of liver disease for more than six months or the physical stigmata of CLD (failure to thrive, clubbing, palmar erythema, caput medusa, spider telangiectasia, and hepatosplenomegaly). The presence of hepatic encephalopathy was defined as a brain dysfunction caused by liver insufficiency proven by synthetic liver dysfunction (INR>1.1 IU and albumin<3 mg/dl) manifesting as a broad spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.

The Ethical Committee of Mashhad University of Medical Sciences approved the study's protocol. Data including the demographic information, etiology of CLD, reason for hospitalization, number of hospitalization days, underlying diseases, the interval between the onset of symptoms and the diagnosis, presence or absence of hepatic encephalopathy, frequency of mortality and infection, history of constipation, gastrointestinal bleeding, and laboratory findings (complete blood cell, blood sugar, blood culture, sodium, potassium, urea, creatinine, albumin, calcium, phosphor, prothrombin time, partial thromboplastin time, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin total and direct) were recorded in a checklist from the patients' files. The files were extracted from the hospital's archive with the following keywords: Cirrhosis,Hepatic encephalopathy,Galactosemia,Tyrosinemia /Bile duct atresia/Glycogen storage disease/Wilson/Hemochromatosis/Hepatitis/Autoimmune hepatitis/Alpha 1 Antitrypsin/Esophageal varices/Portal hypertension/Chronic liver disease/Idiopathic hepatitis/Neonatal idiopathic hepatitis. Our criteria for infection were the presence of a positive culture of blood, urine, or ascites fluid. Data was entered in SPSS software version 20. Qualitative data were analyzed using chi-square, and quantitative data using independent t-tests. A P-value <0.05 was considered significant.

3- RESULTS

Eighty-five patients with CLD were included in this 6-year-long study. 39 (45/9%) of the patients were female; 52 had no hepatic encephalopathy with a female to male ratio of 42.3%-57.7% and 33 cases had the criteria of hepatic encephalopathy with a male to female ratio of 48.5%-51.5%. Our study's most common etiology of liver involvement was

an idiopathic factor, followed by neonatal idiopathic hepatitis, bile duct disorder, metabolic diseases, inflammatory disease, and infectious diseases. There was no statistically significant difference between the two groups regarding sex, etiology of CLD, platelets, potassium, blood sugar, urea, creatinine, gastrointestinal bleeding, constipation, the interval between the onset of symptoms and diagnosis, calcium, magnesium, partial thromboplastin time, alkaline phosphatase, and peripheral edema. However, there was a statistically significant relationship between the two groups regarding the mortality rates (p-value <0.001). The patients' demographics are summarized in **Table 1**.

Table-1: The patients' demographics

Demographic Data		With Encephalopathy	Without Encephalopathy	P-value
Age(mean±SD)/month		47.76±47.62	53.25 ±54.49	0.860
Sex (Female/male)		17(51.5%)/16(48.5%)	22(42.3%)/30(57.7%)	0.406
Underlying Disease	Idiopathic CLD	12(36.4%)	28(53.8%)	0.28
	Autoimmune liver disease	2(6.1%)	2(3.8%)	
	Bile duct disorders	9(27.3%)	12(23.1%)	
	Metabolic disorders	8(24.2%)	10(19.2%)	
	Viral Hepatitis	2(6.1%)	0(0%)	
Outcome/death		20(60.6. %)	10(19.2%)	P<0.001

There was a significant difference between the serum sodium level and the serum calcium level in the two groups with P-values of 0.001 and 0.023, respectively. Transaminase and bilirubinemia levels were significantly high in patients with hepatic encephalopathy. The patients' laboratory data are summarized in **Table 2**.

Among the clinical manifestations, ascites and infection were the only factors significantly associated with hepatic encephalopathy. The patients' clinical manifestations are summarized in **Table 3**.

4- DISCUSSION

Our study on 85 CLD patients showed that in the patients with hepatic encephalopathy, the serum sodium level and serum calcium level were significantly lower than those in the patients without hepatic encephalopathy. Also, serum urea and bilirubinemia levels were significantly higher in patients with hepatic encephalopathy. The mortality rate was lower in patients without encephalopathy.

CLD is recognized as a significant cause of morbidity and mortality among patients worldwide. The establishment and progression of CLD are followed by a change in liver tissue structure, which turns into fibrosis and abnormal nodules. CLD causes a wide range of signs and symptoms inside and outside the liver. Hepatic complications, including ascites, edema, jaundice, hepatomegaly, coagulopathy, and extrahepatic symptoms, affect many different organs, such as the heart and arteries, lungs, kidneys, skin, and nerves. Hepatic encephalopathy is known as one of the most severe neuropsychiatric complications of CLD.

Although hepatic encephalopathy has no well-known pathogenesis, there are known factors that may affect the onset or worsening of encephalopathy in most chronic liver patients. As we know hepatic encephalopathy can be progressed by

certain risk factors such as dehydration, infection, constipation, gastrointestinal bleeding, infection, and the use of certain drugs especially those that act on the central nervous system such as sleep medications and antidepressants. Our study showed a significantly lower level of serum sodium in encephalopathic groups. So, low serum sodium level can be a risk factor for triggering hepatic encephalopathy.

