CHRONIC PYELONEPHRITIS AS A PRECIPITATING FACTOR OF HEPATORENAL SYNDROME IN PATIENTS WITH ALCOHOLIC LIVER CIRRHOSIS

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Introduction. Most attempts to assess renal failure in alcoholic liver cirrhosis have so far focused on acute kidney injury and on the hepatorenal syndrome in particular. However, there are still limited data on the prevalence and clinical impact of chronic kidney disease in cirrhosis. Objectives. This study aimed to assess the influence of chronic pyelonephritis on the incidence of hepatorenal syndrome in patients with alcoholic liver cirrhosis. Material and methods. 165 patients with decompensated alcoholic liver cirrhosis and concomitant chronic pyelonephritis were enrolled in the study. They were divided into two groups according to the presence or absence of chronic pyelonephritis: group 1 had alcoholic liver cirrhosis only (n=82), group 2 had alcoholic liver cirrhosis + chronic pyelonephritis (n=83). Results. The general bacterial infections were more common in group 1 patients. The spectrum of the most frequent bacterial complications in the examined patients typical for alcoholic liver cirrhosis was as follows: the share of urinary tract infection made up 16.0% (95% confidence interval 14.4-27.9), pneumonia constituted 16.7% (95% confidence interval 10.5-22.7, bacteremia made up 4.0% (95% confidence interval 7.7-38.6), the share of skin infections (erysipelas) was 2.7% (95% confidence interval 0.7-6.6). Other infections including pulmonary tuberculosis, lung abscess, right leg abscess, osteomyelitis, bedsores, were less common (6.7%). Spontaneous bacterial peritonitis, taking into account all options, was found in 6 cases (10.5%, 95% confidence interval 4.0-21.5). As expected, the incidence of hepatorenal syndrome within 14 days of inpatient onset was almost twice higher in group 2 – 22 cases (27%), than in group 2 – 13 cases (16%). The group 2 demonstrated a more severe course of alcoholic liver cirrhosis on the Child-Pugh scale compared with group 1 (class B - 29.9%; class C - 70.1% against class B - 46.1%; class C - 53.6%); the differences were statistically significant (χ² = 4.30, p = 0.038). In patients of group 2, the lethal outcome in the hospital occurred in 6 (8.9%) cases. Conclusions: The results of the present study confirm the role of chronic pyelonephritis as one of the major precipitating factors of hepatorenal syndrome incidence in patients with alcoholic liver cirrhosis. This fact should be considered when making the treatment plan for these patients.

Keywords: chronic pyelonephritis, hepatorenal syndrome, alcoholic liver cirrhosis.

This study is conducted as a part of research project "Risk factors for progression of essential hypertension and metabolic syndrome in comprehensive assessment of hemodynamic, renal function, and circadian structure of blood pressure in the justification of antihypertensive therapy", the Department of Patient Care and Higher Nursing Education, Bukovynian State Medical University, Chernivtsi.

Introduction

Most attempts to assess renal failure in alcoholic liver cirrhosis (ALC) have so far focused on acute kidney injury (AKI), and as a result, detailed knowledge of hepatorenal syndrome (HRS) as a part of AKI in cirrhosis is now available [1]. However, there are still limited data on the prevalence and clinical impact of chronic kidney disease (CKD) in cirrhosis. ALC patients are susceptible to HRS development due to cirulatory disorders, neuro-hormonal changes, and other precipitating factors, such as bacterial infection, gastrointestinal bleeding, medication, and paracentesis [1-8]. Depending on the severity, duration, and frequency, CKD might increase the risk of accidental HRS due to decreased renal mass and number of nephrons, vascular insufficiency, and maladaptive recovery mechanisms [8]. There is another condition, acute-on-chronic liver failure (ACLF) that can contribute to the HRS development and cause a sharp deterioration of the liver function in patients with cirrhosis. This condition is becoming more often recognized fulminant hepatitis caused by secondary or extra hepatic causative factors, precipitating factors (PF), such as infections that lead to dysfunction of the target organs. The number of studies in this area is rather limited, but this gap has to be filled.

Material and methods

165 patients with decompensated ALC and concomitant CP were enrolled in the study. They were divided into two groups according to the presence or absence of CP: group 1 – ALC only (n=82), group 2 – ALC+CP (n=83).

The exclusion criteria were: III-IV CKD stages, chronic hemodialysis prior to the admission, hepatocellular carcinoma outside the Milan criteria and other malignancies, viral aetiology of cirrhosis, and lack of informed consent of the patient. ALCI was diagnosed according to the ICA criteria [2], the ALC severity was classified by MELD and Child-Pugh scales [7].

CLIF-C-ACLF score organ/system failure criteria were: liver - bilirubin, kidney - creatinine, brain - liver encephalopathy, coagulation - international normalized ratio (INR), blood circulation - use of vasopressors (dopamine), lungs - SpO²/FiO⁴ [8].

