Hospital Topics

Renal failure in otherwise uncomplicated acute viral hepatitis

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British Medical Journal, 1978, **2**, 338-341

Summary and conclusions

Twelve patients with otherwise uncomplicated acute viral hepatitis (two were HBsAg-positive) developed renal failure. Apart from dehydration due to repeated vomiting in one patient, no factor responsible for precipitating renal failure could be identified. The clinical course was characterised by renal failure with plasma urea concentrations reaching maximum values of 26-69 mmol/l (175-416 mg/100 ml). Ten patients needed dialysis for up to two weeks. Seven patients recovered completely, while the other five died from sepsis. The types of renal failure were similar to those described in fulminant hepatic failure and cirrhosis—namely, functional renal failure in five patients and acute tubular necrosis in seven. Two of the patients with functional renal failure later developed tubular necrosis.

The mechanism responsible for renal failure in acute viral hepatitis is uncertain, though endotoxaemia may contribute.

Introduction

In the most severe form of viral hepatitis, fulminant hepatic failure, renal failure may occur in up to 80% of cases.[1] In less severe hepatitis renal failure has not been reported, although some minor changes in renal function include slight reductions in glomerular filtration rate and renal plasma flow[2,3] and an impaired capacity to excrete a water load[4] and sodium,[5] though these may all be normal.[6] Histological changes include deposits in the capillary wall and mesangium, thickening of the basement membrane, and an increase of the mesangial matrix (changes collectively know as "hepatic glomerulosclerosis"),[7] an inflammatory infiltrate in the interstitium, and fatty change in the proximal tubules.[8] The functional importance of these structural abnormalities is, however, unknown.

We describe 12 cases of severe renal failure in acute viral hepatitis, none of which progressed to fulminant hepatic failure after follow-up for up to five years.

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Clinical and laboratory findings and comment

Eight of the 12 patients were men, and ages ranged from 29 to 60 years (table). In each case the illness started with a typical prodrome of acute hepatitis with malaise and anorexia, followed by the development of jaundice, pale stools, and dark urine. Two patients (cases 1 and 2) were positive for HBsAg on presentation. One (case 3), who was repeatedly negative for HBsAg, may have had "non-A non-B" hepatitis[9] since he had received a blood transfusion two months earlier after being stabbed. Three of the other nine patients (cases 6, 8, and 11) were tested for hepatitis A antibody and found to be positive on admission to this unit. Although compatible with an acute hepatitis A infection, this may merely indicate a past infection.[10] Two patients (cases 11 and 12) developed the first signs of illness during the last month of pregnancy. In one (case 11) labour was induced forthwith and resulted in a live birth. The other (case 12) went into spontaneous labour and had a stillbirth on the day jaundice was first noticed. In both of these patients the biochemical evidence of hepatitis continued to progress after labour. None of the 12 patients had given a history of recent drug ingestion before the onset of hepatitis and no patient subsequently received nephrotoxic drugs. Leptospirosis was excluded in all cases by serological testing.

Results of biochemical tests showed that hepatitis was of variable severity, with maximum abnormalities for serum bilirubin concentrations of 82-1360 μmol/l (4·8-79·5 mg/100 ml (normal < 20 μmol/l (< 1·2 mg/100 ml)), and aspartate aminotransferase concentrations of 105-3760 IU/l (normal < 50 IU/l). The prothrombin time was prolonged by less than 6 seconds in eight cases, but prolonged by up to 12 seconds in the others (table).

Six patients showed no evidence of encephalopathy, but the others (cases 2, 5, 6, 8, 9, and 12) had a mild encephalopathy characterised by drowsiness or confusion or both. It seems unlikely that this was hepatic encephalopathy since none of them showed the characteristic fetor or flap, and in four the prothrombin time was prolonged by less than 6 seconds. In one patient (case 6) encephalopathy seemed to be due to severe hyponatraemia (plasma sodium concentration 99 mmol(mEq)/l, since she became fully alert when this was corrected (fig 1). The others may well have had uraemic encephalopathy, since the plasma urea concentration exceeded 40 mmol/l (241 mg/100 ml) in each case.

