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Progress report

Renal changes in cirrhosis

Renal failure is a frequent complication of advanced cirrhosis of the liver[1-4]. While in some cases azotaemia and oliguria may be due to coexisting primary renal disease or to known causes of acute tubular necrosis, in many others renal failure appears to develop either spontaneously or in response to minor changes in circulating blood volume. The latter variety has become increasingly important as a factor contributing to death in patients with hepatic failure but, despite considerable clinical observation and investigative effort, its cause and nature remain uncertain and its treatment unsatisfactory.

The term 'hepatorenal syndrome' has been used to describe the sequence of events in which cirrhosis is complicated by renal failure. It originally referred to those patients who became oliguric after biliary surgery[5, 6], but over the years the definition has been broadened until it covers all patients with liver disease in whom renal function deteriorates. Because of this, and also because the name implies a specific relationship between the kidney and liver which has not yet been definitely established, most authorities have urged that the term be abandoned. There is now a good deal of evidence that the renal failure which occurs without apparent cause in cirrhotic patients has a functional basis: for this reason and in order to distinguish between this condition and acute tubular necrosis, Vesin[7] introduced the term 'functional renal failure in cirrhosis' and this name is now generally preferred.

Presentation and Prognosis

Functional renal failure has been reported in all forms of cirrhosis but appears to be particularly common in patients with progressive alcoholic cirrhosis[2, 3]. The clinical and biochemical features have been well described[1-4, 7] and may be divided into a number of stages. In the mildest or preazotaemic stage, renal dysfunction may manifest only with a reversal of the normal nycthemeral rhythm of urinary excretion or the inability to excrete a water load normally. Sodium excretion is commonly reduced and hyponatraemia is usual. Jaundice may or may not be present, but hepatic function is severely impaired by most clinical and biochemical criteria and ascites is frequently found.

The more advanced stages are characterized by progressive azotaemia and occur typically in patients with hepatic failure and refractory ascites. The symptoms may be inseparable from those of hepatic failure. The patient commonly complains of anorexia, lethargy, weakness, and fatigue. The blood urea concentration is usually elevated to a greater degree than the serum creatinine level, although in some cases the reverse is true. This disproportional increase in creatinine may reflect diminished urea synthesis and restricted

dietary protein intake[4]. Hyponatraemia is almost invariable and may be severe. Sodium is avidly reabsorbed by the renal tubules and urine osmolality is increased. Fluid accumulates in spite of a normal urinary volume, dietary sodium restriction, and diuretic therapy. Urinary acidification is normal except in those patients with renal tubular acidosis[8, 9]. Although this has recently been described in a variety of hepatic and other diseases characterized by hypergammaglobulinaemia and the presence of non-organ-specific antibodies in the serum[9], it has no known association with functional renal failure.

In the late stages nausea, vomiting, and thirst are added to the earlier symptoms, which are intensified. The patient is often apathetic and drowsy and a non-specific tremor may be present, a picture indistinguishable from that of hepatic precoma. The blood urea level rises progressively and hyponatraemia becomes more profound, the serum sodium concentration being frequently less than 120 m-equiv/l. Hyperkalaemia and acidosis may develop. Urinary sodium excretion is very low and the patient is almost always oliguric. Ascites becomes progressively more refractory to treatment. The terminal stages are characterized by deepening coma, oliguria, and arterial hypotension. The duration of azotaemia until death or recovery ranges from a few days to more than six weeks[3, 10]. Occasionally, renal failure persists for months either in a stable state or fluctuating in severity[11].

At the height of the azotaemia the relative contributions of hepatic and renal failure to the clinical and biochemical changes are difficult to distinguish. Certainly the severity of the illness is out of proportion to the degree of elevation of the blood urea, and the patient dies with azotaemia rather than from renal failure. The prognosis is grave [1, 2, 4, 12], although the syndrome is not invariably fatal[3, 13, 14]. Death is due primarily to hepatic failure and the chances of survival appear to depend on the degree of reversibility of the liver disease[3]; renal function seems to improve only when the liver disease does. Occasionally death results from unrecognized hyperkalaemia[11]. Functional renal failure carries a worse prognosis than acute tubular necrosis[15].

