Indian J Med Res 75, May 1982, pp 739-744

An epidemic of non-A non-B hepatitis in north India

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Received April 30, 1981; revised article received November 4, 1981

A clinical and epidemiological study of an epidemic of viral hepatitis in Azamgarh district of Uttar Pradesh was carried out. A total of 152 patients were examined clinically, and blood and stool samples were collected from patients at different stages of illness, and also from contacts. The study revealed that the epidemic started in July, 1979 and continued till March, 1980. Adults above 15 yr of age were commonly affected. General mortality was 12 per cent with a higher rate in females (20 %) than in males (8·4 %). Pre-icteric phase was severe and prolonged, extending for a week within the icteric phase. HBsAg was positive only in 3·3 per cent. Anti-HAV (IgG) was positive in 95 per cent. IgM anti-HAV was negative in all the 46 samples tested. IgG levels were elevated but IgM and IgA levels were normal. Ten stool samples were examined for virus A particles and all were negative. It is suggested that this epidemic was due to non-A non-B virus as HBsAg and IgM anti-HAV were both negative, and stools in the pre-icteric phase did not reveal the presence of virus A particles.

Non-A non-B (NANB) hepatitis is an important cause of post-transfusion hepatitis (PTH) in Western countries[1]. The diagnosis of NANB infection is done by elimination of the possibility of recent infection with virus A and B, there being no specific diagnostic markers for NANB infection. Virus hepatitis in adults is a common disease in India. Epidemics, primarily affecting the adult population are also quite common. Till recently it was believed that virus A is the etiological agent for epidemics and most of the sporadic cases of viral hepatitis in India. Recent studies[2,3] have indicated that NANB infection could be an important cause of sporadic and epidemic hepatitis in India. We report here a large epidemic of viral hepatitis probably due to NANB infection, in a district town of north India. Some characteristic epidemiological and clinical features of hepatitis due to NANB infection are presented in this communication.

Material and Methods

Azamgarh is district headquarter town in the state of Uttar Pradesh (UP) in north India, with a population of about 70,000. There is no central sewage disposal system. Three overhead tanks draw drinking water from deep tube wells and supply it to the population through the

pipes on zonal basis. Lot of sewage, including human excreta pass through open drains, which are often in close proximity to the pipes carrying drinking water.

Th town has three hospitals *viz.*, the Government district hospital with a bed strength of 200, a Christian Mission hospital poviding services for 100 inpatients and a police hospital with 20 beds. There are over 50 practitioners of modern medicine in the town.

Our attention to the epidemic of hepatitis was drawn by a small newspaper report (January 25, 1980), which indicated occurrence of jaundice in a large number of patients with high mortality in Azamgarh town and surrounding villages. Within two days of the report, the All India Institute of Medical Sciences, New Delhi, sent a team to study the epidemic and to help the health authorities in the management of the patients. Hospital records were reviewed and the practising physicians and some members of the general population were interviewed. Since detailed epidemiological studies could not be done, it was decided to record the clinical and biochemical characteristics of the patients and to investigate the etiological factor(s).

Clinical data of both hospitalised and outdoor patients were collected. Blood and stool samples were obtained from as many patients, contacts and convalescents as possible. Liver biopsies were taken with the consent of the patients. The management of the hospitalised patients was also reorganised. Standard prophylactic measures such as mass education for personal and environmental hygiene, chlorination and boiling of water and administration of 3 ml of 10 per cent gammaglobulin were introduced. Our team stayed in the town for seven weeks to complete these tasks.

Serum bilirubin, serum transaminases and alkaline phosphatase were estimated in 240 samples collected by standard methods. HBsAg was studied by counter-immunoelectrophoresis (CEP) in all the (240) samples. Antibody to hepatitis A virus (Anti-HAV) was estimated in 71 samples by radio immuno assay (RIA HAVAB). Anti-HAV titres were estimated in 12 samples. IgM anti-HAV was investigated in 46 samples which included 10 samples processed by courtesy of Dr L. Mathiesen (Kobanbavans Kommunes Hvidovre Hospital, Copenhagen). Total IgM, IgA and IgG levels were estimated in 50 samples obtained from patients by radial immunodiffusion[4]. Ten stool samples collected within 2 days of appearance of jaundice were examined for the presence of virus A antigen by enzyme linked immunosorbent assay (ELISA).

Results

It was noted that the number of patients with jaundice at the district hospital started to increase in July, 1979 and the high number persisted (Fig. 1) till March, 1980 when the team left the town. Hospital records indicated a mortality of 12 per cent (8·4 % in males and 20% in females). Further, it was noted that pregnant women had a higher mortality rate (39%), as compared to the non-pregnant women (13.4%).

