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Original Article

Plasma renin activity and aldosterone level in patients with hepatic cirrhosis and hepatorenal syndrome

Nasser Abdallah, Khaled Mohei, Sherif A Zaky * and Akram Deghady**

Departments of Tropical Medicine, Internal Medicine* and Clinical Pathology**, Faculty of Medicine, University of Alexandria, Egypt

Abstract

Patients with advanced hepatic cirrhosis and ascites often develop a peculiar form of renal failure in the absence of clinical, laboratory or histologic causes of renal dysfunction. This condition is known as hepatorenal syndrome (HRS). The etiology of HRS is still incompletely understood but the renin aldosterone system could play an important role in its pathogenesis. The aim of this study was to investigate the circulating levels of plasma renin activity (PRA) and plasma aldosterone (PA) in a group of cirrhotic patients with and without ascites and HRS compared to healthy controls. Venous blood samples were drawn at 8:00 am from 45 cirrhotic patients; 15 of these were without ascites (group I), 15 with ascites (group II) and 15 with HRS (group III) as well as from 15 healthy controls (group IV) for the measurement of hepatic and renal functions, serum and urinary sodium and potassium, PRA and PA levels. The PRA and PA were measured by radioimmunoassay. Results showed that PRA and PA levels were significantly higher in HRS patients than those in the other studied groups. Moreover, they were significantly elevated in ascitic patients than those in non-ascitic cirrhotics and controls. In addition, non-ascitic cirrhotic patients showed significantly higher levels than those in controls ($F=33.98$, $F=135.80$, $P<0.01$ respectively). A significant positive correlation between PRA and PA was only evident in controls ($r=0.71$, $P<0.01$) but not in the different studied groups of cirrhotic patients ($r=0.35$, 0.08 and 0.25 respectively). These data indicate that the great derangement in the levels and relationships of the renin aldosterone system plays an important role in promoting and/or in maintaining the fluid and electrolyte imbalance in patients with liver cirrhosis and HRS.

Correspondence and offprint requests to: Dr. Sherif A Zaky, Department of Tropical Medicine, Internal Medicine, Faculty of Medicine, University of Alexandria, Egypt.

Introduction

In most instances, in patients with hepatic cirrhosis, the predominant renal function abnormality is sodium retention resulting in accumulation of extracellular fluid as ascites, pleural effusion and/or edema. In other instances, the derangement of kidney function is more severe resulting in an impairment of water handling or renal vasoconstriction. The main clinical consequences of these abnormalities are dilutional hyponatremia and hepatorenal syndrome (HRS) [1,2].

The HRS defined as a clinical condition that occurs in patients with chronic liver disease, advanced hepatic failure and portal hypertension and is characterized by impaired renal function, marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in low glomerular filtration rate (GFR). On the other hand, in the extrarenal circulation, there is predominance of arteriolar vasodilation resulting in reduction of total systemic vascular resistance and arterial hypotension [3].

The functional nature of HRS has been demonstrated by the normal histologic appearance of the kidneys regaining a normal or near-normal kidney function after liver transplantation to a HRS patient and after renal transplantation from a patient with HRSand also by normalization of the renal vascular abnormalities associated with HRS in pre- and postmortem arteriographs [4,5].

The incidence of HRS in patients with hepatic cirrhosis and ascites is 18% at one year and 30% at five years after the onset of the hepatic pathology [6].

According to the intensity and onset of renal failure, two different clinical forms of HRS have been recently described. Type I HRS is characterized by a rapid impairment of renal function and either doubling of the serum creatinine to a concentration >2.5 mg/dl or a 50% reduction in creatinine clearance to <20 ml/min in less than 2 weeks.

