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Pathophysiology, clinical features and management of hepatorenal syndrome

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Abstract. – **Hepatorenal syndrome (HRS) is a form of functional renal failure occurring in patients with advanced liver disease. Hypoperfusion of the kidney, due to renal vasoconstriction, is the main feature of HRS. Conversely, the extrarenal circulation is characterized by low systemic resistance, especially occurring in splanchnic vessels, and arterial hypotension. It has been postulated that renal vasoconstriction is induced either by a hepatorenal reflex related to the diseased liver or by arterial vasodilation and the subsequent baroreceptor-mediator activation of systemic vasoconstrictor factors.**

The diagnosis of HRS requires the exclusion of other causes of renal failure in patients with liver disease. On the basis of clinical and prognostic differences, two types of HRS have been defined. The prognosis of HRS is poor and, to date, the only effective treatment is the liver transplantation.

Key Words:

Renal failure, Liver disease, Hemodynamic abnormalities, Liver transplantation.

Introduction

Hepatorenal syndrome (HRS) is a form of functional renal failure occurring in patients with severe liver disease. In a large series of patients with cirrhosis, the probability of developing this condition was found to be 18% at 1 year and 39% at 5 years of follow-up[1].

Although the association of renal dysfunction and liver disease was first noted in the nineteenth century[2], a detailed description of the syndrome was made by Hecker and Sherlock[3] and Papper et al[4] in 1950s. Since then it has been recognized that HRS is a form of rapidly progressive renal failure which is not associated with histologic kidney abnormalities, commonly occurs in patients with arterial hypotension and has a poor prognosis. The functional nature of HRS was definitively demonstrated by the observation that kidneys from patients with HRS regained a normal function when transplanted to patients with chronic renal failure[5] and that renal failure recovered after liver transplantation[6].

According to the recently proposed definition criteria, HRS is a clinical condition that occurs in patients with chronic liver disease, advanced hepatic failure and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems[2]. Renal failure with characteristics similar to those of HRS has also been described in patients with acute liver failure[7].

Pathophysiology

Hypoperfusion of the kidney, due to renal vasoconstriction, is the main feature of HRS. Renal vasoconstriction has been demonstrated with a variety of methods, including duplex Doppler ultrasonography, which represents the most recent technique[8].

Conversely, the extrarenal circulation is characterized by low systemic resistance and arterial hypotension, associated with a high cardiac output[9,10].

The sympathetic nervous system (SNS) is highly activated in patients with HRS[11]. It has been demonstrated that the increased intrahepatic pressure is associated with an increased efferent renal SNS activity[12], and that the infusion of glutamine into portal vein, which causes hepatocyte swelling and, presumably, portal hypertension, is followed by a significant decrease in both glomerular filtration rate (GFR) and renal blood flow[13]. This effect

is abolished by renal denervation. These observations are consistent with the hypothesis that the cirrhotic liver induces SNS-mediated vasoconstriction via a hepatorenal reflex.

An alternative hypothesis emphasizes the role of the arterial underfilling and the subsequent baroreceptor-mediator activation of systemic vasoconstrictor factors, such as renin-angiotensin system, SNS and arginine vasopressin[14]. Arterial underfilling in cirrhosis is not due to a reduction in the intravascular volume, which is in fact increased, but is induced by the excessive arterial vasodilation, which especially occurs in the splanchnic circulation.

The role of several vasoactive mediators in renal function impairment has been evaluated. Endothelin-1 concentrations are increased in the HRS and correlate with creatinine clearance in decompensated liver disease, although the role of this potent vasoconstrictor is still controversial[11]. Eicosanoids have also been suspected to play a role, since increased renal production of cysteinyl leukotrienes, especially leukotriene E4, which is a powerful renal vasoconstrictor, has been observed in cirrhotic patients with HRS[15]. Both endothelin and cysteinyl leukotrienes may also impair glomerular filtration by inducing mesangial cell contraction[11].

Renal hypoperfusion in HRS is probably a result of the imbalance between vasodilator and vasoconstrictor mediators. In decompensated liver disease urinary excretion of prostaglandin E2 and prostacyclin metabolites is usually increased[11]. Renal prostaglandins probably play a crucial role in protecting the renal function from the adverse effects of vasoconstrictor factors. It has been demonstrated that the administration of cyclooxygenase inhibitors (NSAIDs) to patients with ascites frequently causes renal failure, and this usually reverses on cessation of NSAID treatment[16]. Experimental studies suggest that in cirrhosis nitric oxide as well as the natriuretic peptide family, also have a role in preserving renal function[17,18].

