Fulminant hepatic failure in childhood

An analysis of 31 cases

H T PSACHAROPOULOS, ALEX P MOWAT, M DAVIES, B PORTMANN, D B A SILK, AND ROGER WILLIAMS

Department of Child Health, King's College Hospital, London

SUMMARY To document the clinical features and complications of fulminant hepatic failure in childhood, 31 consecutive cases (of whom only 9 survived) were reviewed. Of 26 children with acute hepatitis (HbSAg-negative), liver function steadily deteriorated in all but 2, and encephalopathy occurred within 3 weeks of the onset of symptoms in all except 3 of them. Eight of these patients survived, as did one of 3 in which this deterioration was caused by paracetamol overdose. Single cases due to *Amanita phalloides* and halothane died. Encephalopathy lasted from 2 to 16 days in the survivors, and from one to 20 days in the fatal cases. The severity fluctuated by more than one grade in 9 patients. The outcome was not related to the age or sex of patient, clinical or biochemical abnormalities at presentation, or to the duration of the encephalopathy. Prothrombin time was prolonged by more than 90 seconds in 10 fatal cases, but in none of the survivors. The outcome was related to the severity of the encephalopathy, only one (6%) of 19 children in grade 4 coma surviving, and to the occurrence of neurological complications—particularly brain stem dysfunction (9 cases), decerebrate posturing (12 cases), and convulsions (7 cases). Massive gastrointestinal bleeding (14 cases) and renal failure (10 cases) were confined to the fatal group. At necropsy 7 (54%) of 13 had cerebral oedema.

Hypoglycaemia, septicaemia, respiratory tract infections, ascites, and haemopoietic complications occurred both in fatal cases and survivors. Although liver function tests and liver biopsy appearances remained abnormal in survivors for 24 and 30 months respectively, these children developed normally without evident disease during or after this period.

Children with fulminant hepatic failure and severe encephalopathy develop major pathophysiological complications affecting almost every system. Such complications must be prevented or vigorously treated. The mortality is no lower than in adults. Effective treatment must be instituted before grade 4 coma is established.

Fulminant hepatic failure with hepatic encephalopathy is a rare but grave complication of acute hepatic damage from viruses or drugs.^{1–2} The mortality, 70 to 95%, may be lower in children than in adults^{1–3} but in one report age had no

influence on prognosis.⁴ Treatment incorporates intensive supportive care with a variety of measures undertaken to control homeostasis, prevent alimentary bleeding, and control encephalopathy. The rationale for such treatment is based almost entirely on observations in adult patients. If adults survive the acute illness hepatic recovery is usually complete.^{5–6}

In the present study we retrospectively reviewed clinical, biochemical, and pathological features in 31 children with fulminant hepatic failure of whom 9 survived. We wished to document the clinical syndrome and its complications in childhood, to ascertain differences from the syndrome in adults, and to identify features of prognostic importance at the onset or early in the course of the illness.

**King's College Hospital Medical School
Department of Child Health**

H T PSACHAROPOULOS, research fellow
ALEX P MOWAT, consultant paediatrician

Liver Unit

B PORTMANN, senior lecturer in pathology
ROGER WILLIAMS, director and consultant physician

Department of Anaesthesia, Lewisham Hospital, London
M DAVIES, registrar

Central Middlesex Hospital, London
D B A SILK, consultant physician

Patients and methods

31 children reviewed had fulminant hepatic failure as defined by Trey and Davidson⁷—namely, hepatic encephalopathy within 8 weeks of the onset of symptoms of liver disease in patients in whom hepatic function before the illness was presumed to have been normal. These children comprised all such cases seen at King's College Hospital between 1969 and December 1977. Patients with encephalopathy due to Reye's syndrome or to Wilson's disease were excluded by clinical, biochemical, and pathological criteria.⁸ The severity of coma was defined using the criteria of Saunders *et al.*⁴

The presumed cause of the hepatic necrosis was acute viral hepatitis (hepatitis B surface antigen negative) in 26 cases, but in only 4 of these was there history of recent contact with patients with features of infectious hepatitis. Three patients developed acute liver failure after the ingestion of a large dose of paracetamol and in one patient it was after the ingestion of *Amanita phalloides* and in another after halothane anaesthesia. No case was shown to be due to hepatitis B virus infection, infectious mononucleosis, or leptospirosis.

