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INVESTIGATION OF THE CHARACTERISTICS OF HEPATIC ENCEPHALOPATHY OCCURRING IN VIRAL ETIOLOGY LIVER CIRRHOSIS IN RELATION TO INTESTINAL DYSBIOSIS

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Abstract: This experimental article aimed to assess the clinical and laboratory characteristics of liver encephalopathy arising in the context of viral etiology liver cirrhosis, with consideration given to intestinal dysbiosis. A significant positive correlation between the severity of hepatic encephalopathy and the degree of intestinal dysbiosis was found during our research.

As the severity of intestinal dysbiosis increases, it leads to an increase in the number of pathogenic microorganisms in the intestines, which leads to an increase in serum ammonia levels in the bloodstream of patients. This increased ammonia concentration is associated with increased hepatic encephalopathy. In particular, when the amount of ammonia is 1.5 times higher than the norm, symptoms of minimal hepatic encephalopathy appear.

Introduction. Hepatic encephalopathy (HE) manifests in both acute and chronic liver conditions, presenting with cerebral dysfunction and encompassing neurocognitive alterations. Clinical severity is assessed through the West Haven scale, categorizing it into four levels. Minimal hepatic encephalopathy, also known as latent HE, lacks obvious clinical manifestations, necessitating additional diagnostic measures for confirmation [1, 3]. Despite retaining temporal and spatial accuracy at level 1, patients exhibit various cognitive and behavioral disruptions. Level 2 signifies impaired temporal precision. Level 3 indicates the loss of both temporal and spatial accuracy, resulting in a Glasgow scale score of > 8. At level 4, patients are unresponsive to pain and score < 8 on the Glasgow scale [4,5].

Minimal hepatic encephalopathy represents the mildest manifestation of HE, marked by the absence of evident cognitive and mental deficits. The prevalence of minimal hepatic encephalopathy ranges from 20% to 80%, with various studies indicating that hepatic encephalopathy can emerge in cirrhotic patients over time. The variability in these figures is attributed to variations in diagnostic criteria and testing methods employed for detection. Numerous theories regarding the development of hepatic encephalopathy exist, yet their underlying mechanisms remain to be definitively validated [2, 6]. However, there is consensus around the notion of compromised detoxification of neurotoxins in the bloodstream due to liver dysfunction and/or the existence of portosystemic shunts, resulting in alterations in brain neurotransmission. Ammonia NH3/ammonium NH4+ system is recognized as a pivotal neurotoxin implicated in the pathogenesis of hepatic encephalopathy.

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Patients in advanced stages of liver cirrhosis frequently encounter clinical decompensation accompanied by compromised intestinal motility and portal hypertensive vasculopathy. Moreover, alterations in bile acid flow lead to a reduction in the bacteriostatic activity of bile salts, exacerbating endotoxemia and elevating the likelihood of liver disease complications. The intestinal dysfunction observed in cirrhosis patients, marked by shifts in motility and permeability, bacterial overgrowth, and bacterial translocation, heightens the susceptibility to cirrhosis-related complications like bacterial peritonitis and hepatic encephalopathy [4, 5].

However, according to a 2007 survey by the American Association for the Study of Liver Diseases, the majority of physicians acknowledged minimal hepatic encephalopathy as a significant yet inadequately researched issue. Surprisingly, only half of the physicians actively screened for minimal hepatic encephalopathy in individuals with liver cirrhosis, and nearly 40% never conducted a psychometric assessment on these patients [3].

The purpose of the study is to evaluate the clinical and laboratory features of hepatic encephalopathy in viral liver cirrhosis in relation to intestinal dysbiosis.

Materials and Methods. Throughout our study, we observed 115 patients ranging in age from 19 to 66 years who had initially been diagnosed with liver cirrhosis. Initially, all patients were categorized as A, B, or C based on the Child-Pugh scale. The mean age of the observed patients was 36.7±3.3 years. The distribution between males and females was 60% and 40% (62 and 42 patients, respectively). According to the analysis of etiological factors of patients with liver cirrhosis, liver cirrhosis caused by HDV−42 (36.5%) prevailed over others. 33 (28.7%) liver cirrhosis patients with HBV etiology. Based on the Child-Pugh scale, 51 (44,3%) patients diagnosed with liver cirrhosis were classified as class A, 37 (32,2%) as class B, and 27 (23,5%) as class C.

