HEPATORENAL SYNDROME: A REVIEW

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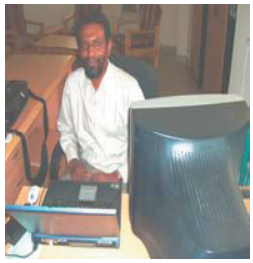
Introduction



The hepatorenal syndrome [HRS]is a reversible functional acute renal failure secondary to intense renal cortical vasoconstriction in a patient with liver disease. It affects around 40% of patients with cirrhosis and ascites[1]. The exact cause of the syndrome is not well understood. The state of liver dysfunction [Child-Pugh score] does not predict the occurrence of the disease.

Genetic factors play no important role except as risk for liver disease and there is no sex difference. Patients with HRS characteristically have increased cardiac output, low arterial pressure, and reduced systemic vascular resistance[2]

Diagnosis of HRS is one of exclusion.The definitive treatment is liver transplant. Nevertheless, a lot of work was done on medical therapy with promising results.

Pathogenesis

The pathogenesis of the disease is ill defined. The structural hallmark of HPS is a reversible preferential renal vasoconstriction in the absence of reduced cardiac out put or blood volume. There are no histopathological changes in the kidneys and the tubules continue to reabsorb sodium during the disease. The kidneys transplanted from patients with HRS function normally in the recipients[3]. Preferential renal vasoconstriction with beading and tortuosity [Fig A] which revert to normal when the patient dies [Fig B] was proved using renal arteriography [4].

It is clear that the imbalance between the systemic vasoconstrictor and the vasodilator systems lead to this disease. Multiple theories were put to explain the hemodynamic disturbances seen in patients with HRS.

The two main theories are the arterial vasodilatation theory and the hepatorenal reflex theory. In the first theory systemic hypotension caused by the intense vasodilatation induced and maintained by the high levels of nitric oxide-seen in patients with liver cirrhosis-is thought to activate the vasoconstrictive systems including rennin-angiotenin-aldosteron system and the sympathetic nervous system resulting in peripheral vasoconstriction.

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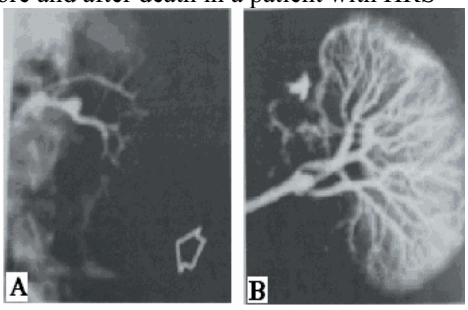
However, the splanchnic vasodilatation does not respond to that because of local production of nitric oxide. Other vasoactive substances including adenosine, prostacycline, endothelin 1, thromboxanes, prostaglandins, leukotrieneE4 and others may also contribute to the pathogenesis of this disease. Whether vasoconstrictor over activity or the vasodilator system under activity is the predominant contributor to this has yet to be proven. The second theory states that renal hypoperfusion is a direct reflex to liver disease irrespective to the haemodynamic status of the patient and here hepatic underproduction of renal vasodilators is thought to play a major ole.

Fig A & B. The vascular changes in the kidney before and after death in a patient with HRS



Estimation of renal function

The decline in liver function and reduced muscle mass in patients with chronic liver disease occasionally lead to inappropriately low levels of urea and creatinine and this usually mask the reduction in glomerular filteration rate. This makes early detection of renal failure in these patients difficult.

Clinical presentation

Patients with the HRS classically present with the symptoms and signs of acute or chronic liver disease. Virtually all patients have ascites and the majority have clinical evidence of portal

hypertension. Features of oliguric renal failure usually supervene.

Based upon the speed of onset of renal failure, two forms of hepatorenal syndrome have been described [5]:

• Type I hepatorenal syndrome which is characterized by the acute onset [within two weeks] of oliguric or anuric renal failure.

• Type II hepatorenal syndrome which is more insidious (> 2 weeks) and less severe than type 1, with relatively better urine output.

Gastrointestinal bleeding, rapid diuresis, paracentesis and infection were considered among the common triggering factors for the HRS[6]. Half of the patients have no identifiable precipitating factor. Spontaneous bacterial peritonitis precipitates HRS type 1 in approximately 20% of patients despite appropriate and timely diagnosis, treatment, and resolution of infection.

HPS is uncommon in patients with primary biliary cirrhosis and this is attributed to the natriuretic and renal vasodilator effect of bile salts[7]

Factors predictive for the development of HRS

Very low urinary sodium due to intense urinary sodium retention, dilutional hyponatremia, low blood pressure, decreased cardiac output, and increased activity of systemic vasoconstrictors are predictive factors for the onset of the syndrome[8]

DIAGNOSIS

There is no diagnostic test for the syndrome and so the diagnosis of HRS depends on the demonstration of renal failure in presence of liver disease and exclusion of interstitial renal disease including acute tubular necrosis, glomerulonephritis and pre-renal failure.