All patients received intensive medical, nursing, and physiotherapy care; since 1973 patients have been managed in a purpose-built liver failure unit. Intravenous infusions of 10% dextrose, neomycin, either orally or via a nasogastric tube, and magnesium sulphate enemas were given to all patients. Oral magnesium sulphate or lactulose was given to prevent constipation. Dietary protein was stopped. All patients received IM vitamin K daily and normal requirements of electrolytes, supplemented by additional potassium and bicarbonate as indicated by laboratory assessment. Fresh whole blood or fresh frozen plasma was given if necessary to replace blood loss, to increase plasma volume, and to provide clotting factors. 22 patients received systemic antibiotics because of the presence of suspected or confirmed bacteriological infection.

Results

Of 31 cases of fulminant hepatic failure, only 9 (28%) survived, 5 of 19 boys and 4 of 12 girls. The mortality was not related to age or to presumed cause. 10 children died within 7 days of the onset of coma, a further 10 within 20 days, and 2 after 40 days.

Hepatitis cases: early clinical course. In the 26 patients with presumed hepatitis, the initial presenting features were jaundice (23; 88%), anorexia (14; 55%), upper respiratory tract infection (7; 27%), skin rash (6; 23%), and abdominal pain (4; 15%).

All patients had progressive deterioration in their

clinical states except for 2 who each had a period of temporary improvement lasting between 7 and 14 days. The interval between onset of symptoms and development of encephalopathy ranged from one to 51 days, the mean being 14 days. Encephalopathy developed within 3 weeks of the onset of symptoms in all except 3 patients in whom it occurred at 25, 31, and 51 days.

In 18 patients, the liver was impalpable and small on percussion at the time of admission.

Features of encephalopathy. The duration of the encephalopathy varied from less than one to 22 days (mean 8.4) in the fatal cases, and from 2 to 16 days (mean 6.4) in the survivors. In those dying rapidly the encephalopathy was steadily progressive but in 9 instances the severity of the encephalopathy improved by at least one grade before subsequently deteriorating. Two patients with relapsing encephalopathy eventually recovered completely. Decerebrate posturing (12 cases), clinical evidence of brain stem dysfunction (9 cases), and convulsions (7 cases) occurred only in fatal cases. There were no survivors among the patients who required mechanically assisted respiration because of brain stem dysfunction. Only one child survived who had been in grade 4 coma for more than 24 hours, although 2 who were transiently in grade 4 coma also survived. It is noteworthy that no patient at any time in his illness developed papilloedema.

Encephalopathy preceded jaundice by 1 to 2 days in all 3 patients with paracetamol overdose. Two died 5 and 11 days after ingestion, the third survived after 6 days in hepatic coma. Nausea, vomiting, and abdominal tenderness with jaundice occurred within 24 hours of ingesting *Amanita phalloides* and proceeded to grade 4 coma 48 hours later; she died on day 3. In one patient jaundice with features of hepatocellular necrosis occurred 5 days after the 4th halothane anaesthetic in a 4-month period. This progressed to encephalopathy within 48 hours and to death 5 days later.

17 of the patients seen since 1973 received IV dexamethasone in a dose of 4 mg every 6 hours given to lessen cerebral oedema. Four survived as did 5 of 12 patients who, in the early years of the study, received prednisolone in a dose of 1–2 mg/kg per 24 hours.

