Clinical types and drug therapy of renal impairment in cirrhosis

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Summary

Four separate types of renal failure in cirrhosis are described: functional renal failure; diuretic induced uraemia; acute tubular necrosis; chronic intrinsic renal disease.

Functional renal failure may arise spontaneously or be precipitated by such factors as haemorrhage, surgery, or infection. It carries a poor prognosis but preliminary results of treating this condition with plasma volume expansion in combination with high doses of furosemide are encouraging.

Introduction

Hecker and Sherlock (1956) gave the first description of a syndrome that makes its appearance in the last stages of hepatic cirrhosis. The characteristics of this syndrome are oliguria, progressive hyperazotaemia, hyponatraemia, very low urinary sodium concentration and in some cases hyperkalaemia.

Later, Vesin (1962) described this condition as Terminal Functional Renal Failure, since he considered that there was no histological renal lesion to justify the renal failure and because of the very poor prognosis carried by this complication.

Koppel *et al.* (1969) showed beyond doubt that the disorder was functional, when they demonstrated that the kidneys of cirrhotic patients who had died with renal failure functioned normally when transplanted to anephric recipients.

The incidence of this condition is very high. In a previous study Rodés *et al.* (1970) found that about 50% of all patients with cirrhosis present this complication before they die.

In this paper are discussed the clinical course, prognosis and therapeutic approach of functional renal failure in cirrhosis, as well as the differential diagnosis of this disorder with other types of renal dysfunction which may occur in patients with cirrhosis of the liver.

Functional renal failure

Clinical course

In 1972 a clinical study of the cirrhotic patients with ascites and renal failure was done in the Liver Unit of the Hospital Clínico. Thirty-one cirrhotic patients with ascites who had a glomerular filtration rate (GFR) below 50 ml/min, a normal urine sediment, and absence of proteinuria, were included in this study. Thirty-four consecutive patients with cirrhosis and ascites and a normal creatinine clearance were used as controls. There were no significant differences between the two groups in respect of aetiology, number of previous episodes of ascites, clinical manifestations of hepatic failure on admission, and liver function tests, except for a more prolonged prothrombin time in patients with functional renal failure.

The clinical course of the thirty-one patients with renal failure was not uniform, and we were able to identify three different patterns of evolution among them.

In eleven patients (Group I) the renal failure followed a rapidly progressive course after admission to hospital, with a progressive increase in plasma urea concentration, very low urinary sodium concentration and a marked fall in urine volume (Fig. 1). All the eleven had a history of a complication very closely related chronologically to the onset of the progressive course of the renal failure, leading to the suggestion that these could have acted as a precipitating factor. Five of the patients had had a haemorrhage (gastro-intestinal in four, massive abdominal haematoma in one), five had had a serious infection (pneumonia in three and a spontaneous bacteraemia in two), and the remaining patient had had a cholecystectomy.

Eleven patients (Group II) were admitted with ascites and renal failure, for which no reason could be found. The renal failure remained steady through-

FIG. 1. Rapidly progressive functional renal failure following gastrointestinal bleeding in a patient of Group I. GIH = gastrointestinal haemorrhage.

FIG. 2. Steady functional renal failure in a 55-year-old cirrhotic patient (Group II). Ascites was uneventfully compensated with diuretics.

FIG. 3. Evolution of a patient of Group III. There was a rapid worsening of renal function in relation to a pneumonia.

out hospitalization. None of these cases presented any complication such as those that were considered as precipitating factors in the preceding group, and most of them lost their ascites with diuretic therapy (Fig. 2). However, transient worsening of renal function was noted after a paracentesis of 2 l in one of these patients but renal function returned to preceding levels after repeated albumin infusions, and the patient was uneventfully discharged from hospital. In two patients of this group, renal function slowly improved on follow-up, the blood urea recovering to normal values.

In the last nine patients (Group III) the initial evolution was identical to that of the group just mentioned, until some complication came up that hastened the course of the renal failure (Fig. 3). The complications that apparently produced this worsening of the condition were a gastro-intestinal bleed in four cases, a serious infection in three, a paracentesis in one, and a laparotomy for acute appendicitis in the last patient.

Prognosis

The immediate prognosis of these thirty-one patients was poor, twenty-three died while they were in hospital. This mortality rate was much higher than in the control group, in which only three of the thirty-four patients died ($P < 0.001$). The eight cirrhotic patients with functional renal failure who did not die were discharged from hospital without ascites and belonged to Group II. On follow-up, we found that after eleven months more than 50% of the patients with steady renal failure had died. This death rate was not reached in the control group until 24 months of follow-up. The mortality between these two groups of patients is significantly different ($P < 0.001$).