In contrast to Type I, Type II HRS is characterized by a more gradual decrement in renal function [3,7].
The major diagnostic criteria that must be present for the diagnosis of HRS are low GFR (serum creatinine >1.5 mg/dl or 24-hour creatinine clearance <40 ml/min) in absence of shock, ongoing bacterial infection, fluid loss and current treatment with nephrotoxic drugs with no sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with 1.5 liters of a plasma expander. Also, proteinuria should be <500 mg/day in the absence of ultrasonographic evidence of obstructive uropathy or parenchymal renal disease. Additional criteria that are not necessary for the diagnosis but provide supportive evidence are urinary volume <500 ml/day, sodium <10 mEq/L, red blood cells <50 /HPF, osmolality greater than that of plasma and serum sodium concentration <130 mEq/L [3].
The pathophysiologic hallmark of HRS is vasoconstriction of the renal circulation [8,9]. The mechanism of this vasoconstriction is incompletely understood and possibly multifactorial. The theory that better explains the development of HRS is the "arterial vasodilation theory" proposing that renal hypoperfusion represents the extreme manifestation of underfilling of the arterial circulation secondary to a marked vasodilation of the splanchnic vascular bed [10,11]. This arterial underfilling would result in a progressive baroreceptor-mediated activation of vasoconstrictor systems including renin angiotensin axis, sympathetic nervous system and nonosmotic release of vasopressin that would eventually cause vasoconstriction not only in the renal circulation but also in the other vascular beds including the lower and upper limbs as well as the cerebral circulation. The splanchnic area would escape the effect of vasoconstrictors and an intense vasodilation would persist because of a markedly enhanced local production of vasodilator factors [12].
The aim of the present work was to study the plasma renin activity (PRA) and plasma aldosterone (PA) levels in patients with hepatic cirrhosis with and without ascites as well as in those with hepatorenal syndrome.

Material and methods

This study was conducted on sixty subjects divided into four groups:
Group I: included 15 patients with hepatic cirrhosis without ascites.
Group II: included 15 patients with hepatic cirrhosis and ascites.
Group III: included 15 patients with hepatic cirrhosis and HRS.
Group IV: included 15 healthy volunteers matched for age and sex as controls.
Patients with history of treatment with nephrotoxic drugs, sepsis, primary renal disease and circulatory disturbances with excessive fluid loss or bleeding as well as those with cardiac or pulmonary disease were excluded from the study.
All patients and controls were subjected to the following:
Complete history taking and thorough clinical examination.
Routine laboratory investigations including complete blood picture, hepatic and renal function tests.
Viral markers assay including HBsAg, HBcAb and HCV-Ab by ELISA to identify the underlying type of viral hepatitis.
Ultrasonographic examination of the abdomen laying stress on the gross pathology of the liver, presence of other organomegaly, masses or ascites as well as any identifiable gross renal pathology.
Percutaneous liver biopsy using Menghini needle was performed for group I, II and 4 selected cases of group III not contraindicated for biopsy. Biopsy specimens were subjected to histopathological examination using the conventional H&E staining. The pathological findings of chronic hepatitis were identified, graded and staged into mild, moderate and severe according to the modified histological activity index (HAI) [13].
Estimation of serum and urinary sodium and potassium [14].
Estimation of plasma renin activity [15] and plasma aldosterone [16] by radioimmunoassay (RIA).
Venous blood samples were drawn at 8.00 am from all subjects included in this study.

Statistical analysis

Data evaluation was carried out using the SPSS software for Windows, Release 6.01. All data were expressed as means ± SD. Differences between groups were evaluated by the "F-test". A "P value" ≤ 0.05 was considered to be statistically significant. Correlation analyses were used to study the correlation between variables.

Results

The clinical manifestations of cirrhotic patients included in this study are presented in table 1. The most common symptoms in group I were easy fatigability and anorexia, whereas in the other two groups were abdominal distension and lower limb edema. Hepatomegaly and splenomegaly were the most frequent signs in the three studied groups of patients.
Regarding the distribution of viral markers of chronic hepatitis in the studied groups of cirrhotic patients, it was as follows: 33.33% were HBsAg and HBcAb positive (8.89% in group I, 13.33% in group II and 11.11% in group III), 55.56% were HCV-Ab positive (17.78% in group I, 15.56% in group II and 22.22% in group III) and 11.11% were both HBsAg and HCV-Ab positive (6.67% in group I and 4.44% in group II).
According to the modified histological activity index, mild, moderate and severe chronic hepatitis were found in 9, 5 and 1 patients of group I respectively and in 7, 4 and 4 patients of group II respectively whereas in group III, 2 patients demonstrated moderate grade and 2 patients showed severe chronic hepatitis. In group I, grades of chronic hepatitis were positively correlated with AST ($r=0.62$, $P<0.05$) and negatively correlated with prothrombin activity ($r=-0.52$, $P<0.05$) whereas in group II, they were positively correlated with ALT and AST ($r=0.77$, $r=0.79$, $P<0.05$ respectively).
As regards the liver function tests, the mean serum bilirubin and ALT levels were significantly higher in

