

Clinical and prognostic differences in fulminant hepatitis type A, B and non-A non-B

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SUMMARY In 73 patients with fulminant viral hepatitis, non-A non-B hepatitis (NANB) was most common (43.8%), with hepatitis type A (HAV) diagnosed in 31.5% and hepatitis type B (HBV) in 24.7%. The non-A non-B group had a significantly longer duration from the onset of symptoms to the appearance of encephalopathy (median 21 days) compared with the HAV and HBV groups (medians 10 and seven days, $p < 0.01$ and $p < 0.005$ respectively). In the HAV group the severity of liver damage, judged by the maximum prolongation of the prothrombin time, was significantly less than in the HBV group (58 and 150 seconds prolonged respectively, $p < 0.005$), and cerebral oedema was significantly less frequent (39% and 72% respectively, $p < 0.05$). Consistent with this, the survival rate was higher in the HAV group (43.4%) compared with the HBV group (16.6%) and NANB group (9.3%) ($p < 0.005$). These variations in presentation and clinical course may be a consequence of differences in the pathogenesis of the hepatic necrosis.

With the advent of specific serological markers for hepatitis A and hepatitis B virus infection, it is now possible to differentiate cases of fulminant hepatic failure due to type A or type B infection from those with presumed non-A non-B hepatitis. Only two studies, from Denmark and the USA, have reported the relative frequency of these three types in patients with fulminant hepatitis,^{1,2} and there has been no comparable information from the United Kingdom. In this paper the serological markers obtained in a series of 73 patients with fulminant viral hepatitis are reported, together with an analysis of possible differences in presenting features, clinical course, and prognosis between the three types. In addition, as the criteria used for the definition of fulminant hepatic failure in other series have differed with respect to the duration of symptoms before the appearance of encephalopathy,³ the data have also been examined to determine whether there is any relation between this period and hepatitis type, or subsequent clinical course.

Methods

PATIENTS

The 73 consecutive patients were admitted to the

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Liver Failure Unit between January 1977 and June 1981. In each instance grade IV encephalopathy was either present on admission or developed subsequently. In all patients the first signs of encephalopathy had developed within eight weeks of the onset of their illness, fulfilling the criteria of Trey and Davidson.⁴ None had evidence of either previous liver dysfunction or a history of potentially hepatotoxic drug administration. All patients were given standard supportive care as previously described,⁵ including RP6 polyacrylonitrile haemodialysis (44 patients) and charcoal haemoperfusion with PGI₂ infusion (19 patients).

Particular note was taken of the development of major complications during the course of the illness, including cerebral oedema, which was diagnosed on the basis of an intracranial pressure of greater than 30 mmHg, or the appearance of defined clinical signs of cerebral oedema (abnormal pupillary responses, myoclonus, decorticate or decerebrate posturing). Renal failure was diagnosed on the appearances of a 24 hour urine volume of less than 300 ml, and/or a serum creatinine greater than 300 $\mu\text{mol/l}$ in the absence of hypovolaemia.

SEROLOGICAL METHODS

Hepatitis A was diagnosed by the presence in serum of the IgM component of hepatitis A antibody (IgM anti-HAV:RIA, Abbott Laboratories). Patients were classified as having hepatitis B if significant

concentrations of the IgM component of hepatitis B core antibody (IgM anti-HBc) were present, detected by an M-antibody capture RIA,⁶ with or without hepatitis B surface antigen (HBsAg; RIA, Travenol Laboratories). The remaining patients, being negative to all serological markers of hepatitis A and B, were cases presumed to have non-A non-B hepatitis.

None of the patients had significant titres of antibodies to other viruses causing hepatitis, such as cytomegalovirus, EB virus, and herpes simplex.

STATISTICS

Results are given as mean \pm SEM or, median and range if data are non-parametric. Analysis was carried out by Student's *t*, χ^2 , and Fisher's exact two tail tests or the Mann Whitney sum rank test where appropriate.

Results

Serological evidence of hepatitis A was found in 23 patients (31.5%) and hepatitis B in 18 (24.7%), leaving 32 patients (43.8%) with presumed non-A non-B hepatitis. There was no significant difference between the three groups with respect to age or sex ratio (Table 1). Five patients in the HAV group had either recent contact with jaundice or had travelled abroad in the previous two months. In the HBV group five patients were known drug addicts, and a further three may have had contact with HBV at work (one doctor, one nurse, one teacher at a school for mentally handicapped). Two other patients had possible sexual exposure, and in one patient a blood transfusion three months previously may have been the source. In only one patient in the non-A non-B

group was a potential source of infection identified – a blood transfusion six weeks earlier.

Analysis of the presenting features in the three groups of patients showed that the only significant differences were with respect to the occurrence of pyrexia, which was significantly more common in the HAV group (78.3%) than in the HBV and non-A non-B groups (44.4% and 37.5% respectively, $p < 0.005$). Significantly fewer of the non-A non-B group had signs of encephalopathy when first admitted to their referring hospital compared with the HBV group (25% and 56% respectively, $p < 0.005$), patients in the former group being admitted more frequently because of malaise and the development of jaundice.

