

HEPATORENAL SYNDROME: A REVIEW

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ABSTRACT

Hepatorenal syndrome (HRS) is defined as a functional renal failure in patients with liver disease that features morphologically intact kidneys, where regulatory mechanisms have minimized glomerular filtration and maximized tubular resorption and urine concentration. The syndrome occurs almost exclusively in patients with ascites. Type 1 HRS develops as a consequence of a severe reduction of effective circulating volume due to both an extreme splanchnic arterial vasodilatation and a reduction of cardiac output. Type 2 HRS is characterized by a stable or slowly progressive renal failure so that its main clinical consequence is not acute renal failure, but refractory ascites, and its impact on prognosis is less negative. Liver transplantation is the most appropriate therapeutic method, nevertheless, only a few patients can receive it. The first line treatment includes terlipressin plus albumin. Renal function recovery can be achieved in less than 50% of patients and a considerable decrease in renal

RÉSUMÉ

Le syndrome hépato-rénal: revue

Le syndrome hépato-rénal (SHR) est défini comme une insuffisance rénale fonctionnelle chez les patients atteints d'une maladie hépatique présentant des reins morphologiquement intacts, où les mécanismes de régulation ont minimisé la filtration glomérulaire et maximisé la résorption tubulaire et la concentration urinaire. Le syndrome survient presque exclusivement chez les patients atteints d'ascite. Le type 1 du SHR se développe à la suite d'une réduction sévère du volume circulant efficace en raison d'une vasodilatation artérielle splanchnique extrême et une réduction du débit cardiaque. Le type 2 du SHR est caractérisé par une insuffisance rénale stable ou lentement progressive, de sorte que sa principale conséquence clinique n'est pas une insuffisance rénale aiguë, mais une ascite réfractaire, et son impact sur le pronostic est moins négatif. La transplantation hépatique est la méthode thérapeutique

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function may reoccur even in patients who have been responding to therapy over the short term. Other therapies include transjugular intrahepatic portosystemic shunts (TIPS), dialysis and peritoneovenous shunts which are most commonly done when patients are awaiting a liver transplant or when there is the possibility of improvement in liver function.

Keywords: hepatorenal syndrome, liver disease, cirrhosis, ascites.

INTRODUCTION

Hepatorenal syndrome is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or in those with fulminant hepatic failure, in the absence of a pre-existing renal pathology. The term is often used for any type and degree of failure renal syndrome that occurs in this context. However, renal insufficiency which occurs in cirrhosis decompensated with ascites, is not classified as hepatorenal syndrome than in about 20% of cases, in the other cases being pre-renal insufficiency (42%) or acute tubular necrosis (38%)¹. The probability of occurrence of HRS in patients with cirrhosis is 18% at 1 year and 39% at 5 years, prognosis being highly reserved in the absence of liver transplantation². Hepatorenal syndrome is an exclusion diagnosis in which hypovolemia, nephrotoxicity, medications, sepsis and glomerulonephritis will be eliminated. In about half of HRS cases, precipitating factors are identified: bacterial infection, gastrointestinal hemorrhage, or paracentesis³. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilation. Tubular function is preserved with the absence of proteinuria or histologic changes in the kidney. Two subtypes of HRS have been identified. Type 1 HRS is a rapidly progressive renal failure that is defined by doubling of initial serum creatinine to a level of 2.5 mg/dL or by 50% reduction in creatinine clearance to a level of 20 ml/min in less than 2 weeks and is associated with severe renal vasoconstriction and failure of compensatory mechanisms that are responsible for maintenance of renal perfusion⁴. Type 2 HRS is a moderate, steady renal failure with a serum creatinine of 1.5 mg/dL. In type 1 HRS, a precipitating factor frequently is identified, whereas type 2 HRS arises spontaneously,

la plus appropriée, mais seulement quelques patients peuvent la recevoir. Le traitement de première ligne comprend la terlipressine plus l'albumine. Le rétablissement de la fonction rénale peut être atteint chez moins de 50% des patients et une diminution considérable de la fonction rénale peut se produire même chez les patients qui ont répondu au traitement à court terme. D'autres thérapies comprennent les shunts portosystémiques intrahépatiques transjugulaires (TIPS), la dialyse et les shunts péritonéo-urinaires, qui sont le plus souvent pratiqués lorsque les patients attendent une transplantation hépatique ou lorsqu'il existe une possibilité d'amélioration de la fonction hépatique.