A liver biopsy specimen was obtained in all cases, in five at the peak of the illness, and during the recovery period (within two months of the onset of disease) in another four. In three of the patients who subsequently died a needle biopsy specimen was taken immediately after death. The findings were invariably typical of acute viral hepatitis—namely, normal liver architecture with spotty necrosis and ballooning of liver cells, inflammatory cells in the lobules, pleomorphism of liver cell nuclei, and focal collections of iron-laden macrophages (fig 2). In 10 cases these changes were relatively mild, with no areas of severe necrosis or reticulin collapse. In the other two necrosis and collapse were somewhat more noticeable, but not to the extent found in fulminant hepatic failure.

RENAL FAILURE

Biochemical evidence of renal failure was first detected between four and 14 days after the onset of jaundice. In one patient (case 2) this may have been precipitated by dehydration due to repeated

Clinical and laboratory data on 12 patients with acute viral hepatitis who developed renal failure. Values for plasma urea, creatinine, and bilirubin and serum aspartate aminotransferase are the maxima recorded

Case No	Age (yrs)	Sex	Creatinine clearance (minimum, ml/min)	Plasma urea (mmol/l)	Plasma creatinine (μmol/l)	Urine volume (minimum; ml/24 h)	Urine sodium (mmol/l)	Urine: plasma osmolality	Dialysis (duration)*	Plasma bilirubin (μmol/l)	Serum aspartate amino-transferase (IU/l)	Prothrombin time (s; prolonged)
1†	60	M	<1	45	640	100	81		P (14 days)	340	105	4
2	33	M	4	41	841	1300	28	0·91		622	1100	0
3	36	M		29		1100	31			1360	3760	12
4	29	M	<1	44	>1400	300	85	0·87	P (6 days)	82	2530	3
5	45	M	<1	41	123	1300	136	1·00	P (11 days)	610	1620	4
6‡	34	F	3; <1	69	>100	90	2; 34	1·13; 1·01	H (7)	315	960	3
7†	29	F	4	45	390	150	11		P (3 days)	630	>500	2
8†‡	49	M	5; <1	51	822	100	2; 98	1·14; 1·01	H (11)	506	860	8
9†	52	M	3	54	110	60	1		H (6)	622	210	5
10†	56	M	<1	57	100	800	56	1·00	H (1)	411	1562	12
11	35	F	<1	37	825	50	30	1·00	H (7)	380	1100	0
12	31	F	4	48	503	475	1	1·12	P (6 days)	340	450	12

*Or number of dialyses.

†Patients who died.

‡In cases 6 and 8 values for creatinine clearance, urine sodium, and urine:plasma osmolality were recorded before and after functional renal failure progressed to acute tubular necrosis.

P = Peritoneal dialysis. H = Haemodialysis.

Conversion: SI to traditional units—Urea: 1 mmol/l ≈ 6 mg/100 ml. Creatinine: 1 μmol/l ≈ 0·01 mg/100 ml. Sodium: 1 mmol = 1 mEq. Bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.

vomiting over 24 hours. In another patient (case 10) it occurred four days after an exploratory laparotomy had been performed at the referring hospital because of doubt about the diagnosis of jaundice. Nevertheless, the plasma urea concentration had been normal for the first three postoperative days. In the others there was no apparent precipitating factor. Blood cultures were performed at the onset of renal failure in eight patients and were sterile, and no patient had clinical or biochemical evidence of pancreatitis.

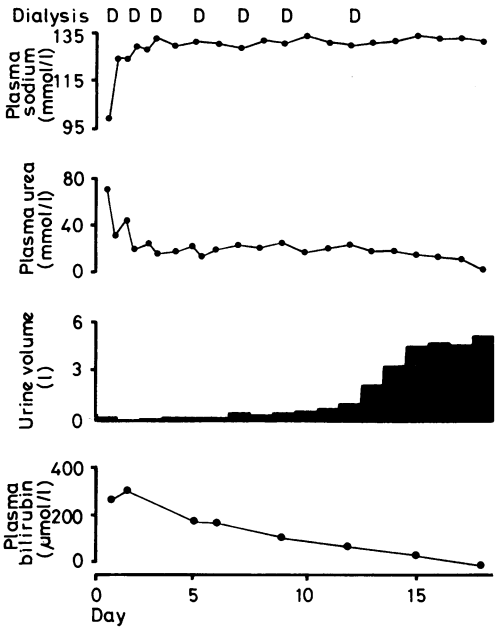

FIG 1—Case 6. Clinical course in patient with acute viral hepatitis who presented with plasma sodium concentration of 99 mmol/l and signs of encephalopathy. This resolved when hyponatraemia was corrected by dialysis.

