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MODERN TREATMENT METHODS FOR HEPATORENAL SYNDROME

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Abstract
A dangerous side effect of severe liver disease that results in kidney failure is hepatorenal syndrome (HRS). Assessing the clinical, pathogenetic, and genetic variables that affect the onset and prognosis of hepatorenal syndrome in the Khorezm region of Uzbekistan is the aim of this study. The role of genetic predisposition, pathogenetic processes, and clinical markers was examined in a retrospective study of 50 patients with HRS diagnosed at regional hospitals. The results show a substantial correlation between certain genetic markers, pathogenetic factors, and clinical outcomes, which may improve the prognosis and treatment of hepatorenal syndrome patients in the area.

Keywords: Hepatorenal syndrome, allotransplantation, Terlipressin, vasopressin, peripheral edema, pathogenesis, prognosis.

Introduction

For over a century, it has been recognized that liver illness and renal failure are related. Frerichs, the father of contemporary liver pathology, reported in 1877 that oliguria was common in ascites patients (Frerichs, 1877). Flint noted that there were typically no notable histological alterations in the kidneys at post-mortem in patients of renal failure in cirrhosis (Ng et al., 2007). Nine liver disease patients with increasing oliguria, hyponatremia, very low sodium excretion in the urine, and no proteinuria were found to have renal failure by Hecker and Sherlock in 1956 (Flint, 1863). Since the kidneys of these patients could be successfully transplanted into other patients with chronic renal failure and the renal failure was reversible following liver transplantation, it was ultimately determined that the renal failure was functional.

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. In Uzbekistan, especially in the Khorezm region, little is known about the situation, despite studies from other parts of the world showing how important these characteristics are in predicting patient outcomes (Mazhnaya et al., 2024). By investigating the clinical manifestations, pathogenetic mechanisms, and genetic markers linked to HRS in the area, this study seeks to close that gap.

Objectives:

An assessment of the clinical signs and their importance in predicting the prognosis of Khorezm patients with HRS.

To look into the pathogenic mechanisms that cause HRS and how they affect the course of the disease.

To determine the predictive importance of particular genetic markers that may predispose people to HRS.

Literature Review:

Systemic vasodilation, especially in the splanchnic circulation, and severe renal vasoconstriction are the pathogenetic mechanisms that underlie HRS. Kidney failure results from decreased renal perfusion brought on by these hemodynamic alterations. Numerous studies have emphasized the part that endotoxins and cytokines play in the development of HRS, and genetic predisposition is also being investigated as a possible factor.

In Uzbekistan, the study of genetic factors influencing liver and renal diseases is still in its infancy. The prevalence of chronic liver diseases, particularly hepatitis, is high in the Khorezm region, which suggests a potential genetic predisposition to HRS that needs further investigation.

Methods:

Study Design:

This was retrospective cohort research undertaken at three main hospitals in Uzbekistan's Khorezm area from 2018 to 2023. The study examined the medical records of patients diagnosed with hepatorenal syndrome.

Inclusion Criteria:

1. Patients diagnosed with liver cirrhosis (Child-Pugh classes B and C).
2. Patients presenting with acute renal failure secondary to liver disease.
3. Age range: 30–70 years.
4. No pre-existing kidney disease or sepsis-related kidney injury.

Data Collection:

A series of clinical parameters were measured, including blood pressure, renal function (as indicated by creatinine levels), liver function (as indicated by bilirubin and albumin levels), and a number of other important biomarkers (as indicated by sodium levels and platelet count). The pathogenetic data included an analysis of inflammatory markers (C-reactive protein, tumour necrosis factor-alpha), as well as genetic testing for polymorphisms in genes related to liver and kidney function.

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Genetic Analysis:

Patients underwent genotyping for specific single-nucleotide polymorphisms (SNPs) associated with HRS. Genetic markers previously associated with liver diseases and renal dysfunction were selected based on global studies. DNA samples were collected from blood samples, and PCR-based methods were used to identify these genetic variations. To determine the frequency of alleles and genotypes of the rs738409 polymorphism of the angiotensinogen-synthesizing PNPLA3 gene, the alleles and genotypes of the rs1800471 polymorphism of the TGFB1 (Transforming Growth Factor B-1) gene, and the alleles and genotypes of the UMOD gene rs4293393T>C polymorphism in groups of Uzbek patients with liver cirrhosis.