Mots-clés: syndrome hépatorénal, maladie hépatique, cirrhose, ascite.

it is the main underlying mechanism of refractory ascites, is gradually progressive and appears in association with the progression of cirrhosis. A special category is represented by patients with underlying chronic renal disease. There is an increasing awareness that patients who fit in this category do exist, but go unrecognized, according to the definitions of the existing criteria. Munoz proposes that patients with HRS superimposed on chronic renal disease should be categorized as having type 3 HRS⁵.

PATHOPHYSIOLOGY

The pathophysiology of HRS is complex and incompletely characterized. Four important components contribute to the initiation and perpetuation of altered renal perfusion: peripheral arterial vasodilation with hyperdynamic circulation and subsequent renal vasoconstriction, stimulation of the renal sympathetic nervous system, cardiac dysfunction contributing to the circulatory derangements and renal hypoperfusion⁶. Splanchnic and systemic arterial vasodilatation is a hallmark of the progression of portal hypertension in patients with cirrhosis and leads to decreased effective circulatory blood volume and ultimately to a decrease in blood pressure. In the early stages of portal hypertension, increases in heart rate and cardiac output compensate for the decrease in effective circulatory volume and create a hyperdynamic circulation. As the liver disease and splanchnic vasodilatation progress, additional compensatory mechanisms are activated. Splanchnic and systemic vasodilatation also lead to compensatory renal vasoconstriction, renal sodium and water retention, in turn leading to hyponatremia and ascites formation. These responses are mediated by stimulation of the sympathetic nervous system, activation

of the renin-angiotensin-aldosterone system (RAAS), and osmotic release and activity of arginine vasopressin, as well as intrarenal events. Ultimately, the balance between vasoconstrictive responses in the kidney and systemic and splanchnic vasodilatation is lost, thereby leading to a prominent increase in renal vascular resistance, a decrease in renal perfusion, and reduction in the glomerular filtration rate (GFR). Finally, intense renal vasoconstriction may lead to tubular damage, and HRS can evolve from a functional syndrome to an organic disease. Impaired cardiac function also may contribute to renal hypoperfusion in patients with HRS. In one prospective study, HRS developed in cirrhotic patients with more severe arterial vasodilatation and lower cardiac output. In another study of a cohort of patients who were treated for SBP, renal dysfunction developed in those with lower cardiac output and lower arterial pressure measurements associated with higher circulating levels of norepinephrine and renin plasma activity⁷.

PRECIPITATING FACTORS

Precipitating factors have been reported based on a large series of patients with cirrhosis and ascites and, for the most part, are related to circulatory and renal function. Three important and easily recognized risk factors are: low arterial blood pressure (<80 mm Hg), dilutional hyponatremia, and severe urinary sodium retention (urine sodium <5 mEq/L)⁸. Interestingly, patients with advanced liver disease, defined by a high Child-Pugh score or worsening parameters of liver function, such as albumin, bilirubin, and prothrombin levels, are not at a higher risk of developing HRS.

HRS may occur spontaneously but it also may be associated with infections (particularly spontaneous bacterial peritonitis), acute alcoholic hepatitis, or large-volume paracentesis without albumin replacement. Some of the risk factors associated with the development of HRS are: low urinary sodium excretion (<5 mEq/L), low serum sodium (dilutional hyponatremia), reduced free-water excretion after water load, low arterial pressure, high plasma renin activity, increased plasma norepinephrine, low plasma osmolality, high urine osmolality, high serum potassium, previous episodes of ascites, absence of hepatomegaly, presence of esophageal varices, poor nutritional status, moderately increased serum urea (>30 mg/dL), moderately increased serum creatinine (>1.5 mg/dL), moderately reduced GFR (<50 ml/min)⁹.