groups II and III than groups I and IV with no significant difference between groups II and III and between groups I and IV (F=16.99, P<0.01, F=25.79, P<0.05 respectively). Also, the mean serum AST levels were significantly higher in the cirrhotic patients than controls. Moreover, groups II and III demonstrated significantly higher AST levels than group I with no significant difference between them (F=29.92, P<0.01). On the other hand, the mean serum albumin levels were significantly lower in groups II and III than groups I and IV with a non-significant difference between groups II and III and between groups I and IV (F=40.47, P<0.01). Also, the mean prothrombin activity values were significantly lower in groups II and III than groups I and IV with significantly lower level in group III than group II (F=49.15, P<0.01) (table 2).

Regarding the renal function tests, the mean serum urea levels were significantly higher in groups II and III than those of groups I and IV with significant higher levels in group III than group II (F=78.78, P<0.01). On the other hand, the mean serum creatinine level was significantly higher in group III than those of the other three groups with no significant difference between those groups (F=49.95, P<0.01) (table 3).

As regards the serum and urinary electrolytes, the mean serum sodium levels were significantly lower in cirrhotic patients than controls, being significantly lower in groups II and III than group I with a non-significant difference between them (F=33.91, P<0.01). On the other hand, the mean urinary sodium concentration (U_{Na}) was significantly lower in group III than in group II, in group II than in group I and in group I than in group IV (F=106.30, P<0.01). Serum sodium concentrations were not significantly correlated with U_{Na} in the different studied groups. Meanwhile, the mean serum potassium level was significantly higher in group III than those in the other three groups with no significant differences between those groups (F=20.10, P<0.01). Whereas, the mean urinary potassium concentrations (U_K) were significantly lower in the cirrhotic patients than in controls with an insignificant difference between cirrhotic patients (F=3.78, P<0.01) (table III).

Table 1. The main clinical symptoms and signs in the studied groups of patients

Clinical manifestations	*Group I n=15*		*Group II n=15*		*Group III n=15*	
	No	%	no	%	no	%
Symptoms:						
*Easy fatigability	5	33.3	10	66.6	12	80
*Dyspnea	0	0	8	60	12	80
*Anorexia	3	20	6	40	11	73.3
*Weight loss	2	13.3	6	40	12	80
*Abdominal distension	2	13.3	15	100	15	100
*Lower limb edema	1	6.66	15	100	15	100
*Epistaxis	0	0	2	13.3	4	26.6
Signs:						
*Pallor	3	20	7	46.6	11	73.3
*Jaundice	0	0	4	26.6	10	66.6
*Clubbing	1	6.6	3	20	4	26.6
*Tremors	0	0	3	20	8	53.3
*Spider angiomata	0	0	2	13.3	6	40
*Lower limb edema	3	20	15	100	15	100
*Hepatomegaly	15	100	15	100	15	100
*Splenomegaly	15	100	15	100	15	100
*Ascites	0	0	15	100	15	100

Table 2. Liver function tests in the studied groups

Parameters	*Group I* n=15	*Group II* n=15	*Group III* n=15	*Group IV* n=15	*Test of significance*	
					F-test	P
ALT (R&F units)	38.33±12.36	48.53±10.59	54.60±11.12	24.00±5.26	25.79	0.015*
AST (R&F units)	46.00±12.38	56.66±11.3	62.06±11.92	28.20±4.85	29.92	0.00*
S.Bilirubin (mg/dl)	1.29±0.48	1.94±0.83	2.11±0.70	0.70±0.21	16.99	0.00*
S.Albumin (g/dl)	3.72±0.40	3.13±0.47	2.84±0.37	4.40±0.42	40.47	0.00*
Prothrombin Activity (%)	83.46±7.18	63.46±9.94	57.06±9.69	88.46±6.12	49.15	0.00*