Conversion: SI to traditional units—Sodium: 1 mmol = 1 mEq. Urea: 1 mmol/l ≈ 6 mg/100 ml. Bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.

The endogenous creatinine clearance was reduced to between 5 and < 1 ml/min (table). The maximum plasma urea and creatinine concentrations were 29-69 mmol/l (175-416 mg/100 ml)—normal < 6·7 mmol/l (< 40·4 mg/100 ml)—and 390- > 1400 μmol/l (4·4-15·8 mg/100 ml)—normal < 100 μmol/l (< 1·1 mg/100 ml)—respectively.

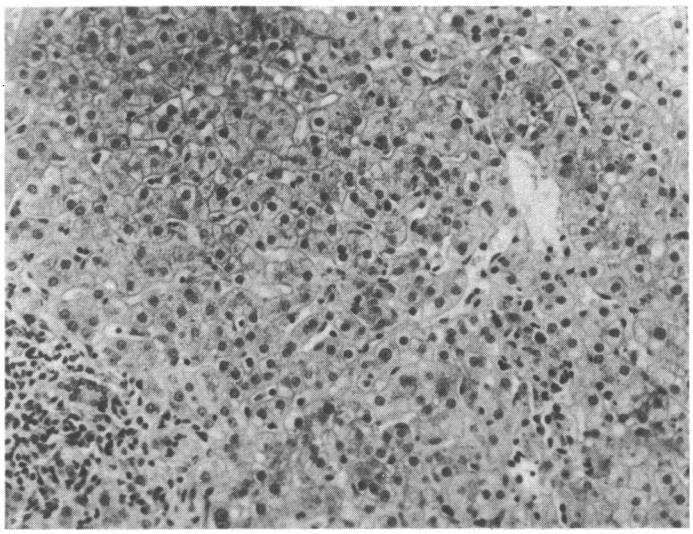

FIG 2—Case 6. Needle biopsy specimen from liver taken three weeks after peak of illness showing features of resolving hepatitis, with disarray of liver cell plates and inflammatory infiltrate which is moderate in the portal tract (bottom left) and spotty in the parenchyma. (Haematoxylin and eosin. × 124.)

In eight patients the course of the renal failure seemed to parallel the hepatitis. In the others (cases 1, 4, 5, and 11) the renal failure progressed as the results of liver function tests improved.

TYPE OF RENAL FAILURE

In five patients the biochemical findings in the urine were those of prerenal renal failure (urine sodium concentration < 12 mmol(mEq)/l, urine:plasma osmolality ratio > 1·10, and no significant proteinuria), but this could not be explained by volume depletion or hypotension ("functional renal failure"). In seven patients features of "acute tubular necrosis" were initially present (urine sodium concentration > 20 mmol(mEq)/l and urine:plasma osmolality ratio < 1·10). In two patients (cases 6 and 8) functional renal failure spontaneously progressed to acute tubular necrosis (fig 3).

Needle biopsy specimens of the kidney were taken immediately after death in three patients. In one of the patients in whom urinary biochemical findings suggested functional renal failure (case 7) no abnormality could be detected except for bilirubin casts in some of the tubules (fig 4). The other two, both with urinary findings suggesting acute tubular necrosis, showed histological changes typical of this lesion (fig 5).