In type 1 HRS, a precipitating event is identified in 70 to 100% of patients with HRS, and more than one event can occur in a single patient, including bacterial infections, large-volume paracentesis without albumin infusion, gastrointestinal bleeding, and acute

alcoholic hepatitis¹⁰. Similarly, large-volume paracentesis without albumin expansion precipitates type 1 HRS in 15% of cases, and 25% of patients who present with acute alcoholic hepatitis eventually develop HRS¹¹. Although renal failure after gastrointestinal hemorrhage occurs more frequently in patients with cirrhosis, ARF develops almost exclusively in patients with hypovolemic shock, making acute tubular necrosis a more plausible diagnosis¹². Exacerbation of renal hypoperfusion and aggravation of renal ischemia create an intrarenal vicious cycle that favors more renal vasoconstrictors release and impairs renal vasodilator synthesis. This vicious cycle eventually will progress to HRS even if the underlying precipitating event has been corrected. Another possible explanation is that the deterioration in renal function is secondary to deterioration in cardiac function, as a result of either the development of septic cardiomyopathy or worsening of a latent cirrhotic cardiomyopathy. In type 2 HRS and in some patients with type 1 HRS, no precipitating factor can be identified. The mechanism of renal failure in these cases is unclear, but it seems to be related to worsening liver disease with subsequent failure of compensatory mechanisms that aim to maintain adequate renal perfusion¹³.

CLINICAL FEATURES AND DIAGNOSIS

Hepatorenal syndrome is a functional disorder and has no specific signs, therefore, laboratory and imaging studies alone are not sufficient for making the diagnosis. It is mainly an exclusion diagnosis and other potential causes of kidney injury are needed. However, detecting the stigmata of chronic liver disease is important because most patients at risk for HRS have advanced cirrhosis. Most findings are not present in all patients with chronic liver disease but we always must look for palmar erythema, leukonychia (white nails), muscle wasting, asterixis (flapping tremors), clubbing, scleral icterus, spider nevi, fetor hepaticus and xanthelasma¹⁴. Circulatory disturbances include a hyperdynamic circulation and reduced systemic vascular resistance. This may manifest clinically as low jugular venous pressure, tachycardia, a bounding pulse, and wide pulse pressure. The following laboratory findings are suggestive of HRS: elevated plasma renin activity, elevated plasma noradrenaline activity, hyponatremia, hyperkalemia, elevated blood urea nitrogen, decreased plasma osmolality, elevated urinary osmolality, and decreased urinary sodium excretion. Serum abnormalities that reflect the severity of the liver disease include hyperbilirubinemia, hypoalbuminemia, and prolonged prothrombin time¹⁵. The majority of patients with HRS are asymptomatic, although some may report decreased urine output.

Differential diagnosis is always needed so we must always consider prerenal azotemia from volume depletion, drug-induced nephrotoxicity: commonly implicated medications include nonsteroids, aminoglycosides, diuretics, and iodine-containing contrast agents; other medications that may contribute to renal dysfunction in these patients are angiotensin-converting enzyme inhibitors, demeclocycline, and dipyridamole, postrenal azotemia from outflow obstruction renal vascular disease¹⁶. The diagnostic criteria for HRS, as defined by the International Ascites Club Consensus Workshop in 2007, include major criteria: cirrhosis with ascites, serum creatinine level higher than 1.5 mg/dL (133 μ mol/L), lack of improvement in the serum creatinine level to 1.5 mg/dL (133 μ mol/L) or less after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight/day, to a maximum of 100 g/day), absence of shock, lack of current or recent treatment with nephrotoxic drugs, and absence of parenchymal kidney disease as indicated by proteinuria of more than 500 mg/day, microhematuria (>50 red blood cells/high power field), or abnormal renal US findings¹⁷. Additional criteria include: urine volume < 500 ml/day, urinary sodium < 10 mEq/L, urinary osmolality greater than plasma osmolality, urine red blood cells < 50 per high power field, serum sodium < 130 mEq/L¹⁸.

