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The Onset and Prognosis of Hepatorenal Syndrome – A Three Year Single Center Experience

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Abstract

Introduction. The hepatorenal syndrome (HRS) refers to the development of acute renal failure in the setting of advanced liver disease. It can occur in a substantial proportion of patients with fulminate hepatic failure from any cause. The aim of our study was to investigate the onset, outcome and prognosis of patients with hepatorenal syndrome hospitalized at our unit.
Methods. This is a cross-sectional retrospective study in a cohort of 543 cirrhotic patients, during a period of 3 years (January, 2008-December, 2010). Hepatorenal syndrome was detected in 20 (3.7%) patients and in all of them a few variables such as: age, gender, history of cirrhosis or other liver disease, etiology of cirrhosis, Child-Pugh classification, other complications of the cirrhosis except for HRS, treatment and survival were analyzed.
Results. The average preceding time up to the occurrence of HRS was around 3 years (36.8±47.8 months), although there were 4 patients who developed HRS only a month after the onset of cirrhotic symptoms. A group of seven patients with HRS diagnosed during the first year of the onset of symptoms. The mean age of patients was 55.5±13.3 years. There was a significant difference in the gender distribution, three quarters of patients being males. With regard to the etiology, 12 patients had alcoholic abuse, and a half of them (50%) were with mixed etiology (Hepatitis B plus alcohol abuse). Two patients had a pure chronic hepatitis B virus (HBV) infection as a cause of cirrhosis. Four were with chronic liver disease of unknown etiology (2 of them with confirmed histology of chronic hepatitis). All of the cirrhotic patients were scored as grade C according to the Child-Pugh classification. Hepatic encephalopathy was the most predominant concomitant complication present in 17 (85%) patients with HRS. Only 2 showed signs of malignancy with suspected hepatocellular carcinoma (HCC). The estimated average hospital stay was 6.15 days, ranging from 1-14 days. The applied treatment was generally unsuccessful. Majority of cases (14) were supported with albumin and fresh frozen plasma transfusion and haemodialysis was performed in 4 patients. The mortality rate was high, reaching 80% (16 patients) with an average time of death at 6.8±4.4 days after the hospital admission. Although the evaluation period was short, there is a clear raising trend in number of detected patients with HRS at our Clinical Center.
Conclusion. Compared to other reports, our single centre experience shows lower occurrence rate. Despite the use of available conservative medical treatment, there was no recovery of the hepatic failure in any of HRS patients. The absence of liver transplantation or TIPS in our country is the second contributing factor related to the high mortality rate in our cohort.
Finally, gastroenterohepatologists should be aware and try to prevent iatrogenic precipitants of HRS as an aggressive diuretic treatment or removal of large volumes of ascitic fluid by paracentesis without compensating for fluid depletion by intravenous replacement could additionally impair the renal failure.

Key words: hepatorenal syndrome, hepatic failure, renal failure

Introduction

The hepatorenal syndrome (HRS) refers to the development of acute renal failure in the setting of advanced liver disease due to cirrhosis, severe alcoholic or other acute hepatitis, or less often in the presence of liver metastases. Nevertheless, it can occur in a substantial proportion of patients with fulminate hepatic failure from any cause. It is a life threatening medical condition that consists of rapid deterioration in kidney function of individuals with cirrhosis or fulminate liver failure [1,2].
HRS is usually fatal unless a liver transplant is performed, although various conservative treatments (including dialysis), can prevent worsening of the condition. Regardless of the etiology (cirrhosis, severe alcoholic hepatitis

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or fulminate hepatic failure), it usually occurs when liver function deteriorates rapidly triggered by an acute injury such as infection, bleeding in the gastrointestinal tract, or abuse of diuretic medications. HRS as relatively common complication of cirrhosis occurs in 18% and 39% of cirrhotics within one and five years of their diagnosis, respecttively [3-6].