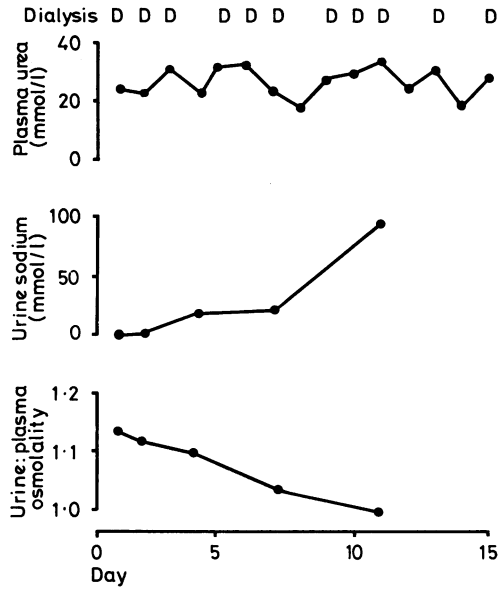

FIG 3—Case 10. Clinical course showing progression from functional renal failure to acute tubular necrosis.

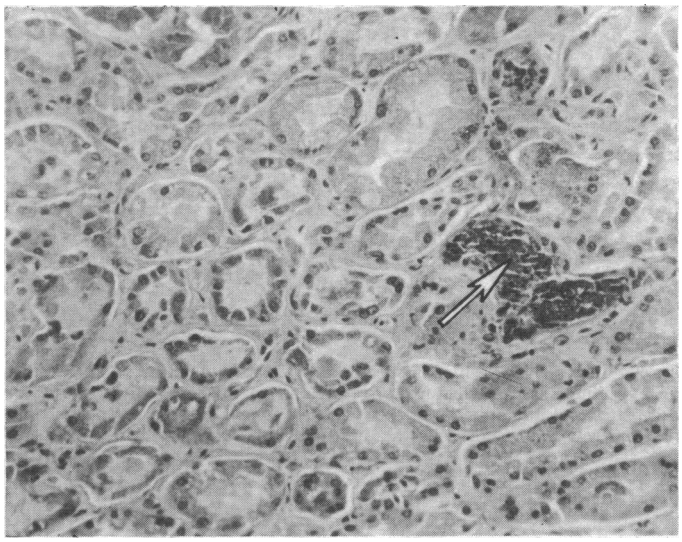

FIG 4—Case 7. Postmortem biopsy specimen showing histologically normal renal tubules in patient with biochemical evidence of functional renal failure. Bilirubin casts are seen in some of the lumina (arrowed). (H and E. × 124.)

TREATMENT AND OUTCOME

Two patients (cases 2 and 3) required no specific treatment, since both hepatitis and renal failure improved spontaneously shortly after transfer to this unit. The others all needed dialysis for renal failure. Four patients received haemodialysis, which was always used when the initial plasma urea concentration was >50 mmol/l (301 mg/100 ml), and if less than this peritoneal dialysis was used in all but one patient (case 11), who also received haemodialysis. Haemodialysis was performed for four to six hours either daily or on alternate days for one day to two weeks. A cuprophane membrane (Travenol) was used in three patients and a polyacrylonitrile membrane (Rhône-Poulenc) in the other two. Peritoneal dialysis lasted from three to 14 days. Both forms of dialysis were well tolerated except in one patient (case 8), whose blood pressure fell to as low as 40 mm Hg with each period of haemodialysis.

Seven patients recovered completely after being in hospital for three to nine weeks. Follow-up for nine months to five years showed no evidence of chronic hepatic or renal disease. Of the five patients who died, the results of liver function tests were improving in three, and in one of these (case 10), renal function had also improved to such an extent that dialysis had been discontinued. Three of the deaths were shown to have been due to septicaemia (*Escherichia coli* in two and a fungal organism in one). The other two deaths were thought to be due to septicaemia, although blood cultures were sterile.