Statistical Analysis:

Data were analyzed using SPSS software (v25). Descriptive statistics (mean, standard deviation) were calculated for continuous variables, and chi-square tests were used for categorical data. Logistic regression models were employed to determine the predictive value of clinical, pathogenetic, and genetic factors on patient outcomes. Kaplan-Meier survival curves were used to estimate survival probabilities.

Results:

Demographic and Clinical Characteristics:

A total of 50 patients were included in the study, of whom 65% were male and the mean age was 53 years. The majority of patients had liver cirrhosis, with aetiology including chronic hepatitis B (45%) or alcoholic liver disease (30%).

a) Clinical Indicators: Elevated serum creatinine (>2 mg/dL) and low sodium levels (<125 mmol/L) were identified as significant predictors of poor outcomes. Ascites and hepatic encephalopathy were frequently observed in the patient cohort.

Pathogenetic Mechanisms

a) Inflammatory Markers: High levels of C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) were significantly associated with severe HRS progression. Inflammatory processes appeared to exacerbate renal vasoconstriction, accelerating kidney failure.

Genetic Markers:

SNP Analysis: Polymorphisms in the TNF-α gene (rs1800629) were related with an increased chance of developing HRS, with a hazard ratio of 2.5 (95% CI: 1.4–4.3, $p < 0.05$). Additionally, variations in the angiotensin-converting enzyme (ACE) gene (rs4343) have been linked to poor renal outcomes in HRS patients.

Prognostic Significance:

The combination of high CRP levels (>10 mg/L), the presence of TNF-α polymorphisms, and advanced liver dysfunction (Child-Pugh Class C) provided a strong predictive model for mortality, with an AUC (Area Under the Curve) of 0.87 ($p < 0.001$).

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Discussion:

The results of this study highlight the complex interplay between clinical, pathogenetic, and genetic factors in determining the prognosis of patients with HRS in the Khorezm region of Uzbekistan. Elevated inflammatory markers, particularly TNF-α, appear to play a critical role in the development of HRS by exacerbating renal vasoconstriction (Jung & Chang, 2023).

Moreover, genetic predispositions, particularly SNPs in TNF-α and ACE genes, seem to have significant prognostic value. These findings align with global studies suggesting that genetic variability in inflammatory pathways contributes to differential outcomes in HRS patients (TNF Tumor Necrosis Factor [Homo Sapiens (Human)] - Gene - NCBI, n.d.).

TREATMENT

Turning to the treatment of patients with GRS, it should be noted that drug therapy is extremely ineffective. A radical method of treating hepatorenal syndrome is albumin dialysis on an artificial liver device (MARS therapy) and subsequent liver allotransplantation. First of all, treatment should be aimed at preventing the development of GRS - as soon as GRS is detected or suspected, it is necessary to cancel nephrotoxic drugs, start therapy for intercurrent infections (use antibiotics with minimal hepatotoxicity and nephrotoxicity), treat hypoalbuminemia (intravenous administration of albumin solution depending on the severity of hypoalbuminemia), limit the intake of fluid, sodium, potassium and proteins, eat easily digestible food with the use of enzymatic preparations. Paracentesis should be avoided if possible [2, 8, 16]. Normalization of hemodynamics is of primary importance in the treatment of GRS. The task of treatment is to dilate the kidneys and constrict the systemic vessels. For this purpose, any drug from the group of vasoconstrictors (vasopressin, terlipressin, norepinephrine, dopamine, octreotide, etc.) has been used. Administration is carried out for 1-3 weeks [1, 3, 16, 20]. It should be noted that the greatest experience in the use of vasoconstrictors is for terlipressin. Terlipressin is a synthetic analogue of vasopressin. The drug forms active metabolites and has a vasoconstrictive effect. Contraindicated in epilepsy, coronary heart disease, arterial hypertension, arrhythmia, bronchial asthma, in the early stages of pregnancy.

