The kidney and liver diseases

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Abnormalities of renal function have been recognised in virtually all acute and chronic liver and biliary diseases. Cirrhosis has received most attention and the abnormalities include renal failure, fluid retention, renal tubular acidosis and glomerulonephritis; ascites is common and may be renal in origin.

Renal failure

Between one half and three quarters of patients dying with cirrhosis show evidence of renal failure.^{1,2} In many cases this is merely part of the complex syndrome of terminal hepatic failure, and the patients die *with* rather than *of* renal failure. However, in one analysis of 253 patients the severity of the renal failure was out of proportion to the degree of hepatic impairment and was considered to be the main cause of death in 11%.³ Several distinct types of renal failure may occur in cirrhosis including hepatic nephropathy, failure due to diuretics and other drugs, and failure secondary to specific parenchymal diseases.

HEPATIC NEPHROPATHY

This accounts for most cases. It was recognised in 1863 by Flint⁴ and described more recently by Hecker and Sherlock⁵ who pointed out that the features were in keeping with a prerenal azotaemia, namely very low urine sodium concentrations, no significant proteinuria and normal renal histology. These findings have since been confirmed by many groups, but in a proportion of patients there is evidence of tubular dysfunction/necrosis in that the urine sodium concentration may be high, the urine isosmolar, and there is histological evidence of tubular necrosis.^{2,6} In other cases the prerenal type may progress to show the features of established acute tubular necrosis and intermediate forms also exist. It has been suggested that these two types of renal failure are really the beginning and end of a single spectrum.⁶

Hepatic nephropathy occurs in advanced cirrhosis, whatever its cause. Ascites is usually present and refractory to diuretic treatment. In one half to two-

thirds of patients the renal failure is precipitated by events that impair hepatic function such as alcoholic hepatitis, gastrointestinal haemorrhage, infection or paracentesis. In others it arises in the absence of any apparent precipitating cause other than advanced cirrhosis. The prognosis is poor, few patients surviving to leave hospital.

An important pathophysiological event would appear to be a moderately severe reduction in renal blood flow,⁷ although values do overlap with those found in patients without overt renal impairment.⁸ The mechanism for this is uncertain. It cannot be explained on the basis of the usual causes for a pre-renal azotaemia in that plasma volume is usually increased as is cardiac output.^{9,10} Although hypotension is often found this generally occurs after the onset of renal failure.⁵ One aspect to received considerable attention is the role of endotoxins, derived from Gram-negative commensals of the gut. Normally endotoxins are absorbed into the portal venous system and cleared by the liver. With the development of liver disease they might escape into the systemic circulation and exert a toxic action without a Gram-negative septicæmia. Using the *Limulus* assay for endotoxin several groups have now reported an association between endotoxaemia and renal failure in cirrhosis.¹¹⁻¹³ The mechanism whereby endotoxins produce renal failure is probably largely their renal vasoconstrictor properties.^{14,15}

There is no satisfactory treatment for hepatic nephropathy. There have been many pharmacological attempts to reverse the renal vasoconstriction, but none of these has produced any more than a temporary benefit.

DIURETIC-INDUCED RENAL FAILURE

Over-aggressive use of diuretics is probably the commonest cause of renal impairment in cirrhosis. The maximal rate at which ascites can be mobilised has been reported to be less than one litre/day¹⁶ and a negative fluid balance in excess of this capacity will inevitably lead to a contraction of the interstitial fluid volume. The fall in creatinine clearance due to diuretics has been shown to be related to the

contraction of the plasma volume.¹⁷ Less commonly, diuretics may induce renal impairment in the *absence* of a negative fluid balance. The mechanism for this is uncertain but β -adrenergic blocking drugs appear to be able to protect against this type of renal impairment.¹⁸

RENAL FAILURE DUE TO OTHER DRUGS

Renal failure may occur secondary to the use of other drugs in cirrhosis. Inhibitors of prostaglandin synthetase such as indomethacin may severely impair renal function¹⁹ in patients with ascites, who thus may be dependent upon renal prostaglandin synthesis for maintaining their renal circulation.

Demeclocycline is a tetracycline which inhibits the effect of antidiuretic hormone on the renal tubules. It has been used in the treatment of hyponatraemia in the syndrome of inappropriate secretion of antidiuretic hormone, but is known to have a toxic effect on the kidney; in cirrhosis it is very liable to produce an impairment of renal function.²⁰

Patients with cirrhosis also appear to be particularly prone to develop renal impairment secondary to the use of other nephrotoxic antibiotics such as aminoglycosides, including oral neomycin given for hepatic encephalopathy.²¹

SPECIFIC RENAL DISEASES

Glomerulonephritis

Rarely, renal failure may be due to glomerulonephritis. Detailed accounts of its occurrence in cirrhosis were published in the 1940's and 1950's. The first abnormalities to be described included a fibrillar thickening of the mesangial stalk and to a lesser extent of the basement membrane of the capillary loops. These changes were reported in about half of all cases of cirrhosis coming to necropsy.^{22 23} More recent studies with immunofluorescence have shown that the mesangial deposits contain immunoglobulins, in particular IgA,^{24 25} but this has not been confirmed by others.²⁶ Despite the fact that these abnormalities may be moderately severe as assessed histologically, it is unusual to see clinical evidence of glomerulonephritis, presumably because the changes are largely confined to the mesangium. However, other more serious types of glomerulonephritis, including mesangiocapillary, may also occur, again with Ig deposition, mainly IgA.^{25 27}