Two aspects from this study may be pointed out. Firstly, a number of patients with functional renal failure can survive for a considerable time, although the appearance of this event is usually an ominous prognostic sign. Secondly, a rapidly progressive renal failure is almost always related to a complication that could act as a precipitating factor. These complications were mainly haemorrhages and infections. The nature of this study does not show the mechanism by which these complications are operative, but some possibilities may be considered. If functional renal failure in cirrhosis is related to a decrease in the 'effective plasma volume' (Tristani and Cohn, 1967; Vlahcevic *et al.*, 1965), even a minor haemorrhage, by further decreasing the circulating blood volume,

would be expected to aggravate the course of the renal failure. On the other hand, endotoxin from Gram-negative organisms has several marked circulatory effects which may decrease the renal perfusion (Cavanagh *et al.*, 1970). A recent study by Wilkinson *et al.* (1974) has shown that it may be of major importance in the development of renal failure in patients with fulminant hepatic failure.

Therapeutic approach

The present knowledge of the pathophysiology of functional renal failure is incomplete. This is the main reason for which therapy of this condition remains poor. Reduced renal blood flow and GFR have been shown in patients with functional renal failure (Baldus *et al.*, 1964; Shear, Hall and Gabuzda, 1965). The cause of this impaired renal perfusion is not clear, but it may be related to at least two abnormalities—an active renal vasoconstriction (Epstein *et al.*, 1970) and a decrease in the effective circulating volume (Tristani and Cohn, 1967; Vlahcevic *et al.*, 1965).

The majority of treatments that have been proposed are directed to the correction of one of these abnormalities. A variety of vasoactive substances have been tried, including norepinephrine, dopamine, phentolamine and large doses of cortisone (Barron, Baldus and Maher, 1970; Conn, 1973). Transient improvement of renal function has followed the use of some of these drugs, but none of them has

FIG. 4. Furosemide plus plasma volume expansion therapy in functional renal failure. Results in seven patients. (a) Urine volume; (b) urinary sodium excretion; (c) GFR.

proved to be an effective therapy. Treatments directed to increase the 'effective' plasma volume through ascites reinfusions and plasma or albumin infusions have induced some recoveries, but they all have the major problem of producing fluid overload, and very often give rise to massive haemorrhage from ruptured oesophageal varices (Rodés *et al.*, 1970; Reynolds, Lieberman and Redeker, 1967).

Recently we have tried a new therapeutic approach to this problem, combining plasma volume expansion with high doses of furosemide, in order to avoid fluid overload. Furosemide was chosen because this drug has been shown to induce a diuresis even if the GFR is below 5 ml/min (Rastogi *et al.*, 1971) and also because there is some evidence that it can improve renal blood flow and GFR through a decrease in intrarenal vascular resistance (Ludens *et al.*, 1968).

We have so far treated seven patients with a rapidly progressive functional renal failure. Plasma volume expansion was achieved by the infusion of human plasma or equivalent amounts of human serum albumin plus isotonic saline. Furosemide was given i.v. at an initial dosage of 200 mg 4-hourly. This dose was doubled if diuresis had not ensued or if there was a rise in the central venous pressure. Furosemide was gradually tapered according to the diuretic response, usually 2–3 days after starting treatment.

In all these seven patients a striking improvement was noted in the GFR (Fig. 4). In two patients this improvement was spectacular, reaching a GFR of about 80 ml/min. Together with the rise in GFR, there was a great increase in urinary flow, from below 500 ml/24 hr to values running between 2000 and 4500 ml, and an increase of urinary sodium excretion from near 0 to 100–400 mEq/day. This was associated with a negative fluid balance and a decrease in ascites volume. The improvement of renal function was long standing in the majority of patients, and survival was high. Two patients died 2 weeks later, and the other five were discharged without ascites. Two of them died 3 months later from a gastrointestinal haemorrhage, one patient at the end of 5 months because of a spontaneous peritonitis, and another patient after 14 months, from an unrelated cause. One patient is still alive after 15 months of treatment. The last study of renal function performed before the terminal event in the patient who died was normal.

These preliminary results appear encouraging, but they are obviously inadequate as a basis for definite conclusions, and more detailed and controlled studies are needed in order to assess the effectiveness of this therapy.

Pre-renal azotaemia induced by diuretics

Functional renal failure must be differentiated from pre-renal azotaemia induced by diuretic therapy,

prognosis of which is usually excellent.

A prospective study was performed in order to characterize this complication (Bosch *et al.*, 1973). Eighty-five cirrhotic patients with ascites were treated by the following therapeutic measures: bed rest and a low sodium diet (Na 40 mEq/day). In the absence of diuretic response we added triamterene (300 mg/day) or spironolactone (150 mg/day). If a diuresis was not achieved, furosemide (40–80 mg/day) was added to the former. Plasma creatinine and urea concentrations, serum and urinary electrolytes, and the endogenous creatinine clearance were determined at 4-day intervals before, during and after diuretic therapy.

