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A Review of Hepatorenal Syndrome

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ABSTRACT

Renal dysfunctions are not uncommon occurrences in liver cirrhosis and hepatorenal syndrome (HRS) is a major one with a very high morbidity and mortality. The major pathophysiological mechanisms have been mostly unravelled, consisting of splanchnic vasodilation and renal cortical vasoconstriction. These vascular anomalies stem from endogenous release of vasodilatory biomolecules such as nitric oxide in the face of high hepatic sinusoidal pressure and portal hypertension. The vasodilatation leads to ineffective tissue perfusion and subsequently triggering the release of vasoconstrcting substances via the rennin-angiotensin-aldosterone system, thus leading to a vicious cycle. Therapeutic intervention is anchored on the reversal of the splanchnic vasodilation and renal ischaemia. Measures that have shown promise include the use of vasopressin analogues like terlipressin or ornipressin, and alpha adrenergic agonists like midodrine and norepinephrine. The use of these vasoactive substances have been combined effectively with plasma expanders especially albumin infusion, using extracorporeal albumin dialysis (ECAD). The most effective therapy however is liver transplantation, though the mortality of this procedure is higher than in non-HRS patients. Transjugular intahepatic potacaval shunt (TIPS) has also been found useful, with good patient selection. Prevention of HRS is principally by prevention of precipitating factors like spontaneous bacterial peritonitis, gastrointestinal haemorrhage and depletion of the intravascular volume.

Keywords: *Hepatorenal syndrome, cirrhosis, ascites, portal hypertension.*

INTRODUCTION

The liver and the kidneys are both essential to sustenance of life in humans and as such disease conditions in either or both tend to present with dire consequences if not treated early. Joint failure of both organs often occurs and may manifest in several settings. Three major ways of joint failure of both organs particular stand out. These are pseudohepatorenal syndrome, Stauffer's syndrome and the hepatorenal syndrome (HRS), with the first two being much rarer. Pseudohepatorenal syndrome describes a clinical condition of joint failure of both organs in which the hepatic failure has no aetiologic contribution to the renal failure [1], while Stauffer's syndrome, also known as the reversed hepatorenal syndrome, describes a liver failure which occurs in a setting of renal cell carcinoma [2]. Stauffer's syndrome has been linked to intravascular coagulation as a result of the presence of circulating fibrinogen: fibrin degradation product complexes [3]. By far the commoner of the three and most explored is the hepatorenal syndrome, a reversible and functional renal failure that occurs in a setting of advanced liver disease, usually advanced liver cirrhosis with ascites and acute liver failure (ALF). Hepatorenal syndrome is one of the major life-threatening complications of cirrhosis, others being hepatic encephalopathy, dilutional hyponatraemia, variceal haemorrhage, spontaneous bacterial peritonitis (SBP) and ascites [4]. Approximately 10% of patients with advanced cirrhosis will develop hepatorenal syndrome [5], with

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90% dying in 10 weeks of onset of the complication, the median survival being 1.7 weeks [6]. In view of this dismal outlook in its prognosis, more research efforts need to be deployed into unravelling the pathobiology and mapping out of novel therapeutic interventional approaches. The objective of this review is to briefly highlight the current trends in the pathogenesis, diagnosis and treatment modalities of hepatorenal syndrome.

Classification

In 1996, the International Ascitic Club led by Vicenti Arroyo proposed the definition and the diagnostic criteria of the hepatorenal syndrome in cirrhosis [7] which was adopted in preference to the previous Sassari's Diagnostic Criteria of 1978 [8]. The diagnostic criteria as shown in Table 1, describes the major and minor criteria. The minor criteria, however need not be present for diagnosis to be made.

Table 1: International Ascites club's diagnostic criteria of hepatorenal syndrome [7, 9].