Deteriorating liver function cause changes altering blood flow and blood vessel tonus in the kidneys, although hepatorenal syndrome may be a consequence of these changes in the blood flow, rather than direct damage to the kidney. In fact, the HRS involves constriction of the blood vessels of the kidneys and dilation of blood vessels in the splanchnic circulation, which supplies the intestines. The kidneys themselves appear with regular size and form and tissue is normal when viewed under the microscope. The kidney function could be also normal when placed in an otherwise healthy environment. The diagnosis of hepatorenal syndrome is based on laboratory tests of individuals susceptible to the condition. The classification of hepatorenal syndrome identifies two categories of renal failure termed as type 1 and type 2 HRS, occuring in individuals with either cirrhosis or fulminant liver failure. In both categories, the deterioration in kidney function is quantified either by an elevation in serum creatinine levels, or by a decreased creatinine clearance in the urine. Type 1 HRS entails a rapidly progressive decline in kidney function and is most commonly precipitated by spontaneous bacterial peritonitis (SBP). It occurs in approximately 25% of patients with SBP. Type 2 HRS is associated with an ascites that does not improve with standard diuretic medication and commonly occurs in patients with relatively presserved hepatic function. These patients are often diuretic-resistant [7-11].

The aim of our study was to investigate the onset, outcome and prognosis of patients with HRS hospitalized at the University Department of Gastroenterohepatology in Skopje.

Patients and methods

This is a cross-sectional retrospective study of 543 cirrhotic patients hospitalized at our Department during the period of 3 years (January, 2008-December, 2010) with HRS detected in 20 patients (3.7%). All of them were analyzed according to a few variables such as: age, gender, history of cirrhosis or other liver disease, etiology of cirrhosis, Child-Pugh classification, other complications of the cirrhosis except for HRS, treatment and survival. The average preceding time up to the occurrence of hepatorenal syndrome in these patients was around 3 years (36.8±47.8 months) since the disease was diagnosed, although there were 4 patients who developed HRS only a month after the onset of cirrhotic symptoms. One of them was determined as a patient with acute alcoholic heaptitis superimposed over the alcoholic cirrhosis. These patients plus another 3 composed a group of seven patients with HRS diagnosed during the first year of the onset of symptoms. The mean age of the patients was 55.5±13.3 years. There was a significant difference in the gender distribution, three quarters of patients being males.

Results

The mean age of our cohort of 543 patients was 53.4± 2.57 years (range 19-78 year), 362 men and 181 women. They have been hospitalized 665 times, and the total amount of hospital stay was 5736 days (Table 1).

Table 1. Distribution of patients with liver cirrhosis in the period 2008-2010

Year	No of pts.	Age	No of hospital	Overall in-hospital days	Average duration of hospital stay per patient
2008	206	57,2	245	1776	8.62
2009	205	55,7	274	2131	10.39
2010	132	53,1	146	1829	9.72
Total	543	/	665	5736	/
Mean	138.75±52.3	53.39	170.5±67.1	1912	9.57

The underlined etiology of our hospitalized cirrhotic patients was HBV, hepatitis C virus (HCV), mixed infections of HBV + HCV, alcohol, nonalcoholic steatohepatitis (NASH), immunological, primary biliary cirrhosis (PBC), secondary biliary cirrhosis (SBC) etc. (Table 2).

Patients were scored according to Child-Pugh classifycation. Child A was found in 215 patients, Child B in 164, and Child C in 164 patients. Hepatocellular carcinoma (HCC) was found in 66 patients, and 67 patients out of 543 died during follow up (Table 3).

Hepatorenal syndrome was detected in 20 patients (15 men) with mean age 55.5±13.3 years (range 21-78). In order to prove the medical history considered for liver cirrhosis in those patients, a complete laboratory, endoscopy, ultrasound examination and chest X-ray were performed. Patients with positive findings have been treated with stan-

Table 2. Distribution of the etiology of liver cirrhosis in the hospitalized patients over the observed period

Year	HBV	HCV	HBV+HCV	Alcohol	Other
2008	38(18.5%)	11(5%)	3(1.5%)	78(38%)	76(37%)
2009	43(21%)	10(5%)	5(2.5%)	61(29.5%)	86(42%)
2010	35(27%)	7 (5%)	29 (22%)	45 (34%)	16 (12%)
Total	**116**	**28**	**37**	**184**	**178**