Clinical Features

The diagnosis of HRS requires the exclusion of other causes of renal failure in patients with liver disease, such as hypovolemia, acute tubular necrosis induced by shock or drug nephrotoxicity, bacterial infections and glomerulonephritis. The values of urine sodium as well as the urine/plasma osmolality ratio are not essential criteria for the diagnosis (Table I)[2].

On the basis of clinical and prognostic differences, two types of HRS have been defined[1]. Type I HRS is characterized by rapid and progressive increase in blood urea nitrogen (BUN) and serum creatinine over a short period of time (days or few weeks). Patients with this type of HRS usually show severe degrees of liver disease. The onset of type I HRS often shows a correlation with some complications of the liver disease or therapeutic interventions. In patients with cirrhosis, spontaneous bacterial peritonitis (SBP) is often associated with signs of renal function impairment[19]. In about 15% of patients with SBP, there is evidence of a type I HRS and this represents an ominous prognostic factor. Type I HRS has been described also in about 10-15% of cirrhotic patients with ascites treated with large-volume paracentesis without plasma volume expansion[20]. In patients with type I HRS, the prognosis is very severe since the median survival time is less than 2 weeks. Type II HRS usually occurs in patients with less severe hepatic function im-

Table I. Diagnostic criteria of hepatorenal syndrome according to the International Ascites Club[2].

Major criteria
1) Low glomerular filtration rate, as indicated by serum creatinine > 1.5 mg/dL or creatinine clearance < 40 ml/min
2) Absence of shock, bacterial infection, gastrointestinal or renal fluid losses and current or recent treatment with nephrotoxic drugs
3) No sustained improvement in renal function following diuretic withdrawal and plasma volume expansion with 1.5 L of isotonic saline
4) Proteinuria < 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Additional criteria
1) Urine volume < 500 mL/day
2) Urine sodium < 10 mEq/L
3) Urine osmolality higher than plasma osmolality
4) Urine red blood cells < 50 per high power field
5) Serum sodium < 130 mEq/L

pairment. This type of HRS is characterized by a moderate and stable decrease of GFR; (BUN) and serum creatinine are usually lower than 50 mg/dL and 2 mg/dL, respectively. These patients frequently have refractory ascites. Although in this type of HRS the prognosis is less severe, the survival is shorter than in patients with ascites and a preserved renal function[1].

Management

In cirrhotic patients, the conditions which can precipitate a HRS should be prevented. In particular, large-volume paracentesis should be followed by the administration of albumin, since this procedure decreases the incidence of HRS[20]. Nephrotoxic drugs should be avoided and bacterial infections should be promptly diagnosed and adequately treated.

Several therapeutic modalities have been evaluated in HRS. Although renal vasoconstrinction plays a pivotal pathophysiologic role, the administration of renal vasodilators, such as prostaglandins[21] or dopamine at low doses[22], does not improve renal function significantly. On the other hand, vasoconstrictor agents have been used in an attempt to improve renal perfusion by increasing the low systemic vascular resistance and, as a consequence, suppressing the activity of systemic vasoconstrictors. Unfortunately, vasoconstrictor agents, such as ornipressin and norepinephrine, even if associated with vasodilators, have failed to improve renal function[23]. The lack of a favorable effect may be related either to the induction of renal vasoconstriction by these drugs or to the persistent activation of vasoconstrictor factors. However, in a recent report, the association of ornipressin and albumin in cirrhotic patients with HRS has been shown to induce an improvement in renal function and hemodynamic abnormalities[24].

Currently, dialysis is considered only in patients awaiting for liver transplantation, whereas peritoneovenous shunt has no therapeutic role[11]. Interestingly, transjugular intrahepatic portosystemic shunt (TIPS), a nonsurgical method of portal decompression, has been reported to improve renal function of patients with HRS[25].

To date, the only effective treatment for HRS is the liver transplantation. In cirrhotic patients with HRS undergoing liver transplantation, 1-year and 4-year survival is 71% and 60%, respectively, and shows only a slight decrease when compared with that of cirrhotic patients without HRS (83% and 70%, respectively)[26].

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