Comparison of normally distributed continuous variables was performed by Student’s t-test or ANOVA. Comparison of non-normally distributed continuous variables was made by Mann-Whitney (U) or Kruskal-Wallis tests. Categorical variables were expressed as numbers and percentages and were compared with each other using the chi-square test (χ²) or Fisher’s exact test. All statisti-
The spectrum of the most frequent bacterial complications in the examined patients was typical for ALC and included urinary tract infection (CP) in 16.0% of cases (95% CI 14.4–27.9), pneumonia in 16.7% of cases (95% CI 10.5–22.7), bacteremia in 4.0% of cases (95% CI 7.7–38.6), and skin infections (erysipelas) in 2.7% of cases (95% CI 0.7–6.6). Other infections were less common (6.7%): pulmonary tuberculosis, lung abscess, right leg abscess, osteomyelitis, bedsores. SBP, taking into account all options, was found in 6 cases (10.5%, 95% CI 4.0–21.5). In group 2 there was a more severe course of ALC on the baseline clinical characteristics of the patients with decompensated ALC are shown in Table 1. The general bacterial infections were more common in group 1 patients. As expected, the incidence of HRS was almost twice higher in group 2 than in group 1 that confirms the important role of CP as an HRS precipitator.

**Results and discussion**

The baseline clinical characteristics of the patients is shown in Table 1. The structure of precipitating factors in examined ALC patients is shown in the Table 2. As expected, the incidence of HRS was almost twice higher in group 2 than in group 1 that confirms the important role of CP as an HRS precipitator.

The spectrum of the most frequent bacterial complications in the examined patients was typical for ALC and included urinary tract infection (CP) in 16.0% of cases (95% CI 14.4–27.9), pneumonia in 16.7% of cases (95% CI 10.5–22.7), bacteremia in 4.0% of cases (95% CI 7.7–38.6), and skin infections (erysipelas) in 2.7% of cases (95% CI 0.7–6.6). Other infections were less common (6.7%): pulmonary tuberculosis, lung abscess, right leg abscess, osteomyelitis, bedsores. SBP, taking into account all options, was found in 6 cases (10.5%, 95% CI 4.0–21.5). In group 2 there was a more severe course of ALC on the basis of HRS within 14 days of inpatient onset, n (%) 13 (16%) 22 (27%)*

**Note:** *the difference is statistically significant compared to group 1*

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The structure of infectious complications established as precipitating factors in the patients is shown in the Table 2.

The spectrum of the most frequent bacterial complications in the examined patients was typical for ALC and included urinary tract infection (CP) in 16.0% of cases (95% CI 14.4–27.9), pneumonia in 16.7% of cases (95% CI 10.5–22.7), bacteremia in 4.0% of cases (95% CI 7.7–38.6), and skin infections (erysipelas) in 2.7% of cases (95% CI 0.7–6.6). Other infections were less common (6.7%): pulmonary tuberculosis, lung abscess, right leg abscess, osteomyelitis, bedsores. SBP, taking into account all options, was found in 6 cases (10.5%, 95% CI 4.0–21.5). In group 2 there was a more severe course of ALC on the basis of HRS within 14 days of inpatient onset, n (%) 13 (16%) 22 (27%)*

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**Note:** *the difference is statistically significant compared to group 1*
The results of our study show that patients with HRS-1 have systemic inflammation with an altered cytokine profile compared with patients with ALC without HRS and, most interestingly, with HRS-2. The study also demonstrates that the systemic inflammatory response in HRS-1 is not associated with the presence of bacterial infections, concomitant ACLF or the intensity of renal dysfunction and is not normalized by improving renal function through pharmacological therapy. Interestingly, the intensity of the inflammatory response correlates with renal function and patients who have elevated levels of some inflammatory markers, especially VEGF, are associated with lack of HRS resolution and mortality.

In this study, a large number of patients with cirrhosis and HRS-1 were examined for the presence of a systemic inflammatory response assessed by a large number of inflammatory and anti-inflammatory cytokines using multiplex technology. For comparison, a control group of patients with ALC without HRS was included. A group of patients with ALC+HRS-2 was also studied. This type of HRS was chosen as a comparison group for HRS-1, because in both conditions AKI has a prerenal origin, but the main pathogenetic cause is very different. While the decrease in blood flow is the cause of renal hypoperfusion in the hypovolemic variant of HRS-2, renal dysfunction in HRS-1 is associated with opposite features of blood circulation, and namely with pronounced vasodilation, especially in splanchnic circulation [2, 4]. The results of this study clearly show that with the development of decompensated cirrhosis to HRS, there is a progressive increase in inflammatory status with significantly elevated levels of some potent inflammatory cytokines. Previous studies have shown that plasma levels of inflammatory cytokines increase significantly in decompensated cirrhosis compared with compensated [8]. It is not known whether this inflammatory driving force is the cause or consequence of liver disease progression. Our data confirm that this inflammatory status due to decompensated cirrhosis increases even more as the disease progresses to HRS, which is considered one of the last stages of cirrhosis due to its high mortality. Our data are thus consistent with the recently proposed theory of systemic inflammation, which causes complications of cirrhosis [6]. Two pieces of evidence suggest that elevated inflammatory status is not associated with ACLF but with CP. First, plasma cytokine levels in patients with HRS but without ACLF did not differ significantly from those in patients with HRS and ACLF. Moreover, cytokine levels were largely unrelated to the ACLF class. On the other hand, the cytokine profile in patients with HRS was markedly different from the profile of patients with ACLF and HRS-2, suggesting that the cytokine profile is mainly associated with HRS and not with ACLF. However, these findings should be taken with caution due to the relatively low number of patients included in our work. Further research is needed to try to determine whether systemic inflammation is caused by hepatorenal syndrome "per se" or ACLF, or both.