To confirm the clinical diagnosis, comprehensive patient history, clinical examination, and standard laboratory methods were conducted. Objective assessments involved anthropometric measurements such as patients' height, weight, and body mass index calculated using the Ketel formula.

Hematological analysis was conducted using hematological analyzers to determine parameters such as hemoglobin, leukocyte, erythrocyte, thrombocyte counts, and erythrocyte sedimentation rate.

Biochemical blood analysis, which included assessing total bilirubin, total protein, and albumin levels, as well as the activity of enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), was performed using photometric methods on the Mindray BA 88 Semi-Auto Chemistry automatic biochemical analyzer.

To identify the causative factor, immunoenzyme analysis was conducted using a range of diagnostic test systems. Molecular-biological analysis was employed to detect the RNA or DNA of the virus qualitatively, along with assessing viral load quantitatively in blood serum through polymerase chain reaction (PCR) utilizing TaqMan and FRET technology. The Rotor-Gene Q QIAGEN kit was utilized for time-mode amplification.

For early detection of minimal hepatic encephalopathy symptoms, several tests were performed. These included the corridor test to assess fine motor skills, a number-

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dialing test (1 to 25) to evaluate concentration levels, the "10 words" test to gauge short-term memory, speech assessment, and observation for the presence of asterixis. The test was timed for 40 seconds. Achieving a completion rate of 90-100% within this time frame is considered normal. A completion rate of 75-85% suggests the presence of minimally active hepatic encephalopathy, while a rate of 70% or below indicates marked hepatic encephalopathy. The patient is presented with a set of 10 simple, unrelated words and asked to repeat them after they are read slowly. This process is repeated until the patient successfully recalls all 10 words, but no more than 5 times. Standard evaluation criteria include memorizing 4-5 words on the first attempt and recalling all 10 words between 3-5 repetitions. If the patient cannot memorize the words even after 5 repetitions, it indicates encephalopathy of minimal activity, speech disorder checked, the presence of asterixis was determined.

Results and Discussion. All 115 participants in the study were categorized into three groups based on the Child-Pugh scale. Patients in Group 1 were classified as class A, those in Group 2 as class B, and individuals in Group 3 as class C. In the study, we assessed the risk of liver encephalopathy development and the clinical progression of liver cirrhosis among patients with viral etiology cirrhosis, categorized by stages of liver encephalopathy: stage 0 for minimal, stage 1 for mild, stage 2 for moderate, stage 3 for severe, and stage 4 for severe (see Figure 1).