Table 3. Distribution of patients according to the Child–Pugh classification in the observed period

Year	Child A	Child B	Child C	HCC	Lethal
2008	88(43%)	66(32%)	52(25%)	24(12%)	24(12%)
2009	90(44%)	46(22%)	69(34%)	23(11%)	28(14%)
2010	37(28%)	52(39%)	43(33%)	19(14%)	15(11%)
Total	**215**	**164**	**164**	**66**	**67**

dard therapy for liver cirrhosis.

The investigation of the etiology of liver cirrhosis in HRS patients showed 12 of them with alcoholic abuse. One half (50%) had mixed etiology (Hepatitis B plus alcohol). Two patients had a pure chronic HBV infection as a cause of cirrhosis. Out of four patients with chronic liver disease of unknown etiology 2 had a confirmed histology of chronic hepatitis on liver biopsy.

While most of the patients (n=19) had chronic liver disease, only one suffered from an acute liver disease caused by serologically confirmed leptospirosis infection-Weil's syndrome. All of the cirrhotic patients were scored as grade C according to the Child-Pugh classification, being at end stage liver disease. As a complication of the cirrhosis eight patients had upper gastrointestinal bleeding and ascites was found in 13 of them. Hepatic encephalopathy was the most predominant concomitant complication. Only 2 patients showed signs of malignancy with suspected HCC (Table 4). The estimated average hospital stay was 6.15±4.4 days, ranging from 1-14 days.

Regarding the other characteristics of the HRS patients, spontaneous bacterial peritonitis or any other infection were excluded in all of them. Beside the one with the Weil's syndrome all others were treated with diuretics, either spironolactone alone or combination of spironolactone and furosemide, before admission to our clinics. Higher doses, up to 200mg/24h of spironolactone and 40 mg/24h of furosemide were used in 13 patients with evident ascites. Large volume abdominal paracentesis (exceeding 5 liters per session) was initiated and performed in 4 of them in their regional medical centers. Interestingly, at the same time these 4 patients with prominent ascites had no peripheral edema. Diuretic therapy was interrupted immediately after admission to our hospital in all patients with HRS and chronic liver disease, and fluid repletion was initiated. However, there was no improvement in renal function and degradation products reduction in any of them. In contrast, it was gradually worsened, thus confirming the ensuing hepatorenal syndrome.

Table 4. Distribution by the etiology and Child-Pugh classification plus complications found in the group of 20 patients with HRS

Etiology			Child-Pugh classification			Complications			
HBV	**HCV**	**Alcohol**	**A**	**B**	**C**	**Bleeding**	**Ascites**	**Encephalopathy**	**HCC**
8	0	12	1	0	19	8	13	17	2

Unfortunately, we could admit that the applied treatment was generally unsuccessful. Majority of cases (n=14) were treated with albumin and fresh frozen plasma as a supportive regimen. Due to the general poor condition, severe thrombocytopenia and coagulopathy, haemodialysis was performed in only four patients.

The mortality rate in this population was very high, reaching 80% (16 patients) with average time until death of 6.8± 4.4 days after the admission. Two patients were dismissed from hospital without any improvement of their condition. One was transferred to the University Department of Nephrology for further treatment and the last one to the University Department of Infectious diseases. Although the evaluation period was short, there is a clear increasing trend in the number of detected patients with HRS at our Clinical Center.

Discusion

Epidemiological data about HRS incidence differ from study to study and are little bit confusing. According to Chan, Tai and Lam, the exact incidence of HRS is unknown. It is estimated to occur in approximately 8-10 percent of individuals with the accumulation of fluid in the abdomen and cirrhosis [7]. Conversely, Betrosian considers HRS as common condition, with a reported incidence of 10% among hospitalized patients with cirrhosis and ascites. In decompensated cirrhotics, the probability of developing HRS with ascites is even higher and ranges between 8-20% per year and increases to 40% at 5 years [12]. Gines A, Escorsell and Gines P in the follow-up investigational study of 234 nonazotemic patients with cirrhosis and ascites, concerning the incidence, predictive factors, and prognosis of the HRS, estimate the probability of occurrence to 18% at 1 year and 39% at 5 years [5]. Furthermore Sandeep and Hemant comment that incidence of HRS is globally similar [11]. Our results show HRS occurrence rate of only 3.7% in hospitalized patients. At present, we cannot comment precisely on causes of this difference in our small cohort.