The median duration of illness before the appearance of signs of encephalopathy was significantly longer in the non-A non-B group, with a median of 21 days compared with the HAV and HBV groups (medians of 10 and seven days respectively, $p < 0.01$ and $p < 0.005$).

The severity of the liver dysfunction, as judged by the prolongation of the prothrombin time, was significantly greater in the HBV group, both with respect to the maximum abnormality and the value present at the time the first signs of grade IV encephalopathy appeared (medians 150 and 92 seconds respectively), compared with the HAV group (medians 58 and 51 seconds respectively, $p < 0.005$), but was not significantly different from that in the NANB group (medians 84 and 64 seconds prolonged respectively) (Table 1). There was no significant difference between the three aetiological groups with respect to serum albumin, bilirubin, aspartate aminotransferase, creatinine, and immunoglobulin levels, this applying to both the

Table 1 Clinical and biochemical data in patients with fulminant viral hepatitis due to HAV, HBV, and presumed non-A non-B

	Hepatitis		
	HAV	HBV	Non-A non-B
Number	23	18	32
Ages years (mean \pm SEM)	31.2 \pm 2.9	32.6 \pm 2.9	28.5 \pm 3.0
Male/female ratio	14:9	9:9	13:9
Length of history (days) (median range)	10 (5–30) ⁺	7 (1–35) [*]	21 (5–56)
Fever (%)	78 [*]	44.4	37.5
Encephalopathy on admission (%)	35	55.5 [‡]	25
Maximum prothrombin time at grade IV encephalopathy (seconds prolonged) (median range)	51 [*] (20–170)	92 (27–270)	64 (19–180)
Maximum serum bilirubin μ mol/l (median range)	296 (174–701)	230 (76–688)	432 (121–1050)
Maximum serum aspartate aminotransferase (IU/l) (median range)	543 (86–3200)	640 (223–5000)	810 (72–2100)
Maximum serum albumin (g/dl) (median range)	28.5 (16–34)	30.5 (23–46)	29 (23–41)
Maximum serum creatinine (μ mol/l) (median range)	160 (30–1315)	86.5 (64–380)	94 (28–646)

^{*} $p < 0.005$ ⁺ $p < 0.01$ [‡] $p < 0.05$.

maximum abnormality recorded and the levels at the time when signs of grade IV encephalopathy were first present.

CLINICAL COURSE AND SURVIVAL

Analysis of the clinical course after admission showed no significant differences with respect to the frequency with which renal failure, gastrointestinal haemorrhage, and systemic infection developed between the three virus groups. In contrast, the development of cerebral oedema was less frequent in the HAV group (39%) compared with the HBV and NANB groups (72% and 65% respectively), the difference with respect to the HBV group being statistically significant ($p < 0.05$).

Survival was better in the HAV group (43.4%) than in the HBV (16.6%) or NANB groups (9.3%, $p < 0.005$) (Table 2). Furthermore, in patients who died the median time from the onset of grade IV encephalopathy to death was significantly longer in the HAV group (median 11, one to 26 days) than in the HBV or NANB groups (median 3.5, range one to 11 days, $p < 0.02$; and median 3, range one to 35 days, $p < 0.05$ respectively) (Figure). Differences in survival in the three aetiological groups could not be accounted for by differences in the frequency with which liver support was performed.

DURATION OF ILLNESS BEFORE ENCEPHALOPATHY

Comparison was also carried out within the whole group, between patients with a short duration of illness (less than 21 days) before the onset of encephalopathy and those in whom this period was longer (Table 3). Differences with respect to age, sex ratio, or severity of liver damage judged by prolongation of the prothrombin time, could not be elicited, but significant differences in the frequency of developing cerebral oedema (71% and 39% respectively, $p < 0.01$) and the survival rate (31% and 7% respectively, $p < 0.025$) were found. The latter could be correlated to the relative frequency

Table 3 Comparison of patients presenting with a history of <21 days and ≥ 21 days before the development of encephalopathy

	<21 days	≥ 21 days
Number	45	28
Male:female ratio	24:21	12:16
HAV (% of group)	17 (38)	6 (21)
HBV (% of group)	14 (31)	4 (14)
Non-A non-B (% of group)	14 (31)	18 (64)
Encephalopathy at presentation	22*	4
Cerebral oedema	32†	11
Survival	14‡	2

* $p < 0.005$ † $p < 0.01$ ‡ $p < 0.025$.

of the serological groups in those with a 'short' as compared with a 'long' history. Thus the low survival rate in those with a 'long' history was related to the higher proportion of patients with non-A non-B hepatitis than in those with a 'short' history (64% and 34% respectively).