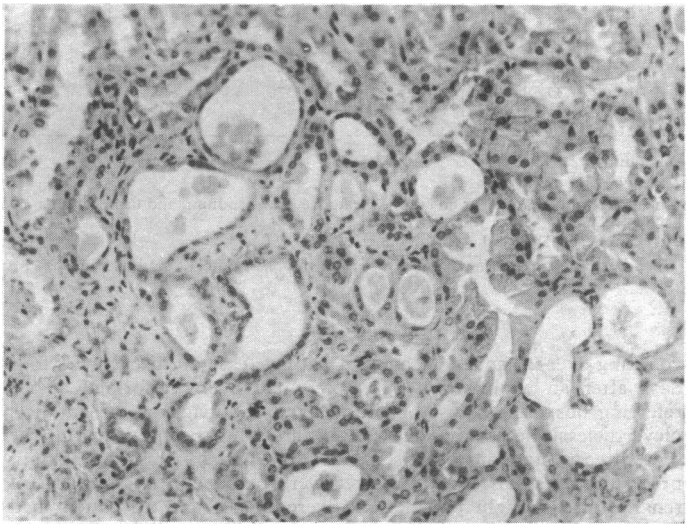

FIG 5—Case 10. Postmortem needle biopsy specimen from patient who was recovering from acute tubular necrosis showing typical histological abnormalities, including dilated renal tubules, and mild oedema and inflammatory infiltrate in the interstitium. (H and E. × 124.)

Discussion

Functional renal failure and acute tubular necrosis may also occur in fulminant hepatic failure[1 11] and advanced cirrhosis.[12] Whether these two types of renal failure are separate entities or the ends of a single range is uncertain.[13] Glomerulonephritis due to immune-complex formation associated with hepatitis B virus infection has been described,[14] but the absence of proteinuria in our patients suggests that this was an unlikely mechanism for the renal failure. Nevertheless, we have seen another patient who recovered from a presumed viral hepatitis, but developed renal failure characterised by proteinuria, red-cell casts in the urine sediment, and a low urine sodium concentration. These features suggested glomerulonephritis, but neither diagnosis could be confirmed by biopsy because of a bleeding diathesis.

In most of our patients the severity of the renal failure was out of proportion to the relatively mild hepatitis. Dialysis was therefore a most important part of treatment, and was well tolerated. This contrasts greatly with our experience in patients with cirrhosis and fulminant hepatic failure, in whom dialysis often seems to precipitate severe hypotension and gastrointestinal haemorrhage.[15] Seven (58%) of the 12 patients survived, which also contrasts with a mortality of 80-100% for renal failure complicating fulminant hepatic failure and cirrhosis.[1 16] Our survival figure compares favourably with that of 50-60% reported for acute renal failure in other illnesses.[17-19]

As in fulminant hepatic failure and cirrhosis, the mechanism responsible for renal failure in acute viral hepatitis is uncertain. In view of the relatively mild hepatitis in many patients it is unlikely to be a direct manifestation of the degree of liver cell damage. Furthermore, in fulminant hepatic failure renal failure is unrelated to the extent of liver cell necrosis as assessed histologically.[20] In fulminant hepatic failure and cirrhosis both functional renal failure and acute tubular necrosis have been attributed to the renal vasoconstrictor effects of endotoxins,[11 21] the endotoxaemia probably being due to Kupffer cells failing to filter endotoxins absorbed from the gut, either as a result of the

presence of a portosystemic collateral circulation or because of impaired reticuloendothelial function. A similar mechanism might explain the development of renal failure in acute hepatitis, since antibody titres to endotoxins may be raised,[22] suggesting the occurrence of endotoxaemia.

We thank the departments of chemical pathology and haematology at King's College Hospital for some of the estimations reported in this paper, and Professor A J Zuckerman, of the London School of Tropical Medicine and Hygiene, for the hepatitis A antibody determinations. Drs V Parsons and M Weston of the renal unit, and Mr P Mellon of the liver unit, King's College Hospital, provided considerable help with the dialysis.

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(*Accepted 10 April 1978*)

From the safety point of view are automatic gear boxes more hazardous to drive than manual gear boxes?

There is no clear answer to this question. Undoubtedly gear changes require more activity by the driver. Under conditions of overload, the additional task of changing gear may lead to more errors in driving. On the other hand, there is an optimum level of arousal for efficient driving, and when activity is low then changing gear might be beneficial. Accident statistics give no clear indications; and presumably being accustomed to one system and not to another leads to an increased risk when a driver tries the unfamiliar one. Recent comparative studies have shown that drivers of manual transmissions have higher breathing and pulse rates over a standardised route than do drivers of cars with automatic transmissions. The consequences of such a physiological response, however, are probably not particularly important.