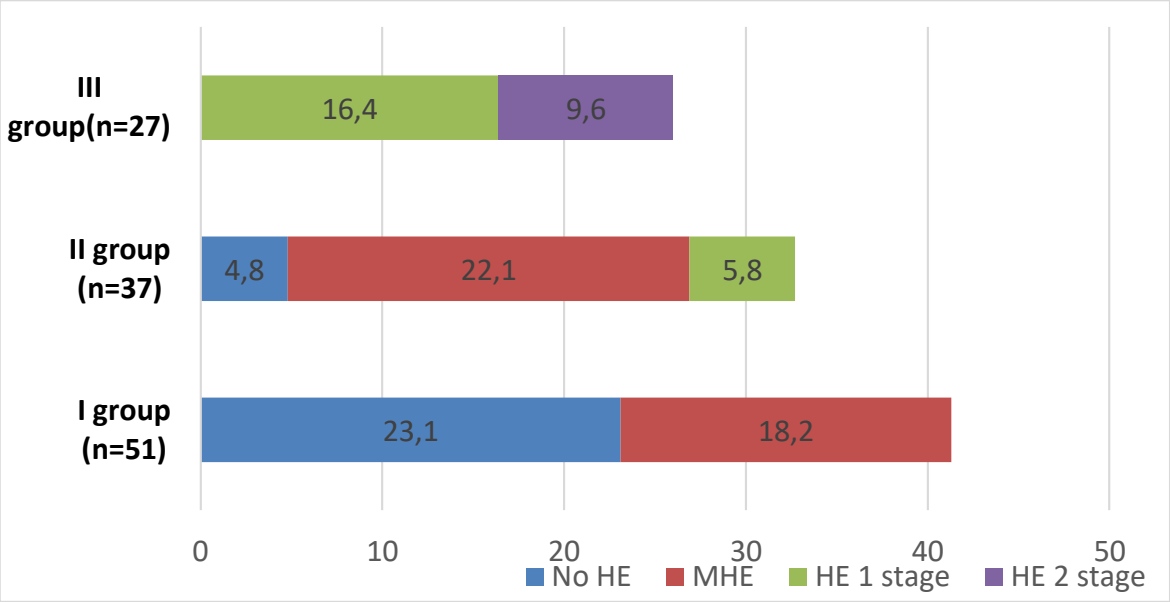

Figure 1. Rate of detected hepatic encephalopathy in patients with liver cirrhosis during follow-up (n=115,%)

Subsequently, an examination was conducted to assess the degree of intestinal dysbiosis among patients stratified into groups based on the Child-Pugh classification of liver cirrhosis, with the intensity of intestinal dysbiosis correlating to the severity of liver cirrhosis classes.

The statistical analysis revealed a significant correlation between the Child-Pugh classification of intestinal dysbiosis or liver cirrhosis and the severity of hepatic encephalopathy (r=1.0) (P<0.05). According to the findings, it was observed that

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minimal hepatic encephalopathy was present in 44.2% of cases within Class A of the Child-Pugh scale for liver cirrhosis and the first level of intestinal dysbiosis. Moreover, the severity of hepatic encephalopathy was found to escalate with the progression of intestinal dysbiosis. In instances where patients were classified as Class C in the Child-Pugh scale of liver cirrhosis or exhibited the third level of intestinal dysbiosis, 63.0% experienced hepatic encephalopathy of the first degree, while 37.0% experienced the second degree (see Figure 2).