International ascites club diagnostic criteria for diagnosis of HRS[5]

Major criteria [All major criteria are required to diagnose HRS]:

1. Chronic or acute hepatic disease and liver failure with portal hypertension
2. Serum creatinine level >1.5 mg/dL (133 micromoles/L) or 24-hr creatinine clearance <40 mL/min (0.67 mL/s)
3. Absence of shock, ongoing bacterial infection, recent use of nephrotoxic drugs, excessive fluid or blood loss
4. No sustained improvement in renal function after volume expansion with 1.5 L isotonic saline solution
5. Proteinuria <500 mg/day and no ultrasonographic evidence of renal tract or parenchymal disease

Minor criteria [Additional criteria are not necessary for the diagnosis but provide supportive evidence]:

1. Urine volume <500 mL/day
2. Urine sodium <10 mEq/L
3. Urine osmolality greater than plasma osmolality
4. Urine red blood cell count <50 per high-power field

Meticulous search for other causes of renal failure has to be carried out before this diagnosis is made as the management and the prognosis differ significantly.

Treatment

HRS especially type 1 carries a poor prognosis. However, with increased understanding of the disease and its hemodynamic disturbances, promising new pharmacologic drugs and methods of treatments have emerged giving significant improvement in short-term outcomes. Improved liver function is the corner stone element in the treatment of the HRS. To date, recovery from acute liver insult if possible or liver transplantation is the only way for the cure of the disease[9]. Instant recovery of the renal failure occurs with improved liver function. The general management is that of renal failure and liver disease. Precipitating conditions-if identified- must be corrected. Keeping adequate circulation and good oxygenation of the blood is mandatory. Nephrotoxic drugs have to be stopped.

Medical therapy: Despite through research to treat the HRS, drug therapy appears to be ineffective in persistently- long term- reversing the disease Interventions that have shown some promise are the agonists of vasopressin V1 receptors, such as ornipressin and terlipressin, which have predominantly vasoconstrictor effects on the splanchnic circulation[10]. The rationale behind that is the theory of vasodilatation of the splanchnic circulation as the initial event in the development of HRS, and use of a vasoconstrictor may thus prevent homeostatic activation of endogenous vasoconstrictors. Other combination of drugs e.g.midodrine with octreotide and norepinephrine plus albumin infusion showed promising outcomes. The use of N-acetylcysteine, misoprstol, norepinephrine gave controversial results and need further studies.

Transjugular intrahepatic portosystemic shunt (TIPS)

Despite the risk of hepatic encephalopathy TIPS- which has been used in the treatment of refractory ascites- is found to help some selected

patients who are not candidates for or are awaiting liver transplantation[11,12]

Dialysis

Dialysis may buy time for patients awaiting liver transplantation and those wit h a c tue reversible liver insult. However, longterm survival following hemodialysis was reported[13]. Nevertheless it is occasionally difficult to be performed in these patients because of the coaggulopathy and the disturbed hemodynamic. Hemofiltration was also tried with some success[14]

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Liver transplantation:

Despite the high risk of postoperative morbidity and early mortality and the need for pre- and postoperative hemodialysis for some time, liver transplantation remains to be the definitive treatment of the HRS[15]

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Summary and recommendations:

HRS is a disease of ill defined pathogenesis. It is common in patients with liver cirrhosis and has significant morbidity and mortality. Through look and aggressive treatment for possible precipitant causes of renal failure in these patients is mandatory. Medical therapy gav e promising results. Nevertheless, liver transplant remains the gold standard treatment to save these patients. Hemodialysis should be attempted while awaiting liver recovery or transplantation. A combination of midodrine and octreotide may be given to patients who are not candidates for transplantation.

Refernces:

1. Gines A, Escorsell A, Gines P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105(1):229-36 .

2. Lee SS, Gaskari SA, Liu H, Cardiac and vascular changes in cirrhosis: pathogenic mechanisms. World J Gastroenterol 2006.12; 837-42.

3. Koppel MH, Coburn JW, Mims MM, et al. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome evidence for functional renal failure in advanced liver disease. N Engl J Med 1969;280: 1367.

4. Epstein M, Berk DP, Hollenberg NK, et al. Renal filure in the patient with liver cirrhois: The role of active vasoconstriction. Am J M 1970;49: 175

5. Wong F, Blendis L. New challenge of hepatorenal syndrome: prevention and treatment. Hepatology 2001; 34(6):1242-51

6. Gines P, Guevara M, Arroyo V, Rodes J Hepatorenal syndrome. Lancet 2003 362:1819-27].

7. Better,OS. Renal and cardiovascular function in liver disease. Kidney Int 1986;29: 598-607].

8. Andrés Cárdenas and Pere Ginès. Therapy Insight: management of hepatorenal syndrome. Nat Clin Pract Gastroenterol Hepatol. 2006 Jun;3(6):338-48.]

9. Arroyo V, Guevara M, Gines P. Hepatopulmonary syndrome in cirrhosis: Pathogenesis and treatment. Gastroenterology 2002;122: 1658-76

10. Ibrisim D, Cakaloglu Y, Akyuz F, et al Scand J Gastroenterol. 2006 Jul; 41(7):862-5Treatment of hepatic hydrothorax with terlipressin in a cirrhotic patient].

11. Guevara M, Gines P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effect on renal function and vasoactive systems. Hepatology 1998; 28(2):416-22

12. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000;47(2):288-95

13. Capling RK; Bastani B.The clinical course of patients with type 1 hepatorenal syndrome maintained on hemodialysis.Ren Fail. 2004; 26(5):563-8].

14. Epstein M. Hepatorenal syndrome: emerging perspectives. Semin Nephrol 1997; 17: 563-75]

15. Møller S; Henriksen JH.Review article: pathogenesis and pathophysiology of hepatorenal syndrome--is there scope for prevention? Aliment Pharmacol Ther. 2004; 20 Suppl 3:31-41; discussion 42-3