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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 group2 – 13 cases (16%). The group 2 demonstrated a more severe course of alcoholic liver cirrhosis on the Child-Pugh scale compared with group I (class B - 29.9%; class C - 70.1% against class B - 46.4%; class C - 53, 6%); the differences were statistically significant ($\chi 2 = 4.30$, $p = 0.038$). 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 circulatory disorders, neurohormonal 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.

AKI 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 - SpO^2/FiO^2 [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 ($\chi 2$) or Fisher's exact test. All statisti-

cal studies were processed by the statistical package SPSS, version 23.0. A p-value of less than 0.05 for all studies was found to be statistically significant.

Results and discussion

The baseline clinical characteristics of the participants 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.

Table 1.
Clinical and laboratory data of ALC patients

	Group 1, ALC (n=82)	Ggroup 2, ALC+CP (n=83)
Age, years	42,34±12,57	44,28±11,82
Gender, male/female, n (%)	56/26 (68%/32%)	57/26 (68%/32%)
Asscites, n (%)	43 (52%)	56 (67%)*
Hepatic encephalopathy , n (%)	6 (7%)	16 (19%)*
Bacterial infections , n (%)	27 (32%)	41 (50%)*
Creatinine, (mg / dL)	0,85 ±0,44	2,68±0,68*
Bilirubin (mg / dL)	2,52±0,94	2,61 ±0,95
INR	1,57±0,57	1,55±0,63
Na serum, (mmol/l)	131,54±6,42	139,68±3,54*
Platelets, ($\times 10^9$/L)	85,18±19,25	77,26±21,18*
MELD score	14,32±2,24	19,21±3,17*
Child-Pugh scale	7,52±1,93	8,47±1,92*
Incidence of HRS within 14 days of inpatient onset, n (%)	13 (16%)	22 (27%)*

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

Table. 2.
The structure of precipitating factors in examined ALC patients

Infectious complications	Share in the structure infectious complications,n=67		Share in the general ALC cohort, n = 165 (%; 95 % CI)
	Absolute no	%	
Spontaneous bacterial peritonitis	6	8,9	4,0 (4,0–21,5)
Urinary tract infections	24	35,8	16,0 (14,4–27,9)
Pneumonia	16	23,9	10,7 (10,5–22,7)
Sepsis	1	1,5	0,7 (0–3,6)
Bacteremia	6	8,9	4,0 (7,7–38,6)
Erysipelas	4	5,9	2,7 (0,7–6,6)
Other	10	14,9	6,7 (3,7–12,7)

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 Child-Pugh scale compared with group I (class B - 29.9%; class C - 70.1% against class B - 46.4%; class C - 53, 6%), the differences were statistically significant ($\chi 2 = 4.30$, $p = 0.038$). In the group 2, the lethal outcome in the hospital occurred in 6 (8.9%) cases. In the group 1 (n = 83) 1 (1.2%) patient died, the differences were statistically significant ($p = 0.030$).

Because many patients with HRS-1 meet ACLF criteria, we investigated whether elevated levels of inflammatory cytokines detected in HRS-1 were potentially associated with concomitant ACLF or with CP only. We classified patients with HRS -1 according to the presence or absence of ACLF. We found out that cytokine levels correlated with the severity of ACLF (Table 3).

Table 3.
Comparison of markers of systemic inflammation and cytokines in plasma and urine in patients with HRS-1 associated with ACLF

	CLIF-C-ACLF I-II (n=82)	**CLIF-C-ACLF II-IV (n=83)**	**P value**
CRP (mg/dl)	3,52±1,23	3,78±1,24	0,855
Leucocites ($\times 10^9$/L)	6,52±1,84	7,56±1,89	0,400
Systemic inflammatory response	7 (32%)	7 (33%)	0,993
INF - γ (pg/ml)	35,81±6,17	19,08±5,14	0,582
IL - 6 (pg/ml)	45,36±5,78	56,44±7,21	0,207
IL - 8 (pg/ml)	44,52±6,37	91,62±7,93	0,006*
TNF - α (pg/ml)	46,41±5,67	49,35±5,84	0,749
VEGF (pg/ml)	169,72±2,51	144,57±9,76	0,936
uMCP - 1 (pg/ml)	1624,32±8,39	1250,63±7,42	0,274

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.

