MEDICAL PRACTICE

Hospital Topics

Frequency and Type of Renal and Electrolyte Disorders in Fulminant Hepatic Failure

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Summary

Of 48 patients with fulminant hepatic failure who progressed to grade III or IV encephalopathy 38 showed evidence of renal impairment. In 32 of these patients the underlying cause could be placed initially into one of three categories—prerenal uraemia (4 patients), acute tubular necrosis (16), and “functional renal failure” (12). The latter differed in several respects from that seen with liver failure secondary to cirrhosis. The frequency and type of renal impairment was the same in those patients in whom the fulminant hepatic failure had resulted from an overdose of paracetamol as in the other aetiological groups.

Abnormalities in plasma electrolytes were common—in particular hypernatraemia occurred in 11 patients from an osmotic diuresis precipitated by hypertonic dextrose or fructose given intravenously, and from the sodium in the fresh frozen plasma used to correct the coagulation disturbance when renal excretion of this ion was inappropriately low.

Introduction

Two types of renal failure may occur in advanced cirrhosis—namely, acute tubular necrosis and “functional renal failure.”¹ The pathophysiology of the latter condition, which has attracted the most attention,² appears to be reduced renal perfusion.³ In fulminant hepatic failure renal impairment is usually considered to be an important part of the clinical syndrome,⁴⁻⁶ but little information is available on either its frequency or the type of renal impairment that occurs. Hecker and Sherlock⁶ described one patient with fulminant hepatic failure who, in retrospect, had the features of functional renal failure, and Ritt *et al.*⁷ found impairment of renal function in 13 out of 31 patients with acute hepatic necrosis but gave no information about its type.

In this paper we describe an analysis of the changes in renal function and plasma electrolytes seen in 48 patients with fulminant hepatic failure.

Patients and Methods

The patients were seen during the period April 1970 to September 1972, and all eventually progressed to grade III or IV hepatic encephalopathy (Trey *et al.*⁸). In 18 of the patients the cause was presumed to be infectious hepatitis; 8 had serum hepatitis with Australia antigen present in the serum; 15 had taken an overdose of paracetamol; 5 had had recent and multiple exposures to halothane; and in 2 the illness was attributed to a hypersensitivity reaction after administration of monoamine oxidase inhibitors. Patients with a known history of renal disease were excluded from the analysis.

CLASSIFICATION OF CASES

Patients in whom the plasma urea or plasma creatinine rose to

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levels greater than 45 mg/100 ml or 1.8 mg/100 ml respectively were separated into the following three groups.

Prerenal Uraemia.—The uraemia could be explained on the basis of dehydration or absorption of nitrogenous compounds from the gut after a gastrointestinal bleed.

Functional Renal Failure.—This term was used, as suggested by Vesin,⁹ to describe an otherwise unexplained renal impairment in the presence of a low urine sodium concentration (in the present series less than 18 mEq/l.) and a normal urinary sediment. In all cases except those in which acute tubular necrosis also developed later the kidney was found to be normal at necropsy.

Acute Tubular Necrosis.—This diagnosis was based on the discovery of numerous granular and cellular casts in the urine and on the necropsy findings. A urine sodium concentration of over 20 mEq/l. together with a urine:plasma urea ratio of less than 10 was considered additional evidence. Information on urine osmolality and specific gravity was not always available.

Results

High plasma urea or creatinine concentration were found in all except 10 patients, the latter group including the only six survivors in the series. In six of the 38 patients with possible renal impairment there were insufficient data to determine the most likely cause. In the remaining 32 patients the lesion initially appeared as prerenal uraemia (4 cases), functional renal failure (12 cases), and acute tubular necrosis (16 cases). Subsequently one of the patients with prerenal uraemia and four of those with functional renal failure developed acute tubular necrosis, so that ultimately there were 21 patients with this renal lesion.

Prerenal uraemia had first appeared in three of the four patients after dehydration and in each instance the blood urea fell with rehydration. In the fourth patient the raised blood urea was thought to be entirely due to absorption of an increased load of nitrogenous compounds from the bowel after a gastrointestinal bleed.