Cause and Nature of the Disturbance

Histological examination of the kidneys of cirrhotic patients dying with renal failure usually reveals nothing abnormal[1–3, 16]; when lesions have been found, these are non-specific and could not account for the severely deranged renal function[17–19]. Many of the changes described, such as widening of the mesangial matrix, patchy thickening or splitting of the glomerular basement membranes, tubular dilatation, areas of interstitial nephritis, and bile staining of the tubular epithelium[17–19], are of doubtful significance and similar changes have been found in cirrhotic patients without renal failure. Tubular necrosis is seldom observed and then only in patients with an obvious cause for this complication[20]. However, it is worth noting that even in those cases in which tubular necrosis is not apparent histologically, an ischaemic cause for the azotaemia cannot be excluded[21].

In keeping with the absence of significant organic changes in the kidney are the observations that urine analysis is either normal or shows only minor changes[3], and that tests of renal tubular function are also normal except in the terminal stages when hypotension supervenes[4, 22, 23]. This provides a sharp contrast with acute tubular necrosis, in which tubular function is

severely deranged and the urinary sediment clearly abnormal. The urinary sodium excretion may be a useful pointer to the integrity of the tubules: in acute tubular necrosis it is characteristically increased (usually to more than 60 m-equiv/l), whereas sodium is avidly reabsorbed through the intact tubules in functional renal failure so that the urinary sodium excretion is very low (less than 10 m-equiv/l). The differentiation between tubular necrosis and functional renal failure may, however, be less precise than is generally depicted[3, 4, 24] and difficulty may be experienced in individual patients in appraising the contribution of exogenous factors.

The successful transplantation by Koppel and his colleagues[16] of kidneys from cirrhotic patients dying with renal failure provides additional evidence of the functional and potentially reversible nature of the renal lesion. The transplanted kidney appears to regain normal function either because it is removed from the deleterious environment of hepatic failure, or because an essential but as yet undefined requirement for normal renal function is provided by the liver of the recipient. The premise that normal liver function may be essential for normal renal function gains support from the experimental finding of Mondon and coworkers[25] that the survival and functional activity of the isolated rat kidney is prolonged when a liver is included in the perfusion circuit. Improved renal function has also been described after cross-circulation between cirrhotic patients with spontaneous renal failure and normal subjects[26] or, in one case, a primate[27].

Although the exact nature of the renal disturbance in liver disease has not been determined, the available information favours a haemodynamic basis for the syndrome. Apart from its being a functional and potentially reversible change, a circulatory disturbance is suggested by the following observations. The abnormality in renal function is similar to that seen in congestive cardiac failure and arterial hypotension when renal perfusion is known to be reduced[28, 29]. Renal failure may develop with great rapidity, and drugs which increase renal blood flow return function to normal, in the early stages at least[30, 31]. Alterations in systemic and regional haemodynamics are common in patients with hepatic cirrhosis[32, 33]. Studies using a variety of methods have consistently shown a significant reduction in renal blood flow [2, 4, 22, 34–38]. This has been associated with an increased renal vascular resistance[35, 39] and a fall in glomerular filtration rate[4, 22]. Whether the increased renal vascular tone is the cause or the result of the renal hypoperfusion has not been determined, but the observation that renal blood flow can be improved in these patients by drugs which lower renal vascular resistance[30, 31] suggests that vasoconstriction is the primary disturbance. A high renal vascular resistance in the face of a normal or reduced peripheral vascular resistance[33] would explain the observed decrease in the renal fraction of the cardiac output[39], blood being shunted away from the kidney. Support for active renal vasoconstriction has been provided by the observation of Epstein and his colleagues [38] that there is extreme haemodynamic instability in these patients, which was not encountered in renal failure from other causes, and also by reversible renal angiographic changes[38]. There is some evidence that the reduced renal perfusion is accompanied by a redistribution of blood flow within the kidney, the blood being shunted away from the main mass of functioning glomeruli in the outer cortex[4, 30, 34, 38–40]. When this occurs, glomerular filtration rate falls[41]. The thesis that functioning nephrons are being underperfused is further suggested by the observation that the urine in these patients remains

hypersomotic and has a low sodium content even after a water load[42].