Nine patients, who had been in grade 4 coma for longer than 12 hours, received temporary liver support using charcoal haemoperfusion (4 cases), and haemodialysis with a polyacrylonitrile membrane (5 cases). All subsequently died. Three in grade 3 coma treated with haemodialysis using a polyacrylonitrile membrane survived. In no case did these measures have an immediate effect on the severity of the encephalopathy.

Laboratory investigations. All patients showed biochemical evidence of severe hepatocellular necrosis with high levels of serum transaminase, bilirubin, and alkaline phosphatase (Table 1). In those who survived longer than 7 days, transaminase values fell to between one and 8 times the upper limit of normal. 16 of the fatal cases and all 9 survivors had serum albumin levels <35 g/l (<3.5 g/100 ml). All patients had prolongation of the prothrombin time. In 10 fatal cases, the prolongation of the prothrombin time was >90 seconds, none of the survivors having values above this level ($P<0.025$). Serum bicarbonate levels were frequently abnormal both in fatal cases and survivors. Both low levels and high levels were found at different stages of the illness in nearly every instance. The bicarbonate levels were significantly higher in fatal cases than in the survivors ($P<0.01$). The severity of other biochemical

abnormalities was similar in the two groups (Table 2). Despite IV glucose infusion, 9 patients, including 2 survivors, had blood sugar levels <2.5 mmol/l (<45 mg/100 ml) at some stage during the course of their illness.

Complications and outcome

Significant melaena or haematemesis occurred in 14 fatal cases and was considered to be associated with permanent deterioration of the patient's condition in 12. Cimetidine in a dose of 20 mg/kg per 24 hours, given to the last 13 patients, had no discernible effect on alimentary bleeding. 10 fatal cases bled also from the nasopharynx, trachea, and urinary tract, while 5 had severe ecchymosis. Such bleeding was not observed in those who survived.

Table 1 Clinical features and maximum abnormalities in laboratory investigations during encephalopathy in children with fulminant hepatic failure

Case	Sex	Age (years)	Days of jaundice before coma	Coma grade on admission	Aspartate amino-transferase (IU/l)	Bilirubin (μ mol/l)	Alkaline phosphatase (IU/l)	Prolonged prothrombin time (s)	Albumin (g/l)	Glucose (mmol/l)
Acute hepatitis (HBsAg-negative)										
1	M	8	6	3	1690	320	607	88	36	3.2
2	F	12	8	4	1500	580	320	167	34	4.9
3	M	6	3	4	4000	260	470	197	31	9.8
4	M	3/12	11	0	2400	459	800	108	33	0.2
5	M	6	10	4	1210	74	56	26	NA	4.5
6	F	6	25	0	214	1030	292	9	19	3.3
7	M	6	10	3	4136	752	616	58	33	2.4
8	M	4	14	2	2430	715	184	93	26	1.0
9	M	9	1	3	275	400	156	82	29	3.7
10	M	7/52	13	0	2630	620	NA	68	23	3.0
11	M	9	6	3	2800	760	810	137	39	15.5
12	F	14	21	3	400	370	302	69	23	4.1
13	M	13	6	4	930	355	251	74	29	
14	M	4	34	4	340	569	140	120	23	1.2
15	M	10	20	3	1000	630	255	67	28	1.3
16	M	5	51	3	2196	172	93	72	35	4.6
17	F	4	21	1	2600	660	340	182	25	3.8
18	M	14	13	2	700	840	300	100	19	1.5
24	M	4	9	2	3000	340	194	83	30	1.6
25	M	4	0	3	1275	350	199	89	25	4.0
26	M	5	31	4	1500	454	360	23	28	4.6
27	M	6	10	3	2200	524	500	30	28	4.6
28	M	6	7	2	555	920	276	47	29	4.0
29	F	3	12	1	912	405	168	32	29	4.5
30	F	7	14	0	575	800	300	58	18	0.5
31	F	2	10	1	1800	445	315	26	29	3.3
Paracetamol overdose										
21	F	15	1	2	2500	209	209	NA	38	NA
22	F	15	0	3	255	282	346	81	31	4.0
23	F	14	0	2	3000	86	172	70	31	5.0
Amanita phalloides										
19	F	5	1	1	4000	170	265	120	28	1.6
Haloethane hepatitis										
10	F	11	8	2	1800	620	420	600	29	8.0
Normal values					10-45	3.4-20.4	30-250	0	35-50	2.8-5.0