Twenty-two (25.8%) of the eighty-five patients showed a significant worsening of renal function

FIG. 5. Pre-renal azotaemia induced by diuretics. Findings in twenty-two patients (mean $\pm$ s.e. mean). (a) Blood urea; (b) urine volume; (c) urinary sodium concentration.

TABLE 1. Differential diagnosis of azotaemia in cirrhosis of the liver*

Type	Precipitating factors	Plasma		U/P osmolality	Urine		Sediment
		Urea (mg %)	Sodium (mEq/l)		Sodium (mEq/l)	volume (ml/day)	
Functional renal failure (seventeen patients)	GIH	89	131.3	1.78	6.9	600	Normal
	Infections Surgery	± 7	± 1.2	± 0.08	± 1.5	± 51	
Acute tubular necrosis (five patients)	Shock	185 ± 36	129.3 ± 3.8	1.01 ± 0.01	40.4 ± 11.1	390 ± 112	Casts Protein
Chronic renal disease (nine patients)		90 ± 16	141.5 ± 1.3	1.10 ± 0.05	51.4 ± 7.5	1317 ± 320	Casts Protein

* Values are mean ± s.e.mean. GIH = gastrointestinal haemorrhage.

during the course of treatment. Pre-renal azotaemia induced by diuretics is characterized by an increase in blood urea and a decrease in GFR, but with a high urinary flow and a high urinary sodium concentration. The raised blood urea returned to normal after withdrawal of diuretics (Fig. 5). This suggests that this complication has a good prognosis if recognized early.

Shear, King and Gabuzda (1970) have shown the possible mechanism of this complication. There is a compartmentalization of the ascitic fluid brought about by the limit of resorption of fluid through the peritoneum. Thus, if diuretic therapy produces a loss of the extracellular fluid volume above the limit of resorption of ascites, a contraction of the plasma volume will ensue, giving rise to a drop in GFR and to renal failure. Since the interstitial fluid accumulated as oedema is more easily resorbed than ascites, pre-renal azotaemia would be expected to be less frequent in patients with both ascites and oedema. In fact, forty-five of the eighty-five patients treated in our prospective study had both ascites and oedema, and forty ascites only. Among patients with oedema, only seven presented pre-renal azotaemia, as against fifteen in the group without clinical oedema ($P < 0.025$). This significant difference leads us to suggest that cirrhotics with oedema and ascites can be treated more energetically with diuretics until the disappearance of oedema than can those who have ascites only.

Differential diagnosis of renal failure in cirrhosis of the liver

A small percentage of cirrhotic patients with ascites may also have an intrinsic renal disease. In such cases, it is important to establish a differential diagnosis so as to have a prognosis and adequate treatment.

In order to settle the basis for a diagnosis we report here the features of a series of patients with chronic renal disease (comprised of patients with chronic glomerulonephritis, interstitial nephritis and Kimmelstiel-Wilson syndrome), and with acute tubular necrosis compared to patients with functional renal

failure. Diagnosis was based in all cases on morphological examination of the kidney.

Table 1 shows the most outstanding features of these three groups of patients. Those with functional renal failure had a very low urinary sodium concentration with a high urinary urea concentration and a urine/plasma osmolality ratio over 1.5. Proteinuria was absent or in a physiological amount, and the urine sediment was normal. In contrast, patients with chronic renal disease and acute tubular necrosis had a much higher urinary sodium concentration, a low urinary urea concentration, urine/plasma osmolality ratio lower than 1.3, significant proteinuria and granular and cellular casts in the urine sediment. Biochemical differences between chronic renal disease and acute tubular necrosis are minimal, but the clinical picture is very different, because the last condition is associated with an extremely low urinary output, in sharp contrast to patients with chronic renal disease.

However, although the differential diagnosis between these three types of renal failure in cirrhotic patients seems fairly simple, some cases present serious diagnostic difficulties. In one case we observed a progressive increase of plasma urea and creatinine concentrations, the diuresis and urinary sodium concentration were relatively high (without diuretic therapy), there were many red cells in the urine sediment, and also proteinuria that rose on occasions to 2 g/l. The clinical diagnosis was of cirrhosis of the liver and a rapidly progressive glomerulonephritis. Post-mortem examination revealed, however, that the kidneys showed no histological abnormality.

This case and others very similar are a demonstration of the urgent need to continue investigation of the renal disorders that occur in cirrhosis of the liver, in spite of the considerable work that has been done already.

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