Discussion

In this series non-A non-B infection was the most frequent type of fulminant viral hepatitis, as it was in the series of Rakela *et al*² from the USA, whereas in the series from Denmark¹ hepatitis B was the commonest group (45% compared with 30% for NANB). In that series, however, a duration of less than four weeks, rather than eight weeks, from the first symptoms of hepatitis to the development of encephalopathy was used as the criterion for inclusion. As shown in the present study, in the NANB group this period is longer than for type A and B infections, and thus it is likely that some NANB cases may have been excluded in the Danish series. In addition, that series came from a community with a known high HBV prevalence, and the frequency of the three hepatitis viruses in any series of fulminant hepatitis will, to some extent, be influenced by the frequency with which these types are present in the community. Nevertheless, this assumes that fulminant hepatic failure occurs as a complication with the same frequency for all three types of hepatitis. Data on this are limited and it is noted that, in a survey of sporadic acute hepatitis in a west London suburb,⁷ non-A non-B hepatitis was considered to be the cause in only 13%.

The differences in presentation and clinical course between fulminant hepatitis type A, B, and non-A non-B have not been recorded before. That patients in the HAV group had a less severe illness was shown by the lower prothrombin time, reduced occurrence of cerebral oedema, and better survival than either the HBV or NANB groups. Although

Table 2 Survival data in the three viral groups

	Hepatitis		
	HAV	HBV	Non-A non-B
Survival (%)	10 (43.3)	3 (16.6)	3 (9.3)
	└───────────┬───────────┬───────────┘ p < 0.005		
Median duration from grade IV to death Days (range)	11 (1-26)	3.5 (1-11)	3 (1-35)
	└──────────┬──────────┬──────────┘ p < 0.02 └──────────┬──────────┬──────────┘ p < 0.05		

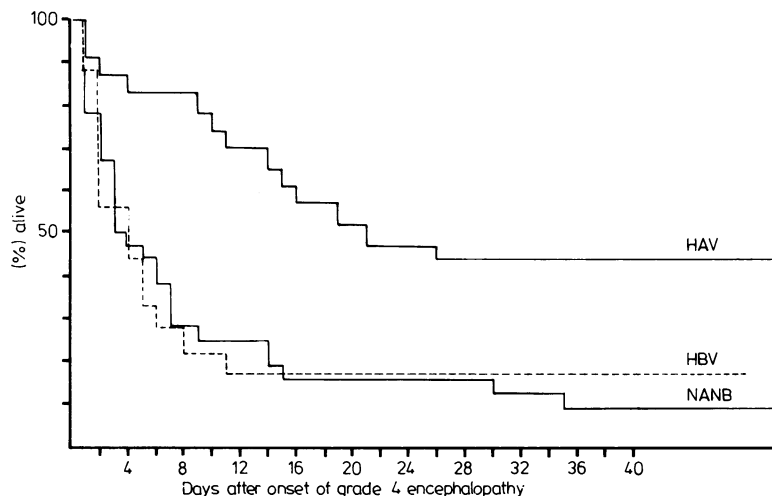


Figure Cumulative survival curves in hepatitis type A, B and non-A non-B after development of grade IV encephalopathy.

the onset of encephalopathy was delayed in the NANB group compared with the HBV group, once it had developed the rate of deterioration was similarly rapid in both, with a high frequency of cerebral oedema and a higher mortality than in the HAV group.

These differences in clinical course and prognosis may be a reflection of differences in the mechanisms underlying the initiation and progression of the hepatic necrosis, as well as the potential for hepatic regeneration upon which survival ultimately depends. In cases of fulminant hepatitis type B we have shown a more rapid clearance of HBV antigens than in uncomplicated cases, because of an enhanced antibody response.⁸ This could be the basis for subsequent immune complex deposition in the liver sinusoids with ischaemic necrosis of hepatocytes as a result, a hypothesis for which there is also experimental evidence.⁹ In contrast, the evidence suggests that the hepatitis A virus is directly cytopathic¹⁰ and the hepatic necrosis that occurs in those patients with a fulminant course could be the consequence of a larger inoculum of the virus or an impaired antibody response. The process underlying the liver damage in fulminant non-A non-B hepatitis would appear to be a slower process, as judged from the longer period before signs of encephalopathy appear. Of crucial importance in the recovery from fulminant hepatic failure is the rate of hepatic regeneration, but this is difficult to assess, and whether there are differences between the three types is not known.

In this study we have been unable to confirm the findings of the Fulminant Hepatic Failure Surveillance Study carried out between 1966 and

1971 of a lower mortality in patients under 15 years of age compared with those over 45 years.¹¹ In that study survival in the 0–14 years group was 37%, and 9.3% in patients over 45 years; in the present study figures were 8.3% and 16.7% respectively. This difference may be related to a higher proportion of HAV cases in the 0–14 years age group in the earlier series, with a better overall survival and a shift in the maximal prevalence of HAV infection over the last two decades from children to young adults.¹²

Finally, the differences in survival shown between patients with a history of less than three weeks from onset of symptoms compared with between three and eight weeks before the appearance of encephalopathy, is consistent with the findings from a large series of patients reported from Japan.¹³ The other findings in the present series show that this difference is simply related to the relative frequency of A, B, and non-A non-B hepatitis in all cases of fulminant hepatic failure separated in this way, for within each aetiological group there was no significant difference in survival between those with a 'short' compared with a 'long' duration of symptoms.

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