Conversion: SI to traditional units—bilirubin: 1 μ mol/l $\approx$ 0.058 mg/100 ml; glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

Table 2 Frequency of electrolyte abnormalities

Electrolyte abnormalities	Fatal cases		Survivors	
	No.	%	No.	%
Na (mmol/l)				
<125	8	36	8	89
>150	3	14	0	—
K (mmol/l)				
<3.0	16	72	5	55
>5.5	7	32	1	11
HCO ₃ (mmol/l)				
>30	14	64	3	33
<18	8	36	8	89
Ca (mmol/l)				
<2.0	5	29	4	37
PO ₄ (mmol/l)				
<0.8	9	54	6	66

Conversion—SI to traditional units—Ca: 1 µmol/l ≈ 4 mg/100 ml. PO₄: 1 µmol/l ≈ 3.1 mg/100 ml.

Renal failure occurred in 10 fatal cases. In 2 there was clinical, biochemical, and necropsy evidence of acute tubular necrosis. Two had the urinary features of functional renal failure⁹ and normal renal histology at necropsy. In the remaining patients the data were insufficient to define the type of renal failure. Nine of 13 who developed ascites survived.

Septicaemia occurred in 5 patients, the organisms being *Staphylococcus aureus*, *Pseudomonas pyocyanea*, *Candida albicans*, group D streptococci, and *Staphylococcus albus*. Four patients had infections of the urinary tract. *Candida* sp. was the major cause of infection in one patient who survived and in 2 fatal cases. In one of these there was severe depression both of erythropoiesis and granulocytes. One patient with complete pancytopenia required red blood cell and granulocyte transfusion before making a complete recovery. Two patients had severe persistent thrombocytopenia with platelet counts <10 × 10⁹/l.

Nine developed lobar collapse, one developed bilateral pleural effusion, and a further child developed a lung abscess. In 3 patients the temperature fell to <35°C without evident cause.

Necropsy findings. Percutaneous liver biopsies obtained immediately after death in 11 patients showed severe hepatocellular necrosis as evidenced by extensive collapse of the reticulin framework, with cellular infiltrate within the portal tracts and in necrotic areas. The amount of cellular infiltrate increased with the duration of the liver disease. There was prominent bile duct reduplication in and around the portal tracts, with disruption of the limiting plates. There were no features of cirrhosis.

Necropsy examinations were performed in 13 cases. The liver weight ranged from 10 to 90% of the average weight for the patient's age¹⁰ except in one infant in whom the liver weighed 2½ times normal. The liver histology in this patient was similar to that in others, except that reticulo-endothelial cell reaction was particularly pronounced. In the remaining cases the histological appearances were similar to those seen in the needle specimens. In 2 patients, there was histological evidence of renal tubular necrosis. One patient had haemorrhagic pancreatitis.

Cerebral oedema was present in 7 patients, 4 showing cerebellar or medullary herniation.

Follow-up of survivors. The duration of follow-up was between 4 and 77 months (mean 34). Time in hospital was between 5 and 13 weeks, but all children returned to normal activities within 4 weeks of discharge from hospital and have remained well subsequently. Height and weight gains have been normal. None has shown clinical features suggesting persisting liver disease, except the patient who was followed for only 4 months who still has hepatomegaly. Serum albumin, prothrombin time, bilirubin, aspartate transaminase, and alkaline phosphatase all returned to normal but, in some instances, this was not until 24 months after the onset of the illness. All have remained normal on more-prolonged follow-up (Table 3).