* Statistically significant at P≤0.05

Table 3. Renal function tests, serum and urinary sodium and potassium, plasma renin activity (PRA) and plasma aldosterone (PA) in the studied groups

Parameters	*Group I* n=15	*Group II* n=15	*Group III* n=15	*Group IV* n=15	*Test of significance*	
					F-test	P
S.urea (mg/dl)	40.20±10.42	48.06±8.37	79.40±12.35	25.53±7.89	78.78	0.00*
S.creatinine (mg/dl)	1.02±0.28	1.38±0.39	2.27±0.50	0.76±0.16	49.95	0.00*
S.sodium (mEq/L)	138.66±5.39	132.26±5.07	128.40±1.84	142.60±3.64	33.91	0.00*
S.potassium (mEq/L)	4.16±0.51	3.76±0.32	5.03±0.57	4.12±0.40	20.10	0.00*
Ur.sodium (mEq/L)	61.13±13.73	28.86±6.91	8.10±6.52	109.8±24.04	106.3	0.00*
Ur.potassium (mEq/L)	59.46±13.53	60.06±17.57	62.13±16.82	75.46±11.28	3.78	0.00*
PRA (ng/ml/hr)	8.35±4.85	11.53±4.01	15.33±4.16	1.90±0.23	33.98	0.00*
PA (pg/ml)	239.26±44.95	344.26±73.44	438.13±46.27	87.60±20.45	135.8	0.00*

S=Serum Ur=Urinary *= Statistically significant at P≤0.05

The mean PRA and PA levels were significantly higher in group III than in group II, in group II than in group I and in group I than in group IV (F=33.98, F=135.80, P<0.01 respectively) (table 3).

The PRA was positively correlated with age and AST level in group I patients (r=0.54, r=0.53, P<0.05 respectively) and with urinary potassium excretion in patients with HRS (r=0.68, P<0.01) whereas it was negatively correlated with prothrombin activity in group II patients (r=-0.71, P<0.01).

No significant correlation could be elicited between PA levels and the liver as well as the renal function tests, serum or urinary electrolytes in the studied groups of patients.

Despite both PRA and PA behaved the same pattern of significance in the patients of this study, a significant positive correlation between them was only evident in controls (r=0.71, P<0.01) but not in the different studied groups of patients (r=0.35, 0.08 and 0.25 respectively).

Discussion

The pathophysiology of circulatory and renal dysfunction in cirrhosis and related conditions as refractory ascites and HRS has been research topics of major interest during the last two decades. However, many aspects of these problems remain unclear and will constitute major areas of investigation in the next millennium.

In clinical practice, renal vasoconstriction and impaired renal function are usually assessed by measuring markers of GFR such as blood urea nitrogen (BUN), serum creatinine and/or creatinine clearance.

In the present study, the mean blood urea levels were significantly higher in cirrhotic patients with ascites and HRS than in those without ascites and controls. Also, it was significantly higher among HRS patients than cirrhotic patients with ascites.

In cirrhotic patients, blood urea nitrogen and urea measurements have important drawbacks because their levels may be higher for reasons other than renal failure such as gastrointestinal hemorrhage or due to prerenal failure caused by significant gastrointestinal fluid losses due to vomiting or diarrhea, or renal fluid losses due to excessive diuretic therapy. On the other hand, their levels may be lower due to a reduced hepatic synthesis of urea. Therefore, clinicians treating patients with cirrhosis must be aware of the limitations of these analytical methods in the evaluation of GFR [4].

In the current study, the mean serum creatinine level was significantly higher in HRS patients than those of the other three studied groups with no significant difference between the three groups. Also, the cut-off value of serum creatinine required for the diagnosis of HRS (1.5 mg/dl) was only exceeded in the HRS patients. Although this value may seem rather low, patients with cirrhosis and a serum creatinine above 1.5 mg/dl have a GFR below 30 ml/min [3].