Other types of glomerulonephritis have also been described. In chronic active hepatitis lupus nephritis may occur.²⁸ With chronic hepatitis B infection glomerulonephritis secondary to deposition of hepatitis B antigen-antibody complexes within the glomerulus has been described.²⁹

Renal tubular acidosis

A sub-clinical or incomplete "distal" renal tubular acidosis occurs in about 40% of patients with cirrhosis whatever its cause. As with distal renal tubular acidosis in other conditions it is often associated with renal potassium wasting, hypercalciuria and nephrocalcinosis. Patients with this appear to be particularly prone to develop encephalopathy.³⁰ The mechanism is uncertain but there is evidence for participation of both an abnormal nephron handling of sodium and an abnormal autoimmune response to the acidification site. With regard to sodium the renal acidosis can be corrected by administering sodium sulphate to increase sodium delivery to the distal tubule, which implies that an increased sodium reabsorption at sites more proximal to the distal sodium-hydrogen ion exchange site may have contributed.³¹ Alternatively an abnormal cell-mediated immune response to the acidification site has been proposed in "autoimmune" type cirrhosis.³²

Renal failure in other liver diseases

Renal failure has been described in association with a wide variety of other liver diseases (Table). In many of them the cause of renal failure may be obvious. Renal involvement in hepatocellular diseases other than cirrhosis, such as fulminant hepatic failure and acute viral hepatitis, appears to be similar to the

Renal failure with liver diseases

Hepatocellular diseases

- Cirrhosis
- Fulminant hepatic failure
- Acute viral hepatitis and other viral infections
- Acute fatty liver of pregnancy

Obstructive jaundice and other biliary tract disorders

Shock

- Septicaemic
- Cardiogenic
- Haemorrhagic (rare)

Specific infective conditions affecting both organs

- Some leptospiral infections
- Hepatitis B
- Yellow fever
- Malaria

Pathological processes affecting both organs

- Congenital hepatic fibrosis⁴⁸
- Caroli's syndrome⁴⁷
- Polycystic disease
- Cerebrohepato-renal syndrome⁴⁸
- Sickle cell disease
- Collagen diseases
- Amyloid
- Eclampsia
- Lymphoma

Toxins or drugs affecting both organs (including allergic reactions)

- Carbon tetrachloride
- Tetracycline
- Methoxyflurane
- Rifampicin
- Phenylbutazone
- Many others

hepatic nephropathy described for cirrhosis.^{33 34}

Renal failure occurring with biliary tract disease is particularly important to the surgeon. It may occur preoperatively or shortly after surgery, and is more likely to occur in the more deeply jaundiced patient and is often associated with infection by bacteria.¹¹

Fluid retention

Ascites with fluid retention is one of the commonest complications of cirrhosis. The relation between the formation of ascites and renal sodium excretion is of particular interest as the accumulation of ascites is always associated with sodium retention. Traditionally sodium retention has been considered as secondary to "effective"* blood or ECF volume depletion. Because of ascites formation extracellular fluid is lost into the peritoneal cavity. Simultaneously, because of portal hypertension, blood is sequestered in the splanchnic circulation. Both of these result in a fall of renal perfusion and hence in stimulation of the renin-angiotensin-aldosterone system which causes sodium retention. Thus the sodium retention is held to be a homeostatic mechanism to maintain the interstitial fluid and blood volumes. However, many recent findings are not in keeping with this concept, at least for the majority of patients. In particular renal perfusion is often normal or even increased.^{35 36} Furthermore renin and aldosterone concentrations are not increased in about two-thirds of patients accumulating ascites.³⁷⁻⁴⁰ Despite this, there is considerable evidence that aldosterone is a major factor in the regulation of renal sodium excretion in cirrhosis. Firstly, a close correlation can be shown between plasma aldosterone concentrations and sodium excretion.³⁸ Secondly, the aldosterone antagonist spironolactone will almost invariably reverse the fluid retention.^{38 41} Finally in a study of the effect of β -adrenergic blockade, sodium excretion was found to change exactly as predicted by the changes in aldosterone, as the latter decreased or increased.⁴² There may even be an increased renal tubular sensitivity to aldosterone, as has been proposed for dogs with constriction of the thoracic inferior vena cava, a model with many similarities to cirrhosis with ascites.⁴³ If this is so, it may be the mechanism whereby sodium retention is initiated in cirrhosis. Ascites might then develop in accordance with

Lieberman's "overflow" concept,⁴⁴ according to which the fluid retained by the kidney is preferentially localised to the peritoneal cavity as ascites because of the presence of portal hypertension and reduced plasma oncotic pressure⁴⁵—that is, ascites is secondary to sodium retention rather than its cause. However, one-third of such patients do have increased values of the components of the renin-angiotensin-aldosterone system so that in them it is possible that ascites formation does occur according to the traditional concept.

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*The term depletion of "effective" blood volume (or ECF volume) was introduced to "explain" the occurrence, in patients whose blood volume is normal or even high, of circulatory and hormonal changes that are associated with a low blood volume. Thus, it is really the effectiveness of the blood volume in maintaining homeostasis that is reduced.—Eds.

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