FUNCTIONAL RENAL FAILURE

Nine of the 12 patients fulfilled all the criteria for this diagnosis (table I, cases 1-9). The urine-plasma urea ratio was always less than 10 and in this respect indistinguishable from acute tubular necrosis, but the urine sodium concentration, urine sediment, and subsequent necropsy findings clearly distinguished these two types of renal impairment. Daily urine volumes varied from 50 to 1,000 ml. The other three patients (table I, cases 10-12) had all the features of functional renal failure except that the urine sodium concentrations were greater than 18 mEq/l. At the time of urine collections, however, these patients had been receiving either intravenous frusemide (250-1,000 mg) or

intravenous mannitol (15-40 g) or both with apparently good responses (urine volumes increasing to between 750 and 1,700 ml daily), which may explain the higher urine sodium concentrations.

In eight of the 12 patients functional renal failure was already present on admission. At that time five patients were considered to have grade I, one grade II, and two grade III encephalopathy. In the others the first signs of functional renal failure were detected during the first three days after admission, two of them having grade II and two grade III encephalopathy at the time. The functional renal failure could not be related to the aetiology of liver necrosis, the treatment given—for example, heparin, fresh frozen plasma, or corticosteroids—or the liver function tests (bilirubin, plasma albumin, or prolongation of prothrombin time). Its course was invariably progressive regardless of clinical hepatic state. Treatment with diuretics appeared ineffective even in cases 10-12, since despite the increasing urine flow the plasma urea and creatinine concentrations continued to rise. In the other nine cases no significant diuresis resulted from treatment with frusemide and mannitol. Three patients in whom the plasma urea concentration rose to greater than 200 mg/100 ml were treated by dialysis but without effect on their clinical condition.

Though a low urine sodium concentration is a feature of functional renal failure plasma sodium concentrations varied between 112 mEq and 158 mEq/l. (table I, cases 11 and 7). No relation between plasma sodium and urine sodium concentrations could be detected; similarly there was no relation between urinary sodium excretion and sodium intake. Furthermore, not all patients with low urine sodium concentrations showed other evidence of renal impairment. Thus of the 48 patients 10 had 24-hour urine sodium excretions of less than 10 mEq/l. when they were not oliguric, and four of these had normal plasma urea and creatinine concentrations.

ACUTE TUBULAR NECROSIS

In 18 of the 21 cases the first signs of acute tubular necrosis appeared after a hypotensive episode due to a gastrointestinal bleed. In 12 patients the lesion developed as a preterminal event in the last 24 hours of life. The biochemical findings in the non-terminal cases are given in table II. The renal failure was oliguric (urine volume less than 100 ml in six hours) in 18 of the cases, the exceptions having daily urine volumes of greater than 900 ml. Mannitol and frusemide were given to these patients in doses similar to those given to patients with functional renal failure, but in none was an appreciable diuresis produced.

As with functional renal failure the development of acute tubular necrosis could not be related to the aetiology, changes in liver function, or treatment of the hepatic failure. Examination of the kidneys at necropsy in the patients who had taken an overdose of paracetamol showed no evidence of papillary necrosis.

TABLE I—Findings in 12 Patients with Functional Renal Failure. Values refer to Single and Representative Day. Cases 10, 11, and 12 were receiving Diuretic at Time of Urine Collection