Conclusions
The results of the present study confirm the role of chronic pyelonephritis as one of the major precipitating factors of hepatorenal syndrome incidence in patients with alcoholic liver cirrhosis. This fact should be considered while choosing the treatment plan for these patients.

References
групей. Спектр наиболее частых бактериальных инфекций у обследованных больных был традиционным для алкогольного цироза печени - инфекция мочевыводящих путей 16,0% (95% доверительный интервал 14,4-27,9), пневмония 16,7% (95% доверительный интервал 10,5-22,7), бактериемия 4,0% (95% доверительный интервал 7,7-38,6), внутригипофизарная инфекция (бешки) 2,7% (95% доверительный интервал 0,7-6,6). Иные инфекции встречались реже (6,7%). Тем не менее, вид спектра бактериальных инфекций, наблюдающихся в группе 2, был традиционным для алкогольного цироза печени.

Выводы: Результаты этого исследования подтверждают роль хронического пиелонефрита в развитии гепаторенального синдрома у пациентов с алкогольным цирозом печени. Эти данные подчеркивают необходимость учета инфекционных факторов в плане лечения для этих пациентов.

Реферат
ХРОНИЧЕСКИЙ ПИЕЛОНЕФРИТ КАК ПРЕЦИПИТИРУЮЩИЙ ФАКТОР ГЕПАТОРЕНАЛЬНОГО СИНДРОМА У БОЛЬНЫХ С АЛКОГОЛЬНЫМ ЦИРРОЗОМ ПЕЧЕНИ
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Ключевые слова: хронический пиелонефрит, гепаторенальный синдром, алкогольный цирроз печени.

Введение. Большинство попыток оценить почечную недостаточность при алкогольном цирозе печени до сих пор были сосредоточены на остром повреждении почек и гепаторенальном синдроме в частности. Однако, до сих пор ограничены данные о распространенности и клиническом влиянии хронической болезни почек при алкогольном цирозе печени. Целью этого исследования было оценить влияние хронического пиелонефрита на частоту возникновения гепаторенального синдрома у пациентов с алкогольным цирозом печени.

Материал и методы. В исследование было включено 165 пациентов с декомпенсированным алкогольным цирозом печени. Они были разделены на две группы по наличию или отсутствию хронического пиелонефрита: группа 1 - только алкогольный цироз печени (n = 82), группа 2 - алкогольный цироз печени + хронический пиелонефрит (n = 83).

Результаты. Общие бактериальные инфекции были более распространенными у пациентов группы 2. Спектр частых бактериальных инфекций, убывая по частоте, включал: инфекция мочевыводящих путей - 16,0% (95% доверительный интервал 14,4-27,9), пневмония - 16,7% (95% доверительный интервал 10,5-22,7), бактериемия - 4,0% (95% ДИ 7,7-38,6), кожные инфекции (рожа) - 2,7% (95% ДИ 0,7-6,6). Другие инфекции встречались реже (6,7%): туберкулез, абсцесс легкого, абсцесс правой нижней конечности, остеомиелит, пролежни. Спонтанный бактериальный перитонит, учитывая все варианты, был обнаружен в 6 случаях (10,5%, 95% доверительный интервал 4,0-21,5). Как и ожидалось, частота гепаторенального синдрома в течение 14 дней от начала стационарного лечения была почти вдвое выше в группе 2 - 22 случая (27%), чем в группе 2 - 13 случаев (16%). Во 2 группе наблюдался более тяжелое течение алкогольного цироза печени по шкале Чайлд-Пью по сравнению с группой 1 (класс В - 29,9%; класс С - 70,1% против класса В - 46,4%; класс С - 53,6%), резидуумы были статистически значимыми (χ2 = 4,30, р = 0,038). У пациентов 2 группы летальный исход в большинстве произошел в 6 (8,9%) случаях.

Выводы: Результаты этого исследования подтверждают роль хронического пиелонефрита в развитии гепаторенального синдрома у пациентов с алкогольным цирозом печени. Эти данные подчеркивают необходимость учета инфекционных факторов в плане лечения для этих пациентов.