MANAGEMENT OF HEPATORENAL SYNDROME

Prevention of HRS

Rapid identification of infection and appropriate antibiotic therapy decreased the mortality rate in spontaneous bacterial peritonitis from 50% to approx. 18-20%¹⁹. Bacterial infection, present in approx. 50% of patients with variceal hemorrhage, is an important cause of renal dysfunction in patients with cirrhosis.

In patients with cirrhosis and HRS, paracentesis is recommended for evaluation purposes in early presence of spontaneous bacterial peritonitis. Antibiotic prophylaxis is recommended in two clinical situations: hemorrhage from esophageal varices and a history of spontaneous bacterial peritonitis.

The presence of spontaneous bacterial peritonitis will require preventive administration of albumin 20% 1 g/kg initially, then 1.5 g/kg on day 3²⁰. Albumin efficiently prevents additional volume expansion and circulatory bloodstream reduction, but also interferes with the binding of nitric oxide and cytokines, which have a negative inotropism and systemic vasodilatory effect. Volumetric expansion with human albumin in order to prevent HRS is also recommended in case of high volume paracentesis – over 5 L of ascites evacuated²¹. The judicious use of

diuretics (the nephrotoxic effect occurs in around 20-50% of patients with ascites) means using minimal effective doses which avoids diuresis to overcome the rhythm of reabsorption of ascites and to reach hypovolemia²². The lowest effective dose will be used because HRS can be precipitated by the direct renal action of the drug by creating an imbalance (diuresis exceeds the absorption rate of ascites fluid). Choosing the diuretic can be done depending on the urine sodium concentration, aiming at a negative balance of sodium: the restriction intake to 50 mEq concomitantly with fluid restriction (1500 ml/ day). If initial excretion of sodium is above 30 mEq/L, only spironolactone will be administered; between 10 to 30 mEq/L, spironolactone will also be associated with furosemide, and below 10 mEq/L will indicate paracentesis. Furosemide should only be given in combination with spironolactone in a proportion of 40 mg: 100 mg spironolactone (maximum doses 160 mg furosemide: 400 mg spironolactone²³. Beside urinary sodium, weight loss up to 1 kg/day in patients with ascites and peripheral edema, and 0.5 kg/day in those without peripheral edema, is an additional target. Hyponatremia below 120-125 mEq/L will require water restriction (<1000 ml/day), with higher plasma sodium being relatively well tolerated by the patient. The HRS diagnosis requires to stop diuretics administration if the hypovolemia induced by them is considered a precipitating factor and immediate albumin infusions²⁴. Advanced cirrhosis with refractory ascites in diuretic therapy is complicated in approx. 20% of cases with hepatorenal syndrome, with 1 year mortality being approx. 50%²⁵.

Initial treatment of HRS

The risk of developing HRS in patients with advanced liver disease requires firstly an optimal fluid management in order to avoid hypovolemia: albumin administration (1500 ml) or saline fluids may be effective in patients with subclinical hypovolemia. This will exclude functional renal insufficiency and diminish the magnitude of vasoconstrictive reactive mechanisms which damage renal function until the recovery of liver function. All precipitating factors will also be treated: hemorrhage, sepsis and nephrotoxic drugs. While monitoring of patients with HRS 1 will be done only in hospital, requiring a central catheter for monitoring and administering fluids, follow-up of patients with type 2 HRS can be done ambulatory, with particular attention to diuretic therapy and monitoring of precipitating factors in order to identify the moment of deterioration to HRS type 1²⁶.

Pharmacotherapy in HRS

The ideal therapy for hepatorenal syndrome is improvement of liver function from recovery of

alcoholic hepatitis or decompensated hepatitis B. However, when improvement of liver function is not possible in the short term, medical therapy has to be instituted in an attempt to reverse the acute kidney injury associated with hepatorenal syndrome. Patients with HRS should be evaluated for liver transplantation, at a liver transplant center if possible. This may be more applicable for patients with type 2 HRS, who have a longer survival time, as opposed to patients with type 1 HRS, whose survival is extremely short and who may require alternative therapeutic methods (eg, TIPS, vasoconstrictors) as a bridge to transplantation.