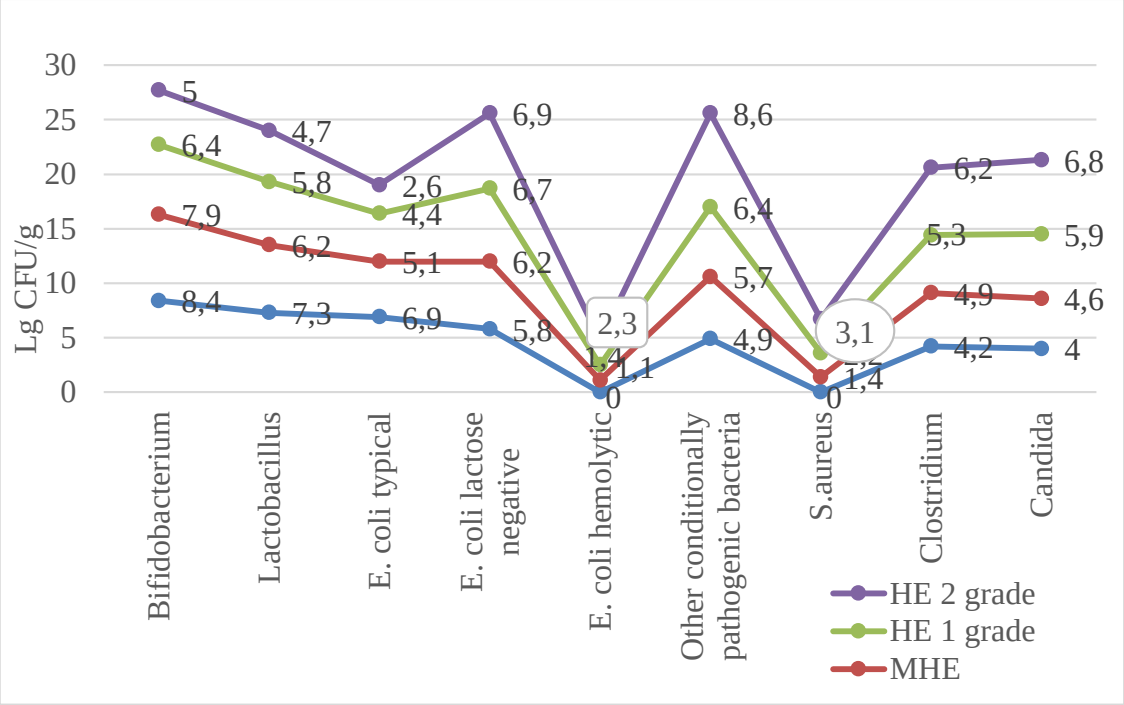

Figure 2. The association between the degree of intestinal dysbiosis and the severity of liver encephalopathy identified in patients undergoing follow-up for liver cirrhosis.

To ascertain the correlation between the severity of hepatic encephalopathy and intestinal dysbiosis, the microbiological findings of patients in the study cohorts were scrutinized. According to the collected data, there was a concurrent rise in the prevalence of pathogenic microorganisms in the intestines with the escalation of intestinal dysbiosis severity. Consequently, this increase in pathogenic microorganisms contributed to the exacerbation of hepatic encephalopathy symptoms. A statistically significant correlation was observed between the escalation in the quantity of pathogenic microorganisms within the intestines and the severity level of hepatic encephalopathy ($r=0,98$) ($P<0,05$).

To elucidate the causal relationship between pathogenic microorganisms within the intestines and hepatic encephalopathy, we conducted a comparative analysis of the serum ammonia levels among patients within the observational research groups with varying degrees of hepatic encephalopathy.

When the incidence of intestinal dysbiosis was studied according to the Child-Pugh scale of liver cirrhosis, the severity of intestinal dysbiosis was related to the

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grades of liver cirrhosis. In the majority of patients (37.4%) diagnosed with class A liver cirrhosis, the first degree of intestinal dysbiosis was identified, with only 6.9% diagnosed with the second degree of dysbiosis. Among those with class B liver cirrhosis, the majority (29.5%) exhibited the second degree, while 1.8% displayed the third degree of dysbiosis. All patients classified under class C liver cirrhosis presented with the third degree of intestinal dysbiosis (23.5%). Thus, a significant positive correlation was observed between the severity of dysbiosis and the class of liver cirrhosis according to the Child-Pugh scale ($r=0.82$; $P<0.01$). These findings indicate that as the severity of liver cirrhosis increases, there is a corresponding decrease in the normal intestinal biocenosis, coupled with an increase in the presence of opportunistic and pathogenic microorganisms detrimental to human health.

According to the analysis, the mean ammonia level in patients without hepatic encephalopathy was 36.9±0.78 µmol/l, closely approximating the value observed in healthy volunteers (37.6±0.12 µmol/l). Conversely, in patients with minimal hepatic encephalopathy, the ammonia concentration increased by 1.5 times compared to healthy volunteers, averaging 53.7±0.4 µmol/l. For patients diagnosed with grade 1 hepatic encephalopathy, the ammonia level was 58.8±0.08 µmol/l (increased by 1.6 times), while for those with grade 2, it rose by 1.8 times, with an average of 66.2±0.53 µmol/l. A statistically significant moderate correlation was identified between the serum ammonia level and the severity of hepatic encephalopathy ($r=0.958$), underscoring the significance of this association ($P<0.05$) (see Figure 3).