In cirrhotic patients, serum creatinine levels are very specific in the detection of a low GFR but have a low sensitivity. Cirrhotic patients with ascites may have important reductions in GFR with normal or only slightly increased serum creatinine levels because of malnutrition, muscle wasting and reduced endogenous creatinine production. In addition, serum creatinine may be underestimated by some analyzers due to interference by bilirubin [4]. As well, creatinine clearance has a low sensitivity in the detection of a low GFR in cirrhotic patients because it overestimates GFR at all levels of renal function and requires a very accurate urine collection. Therefore, repeated measurements of these parameters i.e. serum creatinine and creatinine clearance in cirrhotic patients, may be helpful in the detection of progressive reductions of renal function [4].

In the present work, all patients who developed HRS had ascites. It was reported that if a significant decrease in renal clearances may be observed in the first stages of chronic active hepatitis, true renal impairment often with the typical signs of HRS only occurs in patients with ascites especially when tense and refractory [17].

In the current work, serum sodium was significantly lower in cirrhotic patients than controls with significant lower levels in ascitic and HRS patients than in non-ascitic cirrhotic patients with an insignificant difference between groups II and III. Also, a cut-off level of serum sodium below 130 mEq/L was only found in HRS patients. Arroyo et al reported that the prevalence of spontaneous hyponatremia (serum sodium <130mEq/L) in hospitalized cirrhotic patients with ascites was approximately 30% [18].

In the present work, all patients of group II and III had evidence of increased total body water i.e. bilateral lower limb edema and ascites with variable degrees. As

sodium is retained iso-osmotically in the kidney, it causes fluid retention and expansion of the extracellular fluid volume resulting in ascites and/or edema formation. Therefore, hyponatremia in cirrhotic patients with ascites is almost always dilutional in origin as it occurs in the setting of increased total body water. Sodium retention in cirrhosis is mainly due to an abnormally increased reabsorption of sodium in the renal tubules due to a number of extrarenal and intrarenal factors, the most important of which being hyperaldosteronism and increased renal sympathetic nerve activity [18]. The pathogenesis of water retention in ascitic cirrhotic patients is complex and involves several factors including a reduced delivery of filtrate to the ascending limb of loop of Henle, reduced renal synthesis of prostaglandins and increased secretion of antidiuretic hormone [19,20,21].

The intensity of sodium retention in cirrhotic patients with ascites and HRS included in this study was not uniform. In some patients, sodium retention was moderate and patients were still able to eliminate significant amounts of sodium in the urine, whereas in other patients sodium retention was severe and urine sodium was negligible. The same applied to the abnormal renal water retention that was not uniform in all patients; rather, it varied markedly from a patient to another. Therefore, a normal serum sodium concentration in the cirrhotic patient with ascites is not synonymous with a normal renal capacity to excrete either sodium or water.

In this study, the mean U_{Na} concentration was significantly lower in HRS patients than in ascitic cirrhotic patients, in the latter than in cirrhotic patients without ascites and in non-ascitic cirrhotics than in controls. Also, a cut-off level of urinary sodium below 10 mEq/L was only found in HRS patients.

The low urinary sodium excretion is not specific for HRS since acute glomerulonephritis, contrast nephropathy and myoglobinuric renal failure can be accompanied by low U_{Na} [22]. Although a reduced U_{Na} is considered to be pathognomonic for HRS, the syndrome can also be associated with elevated U_{Na} as occurring with urinary excretion of nonreabsorbable anions as penicillin derivatives, ketones and diatrizoate or excretion of bicarbonate during resolving metabolic or developing respiratory alkalosis and resolving respiratory acidosis [22]. Therefore, both urinary sodium and chloride are recommended to be measured [23].

Two families of drugs, V_2 vasopressin receptor antagonists and kappa-opioid agonists, have been shown to improve free water clearance and correct dilutional hyponatremia in human and experimental cirrhosis with ascites. The first type of drugs blocks the tubular effect of antidiuretic hormone and the second inhibits antidiuretic hormone secretion by the neurohypophysis [24].

In the current study, the mean levels of both PRA and PA were significantly higher in HRS patients than in the other three groups. Moreover, they were significantly higher in ascitic than non-ascitic cirrhotic patients and controls. In addition, non-ascitic cirrhotic patients showed significantly higher levels than controls.