In recent years, good results have been achieved with the combined use of albumin and terlipressin (0.5–2 mg IV 2 times a day for 4–6 hours for 2 weeks) [18, 24]. Terlipressin is started at a dose of 0.5 mg every 4 hours. In the absence of effect, i.e., a decrease in creatinine levels, the dose is increased gradually: after 2–3 days to 1 mg / 4 hours. Then, if necessary, after 2–3 days the dose of terlipressin is increased to 2 mg / 4 hours [13]. The probability of survival increases when the daily dose of terlipressin exceeds 3 mg. Usually, terlipressin is continued when serum creatinine is above 1.5 mg / 100 ml (0.125 mmol / L), but only in patients who have shown positive dynamics during treatment, the duration of the drug does not exceed 15 days. 16,22]. The introduction of terlipressin reduces the initial vasodilation of the arterioles of the mesenteric system, resulting in improved renal perfusion with arterial blood and, as a result, improved glomerular filtration. Side effects (headache, pallor, shortness of breath, increased blood pressure, myocardial ischemia, increased intestinal motility, uterine contractions) are usually observed at doses exceeding 2 mg / 4 h. At the usual dose, adverse ischemic reactions after the use of terlipressin are observed in less than 5% of cases [13]. With effective treatment with albumin and vasoconstrictors, blood pressure levels increase by 10 mmHg or more, and there is also a decrease. serum creatinine to 0.125 mmol / l or less. If the serum creatinine level does not decrease during the first 2 days of treatment.

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A positive effect, especially in combination with arterial hypotension, can be achieved by administering "renal" doses of dopamine (2-4 μg / kg body weight / min), preferably in combination with albumin. However, the effectiveness of dopamine is significantly lower than that of terlipressin, since dopamine alone restores renal function in only 5% of patients. If diuresis under the influence of dopamine does not increase within 12 hours, further use of the drug is hopeless . There are reports of successful treatment of patients with type I GRS by intravenous administration of norepinephrine (0.5-3 mg / h, titration until the mean blood pressure increases by 10 mmHg, continuous administration) in various doses in combination with albumin and furosemide, maintaining the central venous pressure at a level of 4-10 mmHg. and diuresis 100 ml / h. The duration of treatment is up to 15 days. The possibility of "ischemic" side effects of norepinephrine should be considered . Treatment of patients with GRS with endothelin antagonists and NO-inhibitors is considered promising, but researchers have not yet studied the use of prostaglandins A1 and E as renal vasodilators [2]. In the treatment of patients with GRS, it is necessary to remember several important nuances of therapy:

• hypertonic sodium chloride solution cannot be administered intravenously, as this can lead to the development of pulmonary edema and death of the patient;

• administration of mannitol can lead to acidosis;

• potassium-sparing diuretics can lead to hyperkalemia;

• vasoconstrictors should be used with caution in patients with cardiovascular disease, severe atherosclerosis of the brain and peripheral arteries;

• in patients with decompensated cirrhosis, when there is no prospect of liver transplantation, conventional dialysis is usually not performed due to the risk of coagulopathy, hemodynamic instability and sepsis;

• if there is no response to treatment with albumin and vasoconstrictors for 4-5 days, the effect of transjugular portosystemic bypass surgery is not observed;

• dilution due to hyponatremia is usually limited to the administration of 1000 ml of fluid per day (total oral and parenteral);

• to exclude subclinical hypovolemia, 1.5 liters of fluid should be administered immediately after the diagnosis of the disease (preferably albumin solution);

• it is necessary to analyze whether renal failure is caused by iatrogenic hypovolemia, which develops with excessive use of diuretics, laxatives (lactulose, which is prescribed in connection with hepatic encephalopathy).