Case No.	Aetiology of Hepatic Failure	Plasma			Urine				Urine: Plasma Urea Ratio
		Urea (mg/100 ml)	Creatinine (mg/100 ml)	Sodium (mEq/l.)	Sodium (mEq/l.)	Potassium (mEq/l.)	Urea (mg/100 ml)	24-hour volume (ml)	
1	Hepatitis	43	1.9	122	7	61	170	300	4.0
2	"	68	—	118	13	16	200	500	2.9
3	"	83	4.0	118	4.7	26	330	150	4.0
4	"	283	10.9	138	17	31	300	60	1.1
5	"	45	2.6	128	9	23	300	630	6.7
6	Paracetamol	38	4.8	115	11	31.5	180	480	4.7
7	"	83	—	158	4	34.5	380	910	4.6
8	"	63	1.7	150	8	24	250	1,000	4.0
9	Monoamine oxidase inhibitor	23	3.4	140	6	10	140	50	6.1
10	Hepatitis	350	—	113	38	36	550	750	1.6
11	"	216	3.7	112	20	40	650	1,100	3.0
12	Paracetamol	80	2.0	138	49	82	(Creatinine 37 mg/100 ml)	1,700	(Urine: plasma creatinine ratio 18.5)

TABLE II—Findings in Nine Patients with Non-terminal Acute Tubular Necrosis

Case No.	Aetiology of Hepatic Failure	Plasma			Urine				Urine: Plasma Urea Ratio
		Urea (mg/100 ml)	Creatinine (mg/100 ml)	Sodium (mEq/l.)	Sodium (mEq/l.)	Potassium (mEq/l.)	Urea (mg/100 ml)	24-hour Volume (ml)	
2	Hepatitis	73	—	120	22	14	150	300	2
3	"	165	10.5	116	21	20	300	100	1.8
13	"	160	—	140	20	56	890	920	5.6
14	"	147	4.5	131	27	69	280	100	1.9
15	"	83	—	120	22.5	69.5	560	400	6.7
16	"	260	—	124	32	65	520	1,120	2
17	Paracetamol	50	—	140	77	16	100	2,000	2
18	Halothane	80	—	121	—	—	—	300	—
19	"	85	1.8	141	30	34	240	200	2.8

TABLE III—Relevant Data on Seven Patients with Hypernatraemia. (Values for Sodium Excretion, Urine Volume, and Fluid Balance are Mean for Day preceding and Days during Period of Hypernatraemia. Blood Glucose and Plasma Sodium Values are highest observed at this Time)

Case No.	Intravenous Fluids	Blood Glucose (mg/100 ml)	Plasma Sodium (mEq/l.)	Urine		Fluid Balance (l./24 hr)		
				Sodium (mEq/24 hr)	Volume (l./24 hr)	Intake	Output*	Net Balance
1	Fresh frozen plasma, 10% dextrose	374	179	17	4.5	4.5	5.5	-1
2	Fresh frozen plasma, 5% and 20% dextrose	300	161	146	4.0	3.5	5.0	-1.5
3	Fresh frozen plasma, 50% dextrose	850	165	62	3.5	3.0	4.5	-1.5
4	10% Fructose	330	>160	—	2.3	3.8	4.3	-0.5
5	Fresh frozen plasma, 10% dextrose	444	158	18	2.5	3.8	3.8	0
6	Fresh frozen plasma, 10% dextrose	329	150	21	3.5	3.0	4.8	-1.8
7	Fresh frozen plasma, 5%, 25%, and 50% dextrose	805	163	—	4.5	5.0	6.0	-1

*Fluid output includes urine, gastric aspirate, and insensible loss.
N.B. Case numbers do not necessarily refer to cases in table I and II.

ABNORMALITIES IN PLASMA ELECTROLYTES AND FLUID BALANCE

An unexpected finding was hypernatraemia in 11 patients, all of whom died. In seven of these complete fluid-balance charts were available for analysis (table III). In six patients this showed the presence of a persistently negative fluid balance associated in each instance with an osmotic diuresis resulting from the administration of intravenous hypertonic dextrose or fructose. Urine volumes increased out of proportion to the relatively little sodium excreted. There was always an accompanying rise in blood urea, though this did not necessarily exceed the upper limit of normal. The development of hypernatraemia in one patient is shown in the fig. Analysis of the fluid-balance charts in

Sodium and fluid balance in a patient with hypernatraemia.

15 patients without hypernatraemia showed that none had a negative daily fluid balance of greater than 0.5 l. for more than one day.