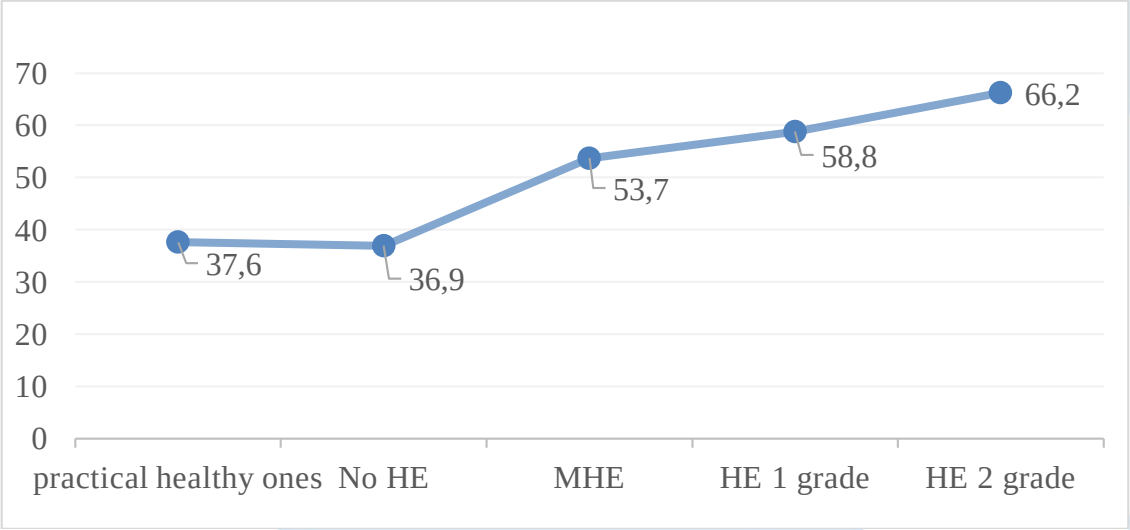

Figure 3. The correlation between serum ammonia levels and the severity of hepatic encephalopathy among patients within the observation group (**µmol/l**).

Upon analysis of clinical manifestations of hepatic encephalopathy within the observational research groups, it was noted that even among patients without evident hepatic encephalopathy, 2.9% exhibited symptoms of memory impairment and attention deficits, 17.6% displayed affective symptoms, and 29.4% reported sleep disturbances. No clinical signs of disorientation, depression, apathy, or behavioral abnormalities were observed in this subgroup. However, in cases of minimal hepatic

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encephalopathy, the prevalence of these symptoms increased, with rates of 37.5%, 25.0%, 38.3%, and 64.6% for memory impairment, attention deficits, affective symptoms, and sleep disturbances, respectively. Additionally, rates of disorientation, depression, apathy, and behavioral abnormalities were recorded at 4.2%, 4.2%, 12.6%, and 39.5%, respectively (See Figure 4).