Major criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dl or 24-h creatinine clearance <40 ml/min
- Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs.
- Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhoea) or renal fluid losses (weight loss >500 g/day for several days in patients with ascites without peripheral oedema or 1,000 g/day in patients with peripheral oedema)
- No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
- Proteinuria <500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Additional criteria

- Urine volume <500 ml/day
- Urine sodium <10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells <50 per high power field
- Serum sodium concentration <130 mEq/L

Based on the adopted criteria, two types of HRS were classified. Type 1 is characterized by a severe and rapidly progressive renal failure, which has been defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dl in less than 2 weeks. Although type-1 HRS may arise spontaneously it frequently occurs in close relationship with a precipitating factor, such as severe bacterial infection, mainly SBP, gastrointestinal haemorrhage, major surgical procedure or acute hepatitis superimposed to cirrhosis [7, 9]. The type- 2 HRS has a less severe course with a slower progression of renal impairment and better prognosis, the major problem being renal failure with refractory ascites. They may however develop type-1 HRS with the presence of infections or other precipitating factors.

Aetiopathogenesis

The aetiopathogenetic mechanism underlying the development of HRS is still a subject of intense research studies for the hepatologist, nephrologists and the basic scientist. Current scientific evidence suggests that there is concurrent severe renal vasoconstriction and splanchnic vasodilatation [9, 10, 11, 12]. Splanchnic vasodilatation occurs in cirrhosis with ascites as a result of portal hypertension that sets in motion the elaboration of vasodilators such as endogenous nitric oxide (eNOS), prostaglandins, natriuretic peptides, calcitonin gene-related peptide, vasoactive intestinal peptide among others [9, 13, 14, 15]. In addition to these vasodilating agents, there is also accumulating evidence of resistance to the effect of vasoconstrictor agents in advanced cirrhosis with portal hypertension. As a consequence of the vasodilating mediators, there is systemic hypotension and ineffective perfusion pressure in spite of the expanded plasma volume and hyperdynamic circulation. The hypotensive effects of the vasodilators lead to stimulation of the baroreceptor mechanisms and subsequently the stimulation of vasoconstrictor mechanisms via the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS) and antidiuretic hormone (ADH) and later endothelin [16-20]. It has been found that urinary excretion of vasodilators produced in the kidneys like adenosine, prostaglandin E2, 6-keto prostaglandin F1 alpha and kallikrein are reduced in HRS [18, 21]. To reinforce the vasoconstrictor theory as a major contributor to HRS, a study by Boyer and his colleagues showed that administration of non-steroidal anti-inflammatory analgesic drugs (NSAID)

to patients with cirrhosis and ascites resulted in diminished renal blood flow and glomerular filtration rate (GFR) due to the prostaglandin inhibiting effect of NSAID [22]. This later finding suggests that there might be reduction in prostaglandin synthesis in the kidneys in the presence of circulating vasoconstrictors. Perfusion anomalies associated with HRS are not, however, limited to the inbalance in the vasoactive substances because of evidence of cardiac dysfunction which has been aptly titled cirrhotic cardiomyopathy.

Pathology

There is usually no histopathological damage in the kidneys of patients with HRS and harvested kidneys from HRS patients have functioned efficiently when transplanted. Thus suggesting that the renal dysfunction in HRS is of a functional nature. Similarly, liver transplantation in HRS leads to complete reversal of the renal dysfunction. There are however some peculiar chemical pathological findings, apart from liver function test abnormalities, that highly suggest HRS when present. One of such biochemical anomalies is dilutional hyponatraemia, which is defined as serum sodium less than 130mEq/L in the presence of an expanded extracellular fluid volume, as indicated by the presence of ascites and or oedema [23]. This phenomenon which occurs in about 30%-35% of hospitalised patients with cirrhosis and ascites is due to impaired water excretory capacity of the kidneys as a result of activation of antidiuretic hormone. This however is a late occurrence in advanced cirrhosis. Other biochemical anomalies are as shown in Table 1.

Diagnosis

Traditionally, functional renal disease is said to occur when the following are present, viz: oliguria, low urine sodium concentration, urine-to-plasma osmolality ratio greater than unity, normal fresh urine sediment and no proteinurria. HRS is classified as a functional renal failure and is a diagnosis of exclusion. This is because there are several types of renal dysfunction in liver disease and HRS has specific diagnostic criteria as delineated in Table 1. There are major criteria, which must be present and other criteria that do not necessarily have to be present for a diagnosis of HRS to be made [7, 9], are referred to as minor.