Table 3 Data on 9 patients surviving fulminant hepatic failure

Case	Follow-up (months)	Duration of abnormal liver function tests (months)	Treatment with corticosteroids (months)	Liver biopsy features	
				Within 3 months from onset of coma	Later
23	43	19	32	Aggressive hepatitis	Postnecrotic scarring with resolving inflammation (12 months). Normal (48 months)
24	32	24	24	NA	Postnecrotic scarring with resolving inflammation (8 months)
25	2	2	—	Aggressive hepatitis	
26	5	2	—	Aggressive hepatitis	
27	27	3	4	Aggressive hepatitis	Postnecrotic scarring with resolving inflammation (18 months)
28	77	1	20	Aggressive hepatitis	Postnecrotic scarring with no inflammation (12 months)
29	3	1	—	NA	
30	46	12	46	NA	Postnecrotic scarring with resolving inflammation (8 months); normal (36 months)
31	42	5	13	Resolving hepatitis	Slight portal tract inflammation (36 months)

NA = not available.

Fig. 1 (Case 26). Percutaneous liver biopsy one month after onset of encephalopathy. (a) Extensive postnecrotic collapse of reticulum with bridging between portal tracts and central veins. Reticulin stain ($\times 120$). (b) Portal tracts are widened with a heavy infiltrate of mixed inflammatory cells extending into the adjacent liver cell plates (piecemeal necrosis). Haematoxylin and eosin ($\times 160$).

Fig. 2 (Case 31) Percutaneous liver biopsy 12 months after onset of encephalopathy. (a) Moderate irregular postnecrotic scarring without clear disturbance of overall lobular pattern. Reticulin stain ($\times 100$). (b) Slight inflammatory cell infiltrate confined to portal tracts. Haematoxylin and eosin ($\times 160$).

Liver biopsies were obtained within 4 months of the onset of the illness in 6 patients. All showed evidence of recent severe parenchymal necrosis with, in three instances, bridging collapse joining adjacent portal tracts and hepatic vein tributaries. In one child (Case 26) there was sufficient distortion of hepatic architecture to raise the suspicion of cirrhosis (Fig. 1). Biopsies from 5 showed enough portal and periportal inflammatory activity to suggest a diagnosis of chronic aggressive hepatitis, while in Case 31 the features were those of a resolving hepatitis (Fig. 2). Biopsies taken at least 8 months after the onset of the illness showed in 5 instances, postnecrotic scarring, 3 having persistent minimal infiltrate with inflammatory cells. Only 2 biopsies were considered normal. Liver biopsy was not performed in the survivor of the paracetamol overdose as hepatic recovery in such cases is usually complete.¹¹

Discussion

The mortality in children with fulminant hepatic failure in this series was 72%, increasing to 94% in those who developed grade 4 coma. These observations are similar to those reported by Saunders *et al.*⁴ who found a mortality of 65% in children in grade 3 coma, but a mortality of 85% in those in grade 4 coma. During the period of this study survival rates in adults with fulminant hepatic failure admitted to our unit ranged from 15% (for those treated conservatively in the earlier years) to 30–38% (for those treated with charcoal haemoperfusion or by haemodialysis more recently).¹² In contrast to the findings of the Boston Fulminant Hepatic Failure Surveillance Study³ in which the mortality in fulminant hepatic failure in children of less than 14 years was 73%, compared with 80–97% in adults, our study suggests that any lessening of fulminant hepatic failure in childhood is at best only marginal and does not extend to those with grade 4 encephalopathy.

No clinical features early in the illness could be correlated with survival nor were laboratory investigations helpful in indicating prognosis in the individual case. The outcome did not correlate with the duration of symptoms before the onset of the encephalopathy nor did they correlate with the duration of the encephalopathy itself.