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Реферат

ХРОНІЧНИЙ ПІЄЛОНЕФРИТ ЯК ПРЕЦИПІТУЮЧИЙ ФАКТОР ГЕПАТОРЕНАЛЬНОГО СИНДРОМУ У ХВОРИХ НА АЛКОГОЛЬНИЙ ЦИРОЗ ПЕЧІНКИ

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Ключові слова: хронічний пієлонефрит, гепаторенальний синдром, алкогольний цироз печінки.

Вступ. Більшість спроб оцінити ниркову недостатність при алкогольному цирозі печінки досі були зосереджені на гострому ураженні нирок, та гепаторенальному синдромі зокрема. Однак, досі є обмеженими дані про поширеність та клінічний вплив хронічної хвороби нирок при цирозі. Завдання. Це дослідження мало на меті оцінити вплив хронічного пієлонефриту на частоту виникнення гепаторенального синдрому у пацієнтів з алкогольним цирозом печінки. Матеріал і методи. У дослідження було включено 165 пацієнтів з некомпенсованим алкогольним цирозом печінки та супутнім хронічним пієлонефритом. Вони були розділені на дві групи за наявністю або відсутністю хронічного пієлонефриту: група 1 - лише алкогольний цироз печінки (n = 82), група 2 – алкогольний цироз печінки + хронічний пієлонефрит (n = 83). Результати. Загальні бактеріальні інфекції були більш поширеними у пацієнтів

групи 1. Спектр найчастіших бактеріальних ускладнень у обстежених хворих був традиційним для алкогольного цирозу печінки - інфекція сечовивідних шляхів 16,0% (95% довірчий інтервал 14,4-27,9), пневмонія 16,7% (95% довірчий інтервал 10,5-22,7), бактеріємія 4,0% (95 % довірчий інтервал 7,7-38,6), шкірні інфекції (бешиха) 2,7% (95% довірчий інтервал 0,7-6,6). Інші інфекції зустрічалися рідше (6,7%): туберкульоз легень, абсцес легені, абсцес правої нижньої кінцівки, остеомієліт, пролежні. Спонтанний бактеріальний перитоніт, враховуючи всі варіанти, був виявлений у 6 випадках (10,5%, 95% довірчий інтервал 4,0-21,5). Як і очікувалось, частота гепаторенального синдрому протягом 14 днів від початку стаціонарного лікування була майже вдвічі вищою у групі 2 - 22 випадки (27%), ніж у групі 2 - 13 випадків (16%). У 2 групі спостерігався більш важкий перебіг АЦП за шкалою Чайлд-Пью порівняно з групою I (клас B - 29,9%; клас C - 70,1% проти класу B - 46,4%; клас C - 53, 6%), різниці були статистично значущими ($\chi 2 = 4,30$, $p = 0,038$). У пацієнтів 2 групи летальний результат у лікарні стався у 6 (8,9%) випадках. Висновки: Результати цього дослідження підтверджують роль хронічного пієлонефриту як одного з основних факторів, що спричиняють поширеність гепаторенального синдрому у пацієнтів з алкогольним цирозом печінки. Цей факт слід враховувати під час вибору плану лікування для цих пацієнтів.

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 циррозе 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 циррозе. Целью этого исследования было оценить влияние хронического пиелонефрита на частоту возникновения гепаторенального синдрома у пациентов с алкогольным циррозом печени. Материал и методы. В исследование было включено 165 пациентов с декомпенсированным алкогольным циррозом печени и сопутствующим хроническим пиелонефритом. Они были разделены на две группы по наличию или отсутствию хронического пиелонефрита: группа 1 - только алкогольный цирроз печени (n = 82), группа 2 - алкогольный цирроз печени + хронический пиелонефрит (n = 83). Результаты. Общие бактериальные инфекции были более распространенными у пациентов группы 1. Спектр частых бактериальных осложнений у обследованных больных был традиционным для алкогольного цирроза 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% ДИ 7,7-38,6), кожные инфекции (рожа) 2,7% (95% доверительный интервал 0,7-6 6). Другие инфекции встречались реже (6,7%): туберкулез легких, 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 цирроза печени по шкале Чайлд-Пью по сравнению с группой I (класс B - 29,9%; класс C - 70,1% против класса B - 46,4%; класс C - 53, 6%) , разницы были статистически значимыми ($\chi 2 = 4,30$, $p = 0,038$). У пациентов 2 группы летальный исход в больнице произошел в 6 (8,9%) случаях. Выводы: Результаты этого исследования подтверждают роль хронического пиелонефрита как одного из основных факторов, вызывающих распространенность гепаторенального синдрома у пациентов с алкогольным циррозом печени. Этот факт следует учитывать при выборе плана лечения для этих пациентов.