Frequency is equal in both sexes and most patients with chronic liver disease and HRS are in their fourth to eighth decade of life, as said by Sandeep and Hemant [11]. In contrast to similar age occurrence in our study, we established that HRS dominantly occurs in males.

The classification of hepatorenal syndrome identifies two categories of renal failure, termed as type 1 and type 2 HRS, occurring in individuals with either cirrhosis or fulminant liver failure. Type 1 HRS occurs in approximately 25% of patients with SBP, despite rapid resolution of the infection with antibiotics. Without treatment, median survival of patients with type 1 HRS is less than 2 weeks, and virtually all patients die within 10 weeks after the onset of renal failure. Type 2 HRS is associated with an ascites that does not improve with standard diuretic medication, and commonly occurs in patients with relatively preserved hepatic function. These patients are often diuretic-resistant with a median survival of 3-6 months. Although this is markedly longer than type 1 HRS, it is still shorter compared to patients with cirrhosis and ascites who do not have renal failure [7-11]. Appenrodt refers that type 1 HRS has a median survival of 2 weeks, with few patients surviving more than 10 weeks. Type 2 HRS has a median survival of 3-6 months [13]. Having in mind that there was no patient with confirmed SBP, we cannot discus about two types of HRS in our study, but median survival of 6.8±4.4 days after admission, suggests that most of them probably suffer from type 1 HRS. The other possibility is that majority of our patients sought for medical help too late or were misdiagnosed for a longer period. In our surrounding, further prospective trials are clearly warranted, if we want to draw definitive conclusions about all issues that could not have been clearly explained from our study.

Progressive liver failure, as manifested by most frequent complications like worsening encephalopathy, jaundice, and coagulopathy, is a preterminal condition if liver transplantation is not performed [11]. In our opinion, hepatic encephalopathy is the most predominant concomitant complication in cirrhotic patients with HRS, reaching 85% [13].

Repeated abdominal paracentesis in neither cirrhotic patients, nor other therapies will prevent insidious progression to HRS type II, nor the precipitation of HRS type I. In contrast, liver transplantation, or transjugular intrahepatic hepatoportal stent shunt (TIPS) in patients with refractory ascites, may prevent the onset of, or reverse the fatal clinical outcome [1]. Due to the deficiency of these treatment modalities in our country, unfortunately, we have to admit that the applied treatment was generally unsuccessful and the prognosis of our patients with HRS is very poor.

Conclusions

Compared to other reports, our single centre experience shows lower occurrence rate. The outcome of patients with HRS, as well as recovery of kidney function, is highly dependent on the possible reversal of the hepatic failure, be it spontaneous, following medical therapy, or after successful liver transplantation. Despite the use of available conservative medical treatment, there was no recovery of the hepatic failure in any of HRS patients. The absence of liver transplantation or TIPS in our country is the second contributing factor related to the high mortality rate in our cohort.

From all identifiable characteristics of HRS patients with cirrhosis or fulminate hepatic failure as bacterial infection, acute alcoholic hepatitis, or bleeding in the upper gastrointestinal tract, according to our modest experience upper gastrointestinal bleeding is the dominant one. Hepatic encephalopathy seems to be the most frequent concomitant complication in predominantly cirrhotic patients with HRS. Males seem at greater risk for HRS development. Finally, gastroenterohepatologists should be aware and try to prevent iatrogenic precipitants of HRS as an aggressive diuretic treatment or removal of large volumes of ascitic fluid by paracentesis without compensating for fluid depletion by intravenous replacement could additionally impair the renal failure.

Conflict of interest statement. None declared.

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