In all survivors prolongation of the prothrombin time was less than 90 seconds, whereas this was so in only 12 of 20 fatal cases. Serum bicarbonate levels deviated above the normal range more often and to a greater extent in fatal cases than in survivors, and low values were more common in survivors. This 2-directional shift in serum bicarbonate values reflects the complexity of the metabolic changes

which occur in fulminant hepatic failure. Record *et al.*¹³ showed that hyperventilation with respiratory alkalosis, metabolic alkalosis, and rarely, metabolic acidosis occur in the absence of renal failure.

A fatal outcome was often associated with at least one major complication. This study stresses the importance of the severity of the encephalopathy and the occurrence of other neurological complications in prognosis. Only one child in grade 4 coma for more than 24 hours survived. There were no survivors in those who developed generalised convulsions, myoclonic jerks, clinical evidence of brain stem dysfunction, or in those who required mechanical ventilation for persistent apnoea. The cause of the encephalopathy and the mechanism of brain swelling or cerebral oedema remain poorly understood. It is uncertain whether cerebral oedema is a toxic or metabolic effect acting directly on cerebral cell membranes, or whether it arises because of increased vascular permeability or hypo-osmolar extracellular fluid.²²

Intravenous dexamethasone as used in this study did not prevent cerebral oedema although it has been shown to be of prophylactic value if used early in an experimental animal model of fulminant hepatic failure.¹⁴ Papilloedema was not evident in any case in this series and thus its absence does not exclude serious brain swelling. Rational treatment to control cerebral oedema can only be evaluated by direct measurement of the intracranial pressure, preferably by an extradural pressure monitor. Such devices have given valuable information in the management of Reye's syndrome.¹⁵

Overt intestinal bleeding (which took place in 14 of 22 fatal cases), the development of renal failure (10 cases), and significant secondary bacterial or fungal infections (6 cases), were factors which were considered to have contributed to the fatal outcome, although in some patients it was often difficult to identify the precise cause of death. Saunders *et al.*⁴ reported a 70% incidence of life-threatening haemorrhage in children. Prevention of alimentary bleeding must be a major aim in management, either by the use of prophylactic cimetidine¹⁶ or by transfusions of fresh frozen plasma, platelets, or fresh whole blood, depending on the circumstances. The prevention and early treatment both of sepsis and renal failure must be major goals in management. The high incidence of respiratory complications in these children possibly results from a combination of the effects of pulmonary oedema (found in 35% of adults)¹⁷ and coma.

Early biopsies in 5 survivors showed the histological appearances of aggressive hepatitis, and subsequently in 5 instances postnecrotic scarring was found. In only 2 instances were the

follow-up liver biopsy appearances normal. The frequency of this persistent histological abnormality after fulminant hepatic failure was unexpected and should be compared with the findings in adult patients in at least 90% of whom there is rapid complete histological recovery,^{5 18} except in hepatitis B surface antigen-positive cases.⁶

In this series of children with fulminant hepatic failure, the clinical and pathological features, and the complications, are similar to those observed in adults with this syndrome. The principles of management should therefore be similar. For recovery to occur in fulminant hepatic failure the encephalopathy must be reversible and the liver capable of regeneration. The difficulties in assessing the former have been mentioned. There is currently no way of assessing the latter in the individual patient, either by the early clinical course of the hepatitis or by special investigations, such as the serum alpha-fetoprotein level.¹⁹⁻²⁰

Maintaining physiological and biochemical homeostasis by intensive monitoring and supportive care, and the early identification and treatment of complications in units familiar with the many complex problems found in fulminant hepatic failure may reduce the mortality. If temporary liver support treatment, such as haemodialysis using a polyacrylonitrile membrane which has given encouraging results in 2 recent series,^{12 21} is to influence survival, this must be introduced before grade 4 coma is established.

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Correspondence to Dr Alex P Mowat, Department of Child Health, King's College Hospital Medical School, 4th Floor, New Ward Block, Denmark Hill, London SE5 8RX.

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