What are the investigations and treatment for pruritus ani?

The causes of pruritus ani may be classified as primary, secondary, or idiopathic. Primary causes include such conditions as threadworm infestation, fungal infection, scabies, or spread of pediculosis pubis to the anal region. When pruritus ani is secondary to other anorectal disease, it is often associated with conditions such as haemorrhoid, fistula, or fissure operations that lead to a mild degree of anal incontinence, which increases perianal moisture. Surprisingly, it is not a common symptom with major degrees of anal incontinence. The symptoms can accompany second-degree haemorrhoids, anal polyps, or large-bowel malignancies. In the idiopathic form sweating, stress, and anxiety, etc, have been implicated, but it is a common symptom on its own in apparently otherwise normal men.

A full history should be taken, the length of which is important. If the symptom is new and not a life-long problem it is probably associated with other anorectal disease. A history of recent antibiotic treatment is important as monilia can complicate long-term tetracycline treatment. A full examination of the external anus, sigmoidoscopy, proctoscopy, and a rectal examination of the anus and rectum are necessary and the urine should be tested for sugar. Proctoscopy or sigmoidoscopy may show threadworms as white mobile structures. If fungal infections are suspected scrapings of the skin should be sent for culture and microscopy. Examination of the anal region with ultraviolet light is valuable in diagnosing erythrasma, which is caused by *Corynebacterium minutissimum*[1]; a characteristic fluorescence can be seen. A fistula is diagnosed by inspection and the gentle use of a fine probe. A fissure can often be seen by gentle retraction of the anal margins, but there will be anal spasm on rectal examination. Haemorrhoids will be seen on proctoscopy, and sigmoidoscopy or proctoscopy will show rectal carcinoma. A barium enema may be needed if there is a change in bowel habit and bleeding per rectum. Colonoscopy may be of value. Treatment in cases that are secondary to other anorectal disease is directed towards the underlying cause. Haemorrhoids will need banding, injection, or surgery. A fissure is treated by anal dilatation or sphincterotomy and fistula by surgery—laying open and excising the fistula. This operation, particularly in high anal fistulae, often results in mild or even severe incontinence and can cause pruritus, as may an unsuccessful haemorrhoidectomy. More serious disease such as rectal carcinoma is treated by radical surgery if operable. Fungal infections, though rare, can be treated with nystatin. Erythrasma is treated by oral erythromycin 250 mg four times a day for 10 days.

More of a problem is the treatment of the idiopathic variety. Attention to anal hygiene is important, and the patient should wash the anal region twice a day using a soft sponge and not a hard cloth. Talcum powder applied to the anal region during the day may help to reduce moisture. Ointments containing steroids, such as fluocortolone pivalate 0·1%, fluocortolone hexanoate 0·1% (Ultradil cream), which should be applied at night locally, can help. Hydrocortisone ointments 1% and a 0·1% cream of betamethasone (Betnovate) are also effective. Regular bowel action should be encouraged and a high-residue diet helps. Highly seasoned food and some forms of alcohol including sweet sherry should be avoided.

If the patient's sleep rhythm is seriously disturbed by the condition nitrazepam (Mogadon) at night and diazepam (Valium) during the day may help. When the condition does not respond to the relatively minor forms of treatment, alcohol may be injected[2] and local anaesthetics administered subcutaneously in the affected area. Undercutting operations to denervate the perianal skin have also been recommended, although these are not often necessary.

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What is benign hypertension?

It is now generally accepted that a person's blood pressure is a graded character like his height and weight. There is no sharp cut-off point between what is normal and what is abnormal. What every insurance company knows is that in young and middle-aged patients every rise in blood pressure increases the risk of death. A systolic blood pressure of 145 mm Hg, for example, increases the mortality ratio (incidence of actual to expected death over the next 20 years) by about half. In old age the mortality rate of women over the age of 70 increases only in relation to blood pressure where the systolic blood pressure is over 200 or the diastolic over 120 mm Hg.

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