The results of the present work were supported by those of Pasqualetti and Casale (1996) [23], who found that HRS patients presented significant higher levels of atrial natriuretic peptide (pANP), PRA and PA than healthy controls. Also, the results of Pasqualetti et al (1997) [26] were in agreement with those of this study as they reported that the healthy controls presented a significant circadian rhythm for pANP, PRA and PA, whereas no rhythm was found in HRS patients. Also, the rhythms for each variable were significantly different between the two groups; HRS patients had higher mean daily concentrations and larger circadian variations than controls. As well, in the study conducted by Uemasu et al (1988) [27], basal PRA in decompensated cirrhotic patients was significantly higher than those in controls and compensated cirrhotics. On the other hand, basal PA was also higher in decompensated cirrhotic than in controls and compensated cirrhotic patients but without statistical significance. The absence of statistical significance may be attributed to the low number of patients as the study was conducted on 11 cirrhotic patients only; 6 compensated and 5 decompensated.

Several investigators explained the existence of markedly increased activation of the renin angiotensin aldosterone system in patients with HRS. Some authors reported that the significant decrease in plasma volume and cardiac output occurring in cirrhotic patients with ascites, play the pathogenetic mainstay role in the development of HRS with increased production of plasma renin as a homeostatic response to hypotension [10, 28, 29]. Others reported that the increased renal artery pulsatility and resistive indices, as measured by color Doppler ultrasonography, with subsequent renal hypoperfusion, correlate with deterioration of liver functions in patients with liver cirrhosis and that changes in both indices were closely correlated to changes in PRA and PA [30] as well as to deterioration of renal functions and activation of endogenous vasoactive systems [31]. In addition, the significantly increased renal venous pressure in the presence of tense ascites or as a consequence of cirrhosis itself, coupled with decreased arterial pressure could cause further decrease in renal blood flow [32, 33]. As well, the CNS was reported to be highly activated in patients with HRS with increased plasma levels of catecholamines causing vasoconstriction of the afferent renal arterioles with a decrease in renal plasma flow and GFR leading to further activation of renin secretion [34].

It was also postulated that renal dysfunction in HRS is due to the failure of the liver to synthesize renin substrate with inability of renal renin to exert its pressor effects resulting in hypotension and renal hypoperfusion with further stimulation of excessive synthesis and release of renin. The overdriven renin system increases renovascular resistance at the level of glomerular arterioles leading to further decrease in renal blood flow and GFR [28].

However, it is unlikely that the development of HRS is purely a consequence of renal vasoconstriction but other factors may be involved. It was shown that the increased synthesis of vasoactive mediators, which in addition to inducing renal vasoconstriction, may also have the important added effect of causing mesangial cell contraction, hence reducing the surface area available for glomerular filtration and lowering filtration fraction.

Such mediators may include endothelin, cysteinyl leukotrienes, thromboxane A_2 and F-isoprostanes [35].

In the current study, despite that both PRA and PA behaved in the same pattern in the different studied groups, a positive correlation between them was only evident in the control group, but not in the cirrhotic groups of patients. Comparable results were reported by Pasqualetti et al (1997) [26] who demonstrated significant relations between the mean daily concentrations of pANP and PRA (r=0.79), PRA and pA (r=0.73) and PRA and pA (r=0.76) in the controls. On the contrary, the HRS patients showed only a significant positive relation between pANP and PRA (r=0.71).

In the study conducted by Gines et al (1993) on 234 nonazotemic patients with cirrhosis and ascites, a multivariate analysis of thirty-nine variables disclosed only three independent predictors of HRS occurrence; low serum sodium concentration, high PRA levels and absence of hepatomegaly [6].

Two new treatments have proved to reverse HRS in cirrhosis. The first based on simultaneous administration of plasma volume expander and vasoconstrictors [36] and the second is transjugular intrahepatic porto-systemic shunt (TIPS) [37].

From the previous study, it is concluded that the great derangement in the levels and relationships of the renin angiotensin aldosterone system could play an important role in promoting and/or in maintaining the fluid and electrolyte imbalance in patients with liver cirrhosis and HRS. Meanwhile, the better understanding of the pathophysiological aspects of HRS should be useful in the design of clinical trials of new approaches in the management of this serious complication in cirrhotic patients.

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