The cause of the renal haemodynamic disturbance has not been established. It does not appear to be due to a low cardiac output[32, 33, 37], arterial hypotension[3, 43] or renal venous hypertension[39] and is not related to hyperbilirubinaemia *per se*[3, 44]. Decreased plasma volume is a commonly cited cause [2, 7, 35]. It has, however, been shown that the plasma volume is normal or increased in cirrhosis regardless of the state of renal function [33, 45, 46]. Others have suggested that a significant proportion of the total plasma volume may be sequestered in the hypertensive splanchnic bed and ascitic pool and that the plasma volume concerned with organ perfusion (effective plasma volume) may be reduced[35, 47]. Further work designed to measure effective plasma volume has, however, shown that this, too, is normal[48], and that further expansion of plasma volume by infusion of albumin or other solutions does not significantly improve renal perfusion or function [49, 50].

Because the syndrome almost always develops in patients with liver failure it has been suggested that some vasoactive substance may be released from or not inactivated by the diseased liver. The occurrence of functional renal failure in patients with malignant disease of the liver[51] and fulminant viral hepatitis[52] supports this mechanism. Attempts to identify endogenous vasoactive substances which normally depend in part on the liver for their catabolism have thus far failed[53]. Although plasma renin activity was found to be increased and showed an inverse relationship with renal function, the increased activity appeared to be the result and not the cause of the renal circulatory changes, since increasing renal blood flow with dopamine caused the renin levels to fall[53]. Alternatively, renal arteriolar constriction may be mediated via reflex autonomic stimuli. The rich adrenergic and cholinergic innervation of the renal vessels and their responsiveness to neurogenic stimulation suggests that the autonomic nervous system may play an important role in the regulation of renal and intrarenal blood flow[54]. There is some experimental support for a neurogenic connexion between the hepatic arterial circulation and renal perfusion: in dogs, occlusion of the hepatic artery produces a marked fall in renal blood flow which can be prevented by sympathectomy or splanchnicectomy[55]. The redistribution of blood flow within the kidney may also be explained on this basis, for it has been shown that the outer cortical vessels are especially sensitive to sympathetic vasoconstrictor stimuli and an increase in sympathetic tone might therefore be expected to affect mainly cortical blood flow[54]. Attempts to improve renal perfusion in cirrhotic patients by the use of adrenergic blocking drugs have, however, met with mixed success[38, 56].

Treatment

The fact that a potentially reversible condition should carry such a grave prognosis reflects ignorance of the basic aetiology of the syndrome and our limited capacity to treat the underlying liver disease. Nevertheless, as the outlook appears to depend primarily on recovery of hepatic function, every effort to achieve this should be made. Hepatic failure is treated in the usual way except that neomycin, which may be nephrotoxic when renal function is impaired[57], should be replaced by another antibiotic. Complications which may precipitate or aggravate renal failure, such as gastrointestinal haemorrhage, should be treated vigorously, and therapeutic procedures likely to com-

promise renal perfusion and glomerular filtration, such as abdominal paracentesis and the use of potent diuretics, should be avoided. The serum potassium level should be closely watched. Dietary sodium restriction should be continued in patients with ascites and be supplemented by fluid restriction when dilutional hyponatraemia is severe or oliguria supervenes[24].

None of the various specific therapeutic approaches employed has produced more than temporary improvement in renal function. Plasma volume expansion with the use of albumin or other solutions, while temporarily improving renal plasma flow in some patients, has not benefited those with more severe impairment of renal function[35, 49, 50]. Attempts have been made to improve renal perfusion with a variety of drugs known to increase renal blood flow. These drugs have either proved ineffective, temporarily effective, or been unsuitable for clinical use[24, 31, 58, 59]. The place of peritoneal or haemodialysis, exchange transfusion, and the specialized procedures of extracorporeal pig liver perfusion and cross-circulation in the treatment of cirrhotic patients with functional renal failure has not yet been evaluated.

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