Six of these seven patients had also received at least 300 mEq of sodium each day as fresh frozen plasma to treat the coagulation disturbance. Similar amounts of plasma had been given to another 28 patients, who had not developed hypernatraemia, but none of those patients had evidence of a persistently negative fluid balance.

The other changes in the plasma electrolytes included hyponatraemia (plasma sodium concentration less than 130 mEq/l.) in 23 patients, which usually developed late in the course of the illness. In contrast hypokalaemia (plasma potassium concentration less than 3.8 mEq/l.), found in 23 patients, was often present on admission. In five patients there was subsequently a rise in plasma potassium concentration to over 5.2 mEq/l. as renal failure developed.

Discussion

The functional renal failure seen in these patients with fulminant hepatic failure was somewhat similar to that found in advanced cirrhosis—for instance, the urine sediment and necropsy findings were normal. There were, however, differences. The mean urine:plasma urea ratio in the cirrhotic patients with functional renal failure reported on by Baldus *et al.*² was 25, whereas it was always less than 10 and usually less than 5 in our patients. The urine:plasma urea ratio may be a poor guide to renal function at low urine flow rates,¹⁰ but seven of our 12 patients had a daily urine volume of 500 ml or more (table I). Possibly the changes in renal haemodynamics are different. If there was a relatively higher medullary blood flow in fulminant hepatic failure this would be expected to “wash out” the medullary urea, thus accounting for the comparatively low urine urea, since equilibration occurs between urea in the medullary interstitium and collecting ducts. The plasma sodium and urinary sodium concentrations were often higher in our patients than in those suffering from cirrhosis with functional renal failure. This may be because they were receiving large quantities of sodium intravenously, as fresh frozen plasma, whereas strict sodium restriction is usually employed in patients with advanced cirrhosis.

The lack of correlation between renal function and the results of liver function tests in the present cases was similar to that found in cirrhosis.¹¹ A frequently quoted theory to explain functional renal failure in cirrhosis is that portal hypertension causes a pooling of blood in the splanchnic circulation with a resulting decrease in "effective" systemic (and therefore renal) blood volume. An increase in portal pressure may occur in acute hepatitis.¹² Though this was not measured in our patients 10 of the 12 had ascites and one had oesophageal varices, which indicate portal hypertension.

The same types of renal lesion were encountered regardless of the aetiology of hepatic failure. Though paracetamol overdosage has been said to be a specific cause of renal damage¹³ this has not been our experience. Development of renal failure in fulminant hepatic failure clearly indicates a poor prognosis. Nevertheless, we have recently seen five patients with acute tubular necrosis in association with acute hepatic damage (three due to serum hepatitis, and two due to paracetamol overdosage) in whom encephalopathy did not occur and whose kidney function finally recovered.

When renal impairment does develop in these patients it is likely to have certain adverse consequences. Uraemia may contribute towards the coma, bleeding diathesis, high risk of infection and raised blood levels of ammonia.¹⁴ Bilirubin is potentially toxic to cellular metabolism,¹⁵ and bile salts are toxic to various tissues including liver,¹⁶ kidney,¹⁷ and brain.¹⁸ These substances probably attain higher blood levels where there is renal impairment.^{19, 20}

Our finding of hypernatraemia in several patients was of particular interest. In most instances the mechanism appeared to be dehydration secondary to an osmotic diuresis which had been precipitated by the intravenous administration of hypertonic dextrose of fructose. Hypernatraemia resulting from an osmotic diuresis has also been described in cirrhosis.²¹ An additional factor may have been the intravenous administration of large quantities of sodium when renal excretion was inappropriately low. Another possible cause of excess renal water loss in fulminant hepatic failure is the development of a pituitary diabetes-insipidus-like syndrome.²² Hypernatraemia may itself cause coma,²³ and hypertonic dextrose solutions should therefore be given to these patients only with considerable caution.

No rational suggestions can be made for preventing or reversing functional renal failure until the pathophysiology is better understood. Mannitol and frusemide are of no real value, and this is also the case in cirrhosis.² Indeed, most workers agree that diuretics may be positively harmful in these cases.²⁴

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