The most effective treatment for type I GRS is liver transplantation. The positive effect, which consists in increasing the average life expectancy, is provided by extracorporeal albumin dialysis using a transjugular portosystemic bypass operation or a molecular adsorption system (MARS) . The use of vasoconstrictors (terlipressin) and albumin as conservative therapy is mandatory . The effectiveness of conservative therapy with vasoconstrictors and albumin in the treatment of patients with type II GRS has been proven so far only in pilot studies. The main problem of this category of patients is refractory ascites. Liver transplantation can also be performed in such patients. And the available data on the effectiveness of transjugular portosystemic bypass surgery in patients with type II GRS do not fully answer the questions about the complications of therapy and patient survival against the background of positive dynamics of ascites and a decrease in serum creatinine [5, 11]. The effectiveness of conservative treatment of GRS without the use of vasoconstrictors and albumin is very low - the mortality rate is close to 100% [2, 3, 8, 25]. A

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satisfactory effect of albumin therapy with terlipressin is observed in 60-75% of patients with type I GRS with Child-Pugh A and B severity within 7-14 days of treatment
. Similar treatment of type II diseases in most cases ensures survival. It should be remembered that the combination of azotemia, hyponatremia and hypotension should be taken as a harbinger of death. And the most common cause of death in hepatorenal syndrome is not renal failure, but hepatic coma. In general, the prognosis of HRS largely depends on the course of the liver process. Complete reversal of HRS is observed with spontaneous recovery of liver function or transplantation of a donor liver, while survival after liver transplantation in patients with previous GRS is worse than without it. The prognosis of hepatorenal syndrome against the background of acute hepatitis is very favorable. Mortality in this pathology with cirrhosis reaches 90%. The prognosis is especially serious when the serum creatinine level exceeds 221 mmol/l and the serum sodium level is less than 120 mmol/l . Given the high mortality rate and complexity of the correction of GRS, prevention of its development saves the patient's life. Prevention of GRS involves strict control of the use of diuretic drugs, evacuation of large amounts of ascitic fluid by paracentesis, preventive and emergency measures to stop bleeding, prevention of the development of infectious complications and their timely and adequate control, avoidance of the appointment of nephrotoxic drugs. drugs (aminoglycosides, X-ray contrast agents, NSAIDs) to patients with severe liver pathology. It should also be remembered that arginine, as a component of citraarginine, is a nitric oxide donor, the use of which can worsen renal failure in HRS.
As mentioned above, the causes of the development of GRS are often iatrogenic in nature. Therefore, it is especially important to pay attention to the correctness of ascites treatment - as a prevention of the development of HRS. As a rule, the stereotype of prescribing a doctor to a patient with ascites involves the parenteral administration of large doses of furosemide. In this case, this is unacceptable - in the treatment of ascites in patients with cirrhosis of the liver, oral administration and, preferably, spironolactone are preferred. Furosemide can be used, but in moderate doses and with strict control of diuresis. If diuresis under the influence of diuretics in a patient without peripheral edema exceeds 700-1000 ml, then intravascular fluid loss can provoke HRS.

Clinical Implications:

This study implies that early detection of patients with high inflammatory markers and certain genetic risk factors may allow for more focused interventions, such as the use of anti-inflammatory medicines or ACE inhibitors to enhance patient outcomes.

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Table 1: Medications commonly used in the treatment of HRS

Class	Drug	Action	Comment
Albumin		Intravascular volume expansion	Complimentary component of most vasoconstrictor therapies
Vasopressin analogs	Vasopressin, ornipressin	Vasopressin receptor agonist	Some improvement in HRS: serious side effects
	Terlipressin	V1 receptor agonist	Most well-validated vasopressin analog: unavailable in United States
Alpha-adrenergic agonists	Noradrenaline	Adrenergic agonist	Benefits comparable to terlipressin: greater availability
	Midodrine	Selective alpha-1 adrenergic agonist	Frequently paired with octreotide: less effective than noradrenaline or terlipressin
Somatostatin analog	Octreotide	Inhibits splanchnic blood flow	Improves renal blood flow: decreases GFR
Dopamine agonist	Dopamine		Improves renal blood flow: no improvement in renal function

Abbreviations: GFR, glomerular filtration rate; HRS, hepatorenal syndrome

Limitations:

a) The study was limited to a specific geographic region, and the findings may not be generalizable to other populations.

b) The retrospective design may have introduced biases, particularly in the selection of patients for genetic testing.

Conclusion

The clinical, pathogenetic, and genetic parameters analysed provide important information on the prognosis of HRS patients in the Khorezm region. The discovery of specific genetic markers and inflammatory pathways that influence disease progression may pave the door for more personalised therapeutic approaches. Future research should examine the therapeutic implications of targeting these pathways to enhance survival rates in patients with HRS.

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