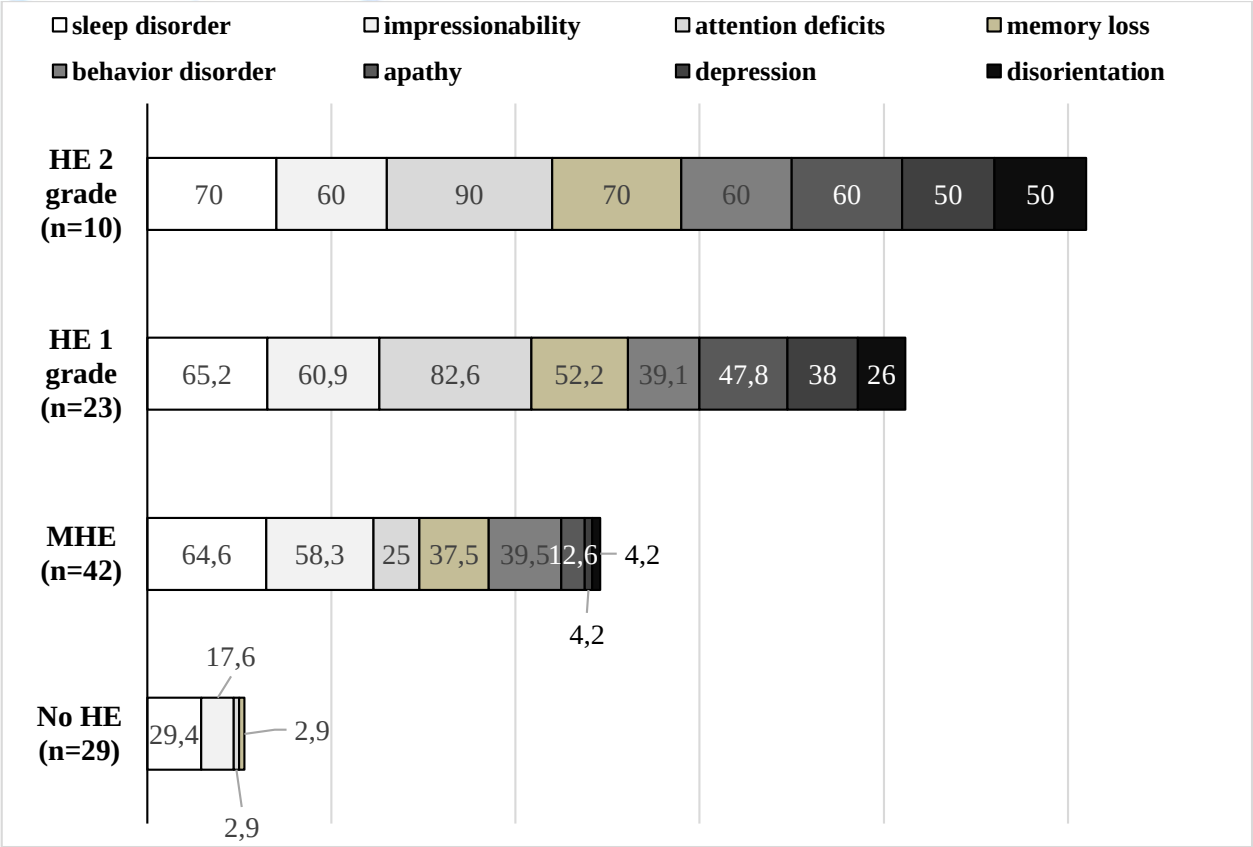

Figure 4. Incidence of signs of hepatic encephalopathy in patients under observation

According to the findings depicted in Figure 4, attention deficits were prevalent in nearly all patients diagnosed with grade 2 hepatic encephalopathy, occurring in 90% of cases. Patients experiencing grade 2 hepatic encephalopathy exhibited disorientation and depression at a rate 12 times higher (50.0%) than those with minimal hepatic encephalopathy. Similarly, apathy and behavioral abnormalities were observed at a rate 5 times higher (60.0%) in patients with grade 2 hepatic encephalopathy compared to those with minimally active hepatic encephalopathy.

Based on the data obtained, it can be inferred that within class A of liver cirrhosis with concurrent intestinal dysbiosis, minimal hepatic encephalopathy manifests in 44.2% of instances. There exists a significant positive correlation between the severity of hepatic encephalopathy and the extent of intestinal dysbiosis. As the severity of intestinal dysbiosis escalates, it induces an elevation in the abundance of pathogenic microorganisms within the intestines, subsequently leading to an increase in serum ammonia levels in patients' bloodstreams. This heightened ammonia concentration correlates with the exacerbation of hepatic encephalopathy. Specifically, an ammonia level 1.5 times higher than the norm triggers the onset of minimal hepatic

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encephalopathy symptoms. Moreover, a 1.8-fold increase in ammonia levels precipitates disorientation and depression symptoms in 50.0% of cases, as well as apathy and behavioral abnormalities in 60.0% of cases.

Conclusion.

1. A robust positive correlation exists between the severity of liver cirrhosis according to the Child-Pugh scale and the extent of disruption in intestinal microflora (r = 0.83).

2. In 44.6% of cases involving class A liver cirrhosis or the first degree of intestinal microflora disturbance, minimal hepatic encephalopathy was identified, characterized by a 1.5-fold increase in serum ammonia levels compared to the norm. Furthermore, a significant positive correlation was established between the severity of liver cirrhosis or intestinal microflora disturbance and the degree of hepatic encephalopathy (r=0.93). Additionally, 37.0% of patients diagnosed with class C liver cirrhosis or the third degree of intestinal microflora disturbance exhibited grade II hepatic encephalopathy.

Conflict of interest. The authors declare no conflict of interest.

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