In patients with hepatorenal syndrome who are critically ill, initial treatment is represented by **norepinephrine in combination with albumin**. Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/hr) with the goal of raising the mean arterial pressure by 10 mmHg, and albumin is given for at least two days as an intravenous bolus (1 g/kg per day [100 g maximum]). Intravenous vasopressin may also be effective, starting from 0.01 units/min and titrating upward as needed to raise the mean arterial pressure as noted below²⁷.

Use of systemic vasoconstrictors in combination with albumin 1 g/kg in the first day followed by 20-40 g/day was associated with satisfactory results in HRS type 1 (recovery of renal function in 40-60% of cases). In SHR type 2, recovery percentage of renal function is similar to type 1 but with a survival rate of 100% up to 3 months²⁸.

Terlipressin (glypressin) is a synthetic analogue of vasopressin with vasoconstriction action on the splenic V1- receptors. Compared with vasopressin it has the advantage of a longer half-life that allows administration at 4 hours (0.5-2 mg at 4-12 hours) or in continuous infusion, maximum 12 mg/day²⁹. Possible effect on potassium excretion at the tubular level can contribute to ameliorating HRS associated hyperkalemia. An analysis in the Cochrane Database of Systematic Reviews 2006, which included 645 patients and 6 randomized trials, suggests that terlipressin may improve renal function and reduce mortality in HRS³⁰. Recently, in a meta-analysis of clinical trials, Fabrizi et al concluded the efficiency and safety of terlipressin in HRS³¹.

Octreotide is a prolonged action-effect somatostatin analogue variable on splanchnic circulation at a dose of 100-200 µg three times a day s.c. Noradrenaline (0.5-3 mg/h) or midodrine (7.5-12.5 mg three times a day orally) are alpha-agonist alternatives³². By administering midodrine alone or in combination with octreotide, encouraging results were obtained in SHR. Good results (recovery of renal function in 60-80% of cases) were obtained

in the last years in type 1 HRS by association between vasoconstrictor and albumin for 10-15 days. Terlipressin and TIPS were associated with the best results³³. Several recent studies have shown promising results in HRS therapy: terlipressin in combination with albumin, albumin alone whether or not with furosemide under central venous pressure control or noradrenaline in combination with albumin and furosemide³⁴. The follow-up period for the improvement of renal function after administration of vasoconstrictors has to be prolonged at 2-3 weeks, (the period of healing from an acute tubular injury and necrosis that may occur in the evolution of a HRS). This aspect was not taken into account, most studies focusing on observing the effects of therapy on a range of days which limits the results interpretation³⁵.

Dopamine was the first drug used for renal vasodilatation, but the results were not convincing. Low dose of dopamine is recommended for limited use up to 12 hours and to be stopped if does not show diuretic growth response. Dopamine is no longer recommended for the treatment of HRS due to its secondary effects and lack of evidence to support its use³⁶.

Endothelin antagonists appear to improve renal function without improvement of prognosis in HRS. To improve intramural hemodynamics, small groups of patients have been studied with administration of misoprostol (synthetic analogue prostaglandin E1), endothelin and N-acetylcysteine antagonists, but further studies are required³⁶. Endothelin and N-acetylcysteine antagonists have not yet been extensively tested⁶.

OTHER THERAPIES include transjugular intrahepatic portosystemic shunts (TIPS), dialysis and peritoneovenous shunts which are most commonly done when patients are awaiting a liver transplant or when there is the possibility of improvement in liver function. In addition, these methods improve the priority score for a near future transplant.

CONCLUSIONS

The hepatorenal syndrome is one of many potential causes of acute kidney injury in patients with acute or chronic liver disease³⁷⁻⁴¹. Affected patients usually have portal hypertension due to cirrhosis, severe alcoholic hepatitis, or metastatic tumors, but can also have fulminant hepatic failure from any cause. Without therapy, most patients die within weeks of the onset of the renal impairment. In turn, the outcome of patients with hepatorenal syndrome, as well as recovery of kidney function, is strongly dependent upon reversal of the hepatic failure, whether spontaneously, following medical therapy, or following successful liver transplantation.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study“

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