Investigation

In investigating HRS, a reduced glomerular filtration rate (GFR) must be established. However, this may be misleading, as cirrhotic patients usually have reduced muscle mass, thus leading to a deceptively low or normal serum creatinine levels in the face of significant renal impairment. Also, because the liver manufactures urea, the decompensated cirrhotic liver produces less urea. This aberration may be responsible for cases of false negative diagnosis of HRS [9, 24, 25]. The general consensus, therefore, is a creatinine level above 1.5mg/dl or creatinine clearance of less than 40ml/min [7]. In addition, serum and urinary sodium and osmolalities, urinary protein, sediments and daily volume as well as ultrasonography of the kidneys, ureters and bladder to exclude obstruction, need to be carried out (Table 1). It should however be noted that cirrhotic patients with superimposed acute tubular necrosis may present with features of HRS and rarely HRS patients may present without avid sodium retention [26, 27].

Complications

Complications of HRS are not quite distinguishable from the symptoms and are mainly the consequences of acute renal failure in addition to the complications of the underlying cirrhosis. These are coagulopathy, multiple organ dysfunction, dyselectrolytaemia, oliguria among others.

Treatment

Although spontaneous recovery occurs in about 3.5% of HRS [6], treatment modalities that increase survival have witnessed some advances in recent times and may be either surgical or pharmacological. Precipitating factors such as large volume paracentesis and spontaneous bacterial peritonitis, if identified, also need to be treated. The choice treatment is, however, liver transplantation, though mortality and complications after a liver transplantation is higher than is observed among non-HRS transplant recipients [28,29]. Pharmacological therapy mainly takes advantage of the pathophysiological mechanism of HRS which is hinged on intense renal cortical vasoconstriction and splanchnic vasodilatation associated with hypotension in patients with advanced cirrhosis with portal hypertension and refractory ascites. The best approach is a combination of systemic vasoconstrictors and plasma expanders, which lead to improvement in the mean arterial pressure and renal perfusion, as well as reversal of HRS, as described in a recent review by Barada [30]. Useful splanchnic vasoconstrictors include vasopressin analogues (ornipressin and terlipressin) and alpha-

adrenergic agonists (norepinephrine and midodrine), while the plasma expanders include albumin and fresh frozen plasma. Side-effects of the splanchnic vasoconstrictors include ischaemic features like angina and sometimes arrhythmias, especially with ornipressin [31]. Some studies have shown benefits in combining midodrine with octreotide, a somastotatin analogue that inhibits the release of endogenous vasodilatory agents like glucagons and vasoactive intestinal peptide. Others have combined misoprostol and sub-pharmacological doses of dopamine. A pilot study also showed a reversal of HRS in 83% of patients when norepinephrine was combined with albumin and frusemide [32]. Other modalities of therapy that have shown variable benefit include transjugular intrahepatic portacaval shunt (TIPS) and extracorporeal albumin dialysis/molecular adsorbent recirculation system (ECAD/MARS) [33, 34].

Prognosis

Hepatorenal syndrome generally has a poor prognosis, with the type 1 being worse, as it is characterised by a rapidly progressive renal failure. HRS has a ten week mortality rate of about 90% and median survival of 1.7 weeks [6]. Current approaches to management have improved the prognosis with reversal of HRS in 83% of patients being reported [32]. The major problem in type-2 HRS is refractory ascites with moderate renal failure and it carries a better prognosis than type-1.

Prevention

Available preventive measures for HRS are measures taken to tackle the major known precipitating factors such as large volume paracentesis, gastrointestinal haemorrhage and spontaneous bacterial peritonitis. Other measures include ensuring effective circulation and adequate mean arterial pressure in patients with liver cirrhosis by infusion plasma expanders and judicious use of diuretics.

The Future

A number of clinical trials that may improve the grim prognosis in HRS are still ongoing. There are efforts towards development of aquaretic drugs which are specific antagonists of tubular effects and release of antidiuretic hormone. They will be useful in normalising renal water metabolism [35].

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