Table-2: The patients' laboratory data

Laboratory test (mean±SD)	With Encephalopathy	Without Encephalopathy	P-Value
PLT*	188.40±156.85	125.77±81.39	0.14
Urea, mg/dl	34.93±30.88	22.82±14.37	0.032
Creatinine, mg/dl	0.65±0.46	0.78±1.18	0.371
Sodium, mg/dl	133.66±5.59	137.62 ±4.72	0.001
Potassium, mg/dl	4.50±1.18	4.13±0.57	0.096
Calcium, mg/dl	8.79±0.69	9.24±0.66	0.023
Magnesium, mg/dl	2.25±0.31	1.77±0.33	0.11
Phosphor	5.03±1.6	4.8±0.46	0.88
Blood sugar	89.43±33.57	97.54±45.58	0.812
PT*, sec	26.43±10.47	20.46±10.04	0.01
PTT*, sec	60.06±29.18	47.62±24.80	0.08
Total Bil*, mg/dl	27.69±18.04	13.48±15.48	0.001
Direct Bil*, mg/dl	12.26±7.8	20.90±99.08	0.001
AST*(U/L)	473.31±568.01	264.72±433.07	0.002
ALT*(U/L)	535.10±1137.92	150.97±322.56	0.004
ALP *(U/L)	976.69±601.51	957.25±656.19	0.58
PH*	7.373±0.13	7.378±0.10	0.87

* WBC: White blood cells, HB: Hemoglobin, PLT: Platelet, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, Bil: Bilirubin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, PH: Potential of Hydrogen

Table-3: The patients' Clinical manifestations

Clinical Manifestations	With Encephalopathy	Without Encephalopathy	P-value
Constipation	4(12.1%)	2(3.8%)	0.201
GI bleeding	10(30.3%)	13(25%)	0.592
Infectious	17(65%)	20(71.4%)	0.009
Ascites	27(82%)	27(52%)	0.005
Peripheral Edema	6(18.2%)	6(11.5%)	0.52

Hyponatremia in patients with CLD can cause a variety of manifestations. Hyponatremia can lead to mild cerebral edema, which results in increased osmotic pressure on astrocytes. Eventually, it leads to many neurological dysfunctions. A study by Lars Bossen et al. showed the hazard rate of hepatic encephalopathy development increased by 8% for every one mmol/L decrease in serum sodium (6). Also sodium levels of <130 meq/L were associated with higher morbidity and

mortality rates in other studies, showing that the patients with lower levels of sodium had higher grades of hepatic encephalopathy (7-11). In some studies such as the one by Zheng Ning et al., it is reported that higher serum Sodium concentrations were significantly associated with the in-hospital mortality of CLD patients (19), which is contrary to our findings in the study.

The association between hepatic encephalopathy and hyponatremia may be explained based on the higher severity of the liver disease among the patients with hyponatremia. On the other hand, the very nature of CLD by activating the effective volume of arteries activates the renin-angiotensin system and retains water and sodium. Therefore, it appears that with proper treatment of water and electrolytes in children and regular and periodic checkings of electrolytes in patients, we can reduce the effect of this factor on exacerbating hepatic encephalopathy.

Our study's most common etiologies of CLD were an idiopathic factor and neonatal idiopathic hepatitis. However, in studies on adults, the most common causes of CLD were alcoholism and viral hepatitis (10-12). Also in Western studies and countries where alcohol consumption is not legally prohibited, alcoholism is considered one of the most common causes of the patients' involvement. This difference between etiology of CLD in pediatric and adult patients can lead to different findings in electrolyte and biochemical results.

Serum calcium level was significantly lower in patients with hepatic encephalopathy compared to the patients without hepatic encephalopathy in our study. Hypocalcaemia can occur in patients with CLD due to vitamin D-dependent metabolism. In both parenchymal and cholestasis liver diseases, intestinal fat malabsorption may cause vitamin D deficiency, resulting in hypocalcaemia. Also, it is necessary to mention that hypoalbuminemia due to liver dysfunction can result in a lower serum calcium level in CLD. In studies by Devaraj (13) and Schafer AL (14), similar to our study, hypocalcemia was found to be a predictive factor for hepatic encephalopathy.

The significant relationship between high urea and hepatic encephalopathy in our study was similarly reported in other studies (8, 9, 12, 15). The main reason for high urea in our patients may be prerenal azotemia due to the reduced effective vascular volume because of the reduced fluid intake by the patients. On the other hand, these patients were treated with diuretics due to ascites and peripheral edema, which can exacerbate dehydration and prerenal azotemia. And the progressive course of CLD in the case of involvement of the renal system, called hepatorenal syndrome, can cause azotemia of renal origin; all these factors can increase a person's blood urea level.

Prothrombin time and INR in our patients were elevated, as expected. The reason is that both are parts of the diagnostic criteria of the disease. A similar study, Lee (16) reported the elevation of prothrombin time and INR in patients with fulminant hepatitis and hepatic encephalopathy. Our study showed that serum bilirubin also increased in patients with hepatic encephalopathy, since the increase in bilirubin among CLD patients was a prognostic factor. In liver cirrhosis, direct bilirubin (DB) level increases due to intrahepatic cholestasis and decreased hepatic bilirubin clearance, resulting from portal flow distortion. This point has been also found in the other similar studies, such as the study by Han Ah Lee1 (17).

The mortality rate among the patients with hepatic encephalopathy was between 27-75% in various studies (18). The overall mortality rate in our study was 30 (35.3%), of which 20 (60.6%) were in the group

with hepatic encephalopathy. It is predictable due to the higher severity of CLD among patients with hepatic encephalopathy.

We evaluated that the electrolyte disturbance in CLD patients with and without hepatic encephalopathy as the timely identification, management, and treatment of predisposing factors for hepatic encephalopathy will play an essential role in reducing mortality in CLD.

4-1. Limitations of the study

Our study had some limitations which may affect the interpretation of our results including the single-center design and the inclusion of a small number of patients. Therefore, we suggest multicenter studies with larger sample sizes for future research.

5- CONCLUSION

It seems that the decrease in serum sodium and calcium levels, and the increase in serum urea and bilirubin can be predictive of hepatic encephalopathy in CLD among pediatric patients.

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