Clinical examination was carried out in 152 patients registered during the seven week stay of the investigating team. Age and sex distribution of the patients are presented in Table I. Only 7 patients were

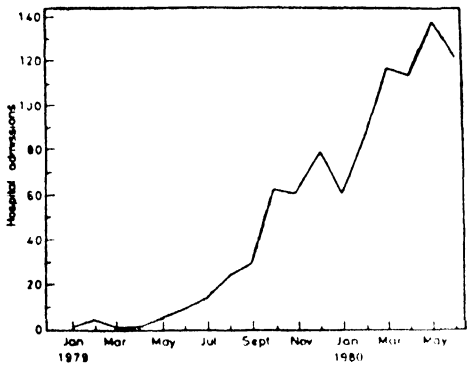

Fig. Graph depicting month wise hospital admission of AVH from January 1979 to May 1980.

children below 12 yr of age. Maximum number of patients belonged to 15-40 yr age group. The male-female ratio was 2:1. History of close contact with jaundiced patients was recorded in 70 per cent of the cases.

The pre-icteric phase was severe and prolonged, with fever and nausea lasting for 4-5 days of the icteric phase as well. Major symptoms like fever, nausea and fatigue were present in 70, 94 and 100 per cent of the patients respectively.

The icteric phase lasted for 6 wk or less and was characterised by classical symptoms and signs of viral A hepatitis[5]. Cholestatic features were noted in less than 10 per cent of the patients.

The mean serum bilirubin level was 5 mg/dl. Ninety six per cent had higher than normal levels, with only 14 per cent having a level over 10 mg dl. The mean SGOT level was 300 KU and SGPT was 318 KU. Only 13·3 per cent had levels above 100 KU. Mean serum alkaline phosphatase level was 21 KA units being above normal in 65 per cent with only 4·6 per cent having levels over 30 KA units.

Table 1. Age and sex distribution in 152 patients of AVH seen during acute phase

Age (yr)	No. of patients	
	Male	Female
0— 9	—	—
10—19	28	12
20—29	26	16
30—39	24	12
40—49	15	6
50—59	6	1
60—69	4	—
70 and above	2	—
Total	105	47

HBsAg tested in all the 240 samples showed positive results in only six cases. Fifty acute phase samples were tested for HBeAg and all were negative. Anti-HAV was positive in 67 out of 71 samples, being positive in less than 1:300 in seven, 1:300 in four and 1:600 in one of the 12 samples tested for titres during the icteric phase of the illness. IgM anti-HAV was negative in all the 46 samples tested. Total IgG, IgM and IgA were tested in 50 samples (Table II). IgM and IgA were within the normal range. IgG levels were markedly elevated in the patients. None of the ten stool samples screened for virus A particles showed the presence of the virus.

Liver biopsy was available in two patients during acute stage which showed the classical features of acute viral hepatitis. One postmortem biopsy from a patient of fulminant hepatitis showed massive necrosis.

Gammaglobulin was administered to 500 individuals including pregnant women and hospital staff. None of the hospital

Table II. Serum immunoglobulins in 50 patients of acute viral hepatitis and 20 control subjects

Subjects	No.	IgG	IgA	IgM
Controls	20	153±26 (112—198)	158±49 (93—240)	162±77 (70—361)
Patients	50	401±241* (132—1207)	150±55 (58—240)	180±83 (59—380)

Figures in parentheses show range; *$P<0.001$

hospital staff members who had received gammaglobulin developed hepatitis during 3 months of observation. Though no close follow-up of pregnant women could be done, it was observed that of those who had received gammaglobulin none reported to the hospital, with jaundice.

Discussion

As it was firmly established that the epidemic of viral hepatitis reported here was neither due to virus B nor virus A, it was concluded that it must be due to the third group of virus designated as non-A non-B.

The histopathology of the liver against the background of clinical picture and liver function tests showed convincingly that the epidemic was of viral hepatitis and not of toxic hepatitis such as those reported in the recent past from some parts of the country[6]. Virus B etiology was excluded by investigation of HBsAg in the serum, which was positive only in 3·3 per cent and which is known to be the carrier rate for virus B in India[7].

Virus A etiology was excluded by the following set of findings : (*i*) Total IgM levels in the serum was quite normal though the IgG level was markedly elevated. It has been reported that virus A hepatitis is associated with increase in the levels of IgM immunoglobulins[8,9]; (*ii*) Anti-HAV was positive in 95 per cent of the patients tested but the same positivity rate was noted in control population (94%). Others also have reported such a high positivity rate for anti-HAV in Indian population[2]. HAVAB test measures primarily the IgG antibodies, which is an indication of past virus A infection, unless paired sample shows rising titres. The anti-HAV levels were tested in 12 samples, and seven were positive in titres less than 1 : 300, four in 1 : 300 and only one was positive in 1 : 600 dilution. None were positive in higher dilutions. The titres of anti-HAV during acute illness are usually reported to be higher[10]; and (*iii*) All the 10 stool samples tested were negative for virus A antigen.

Exclusion of virus A and virus B etiology suggests that the epidemic was due to NANB group of virus, which

is a group of virus established to play a role in the etiology of PTH in developed countries[1]. Lately Mathiesen and co-workers[11] have also incriminated it in the etiology of fulminant hepatitis[1]. In Jammu and Kashmir an epidemic of NANB hepatitis[3] has been reported. On testing sera stored from the 1955 epidemic in Delhi, it was found negative[2] for A and B markers, suggesting NANB as the possible etiological agent. The present study further proves that NANB group of virus is a common etiological agent for epidemic hepatitis in India.

Some important clinical and epidemiological characteristics, noted in the present study need attention and further studies as possible diagnostic features of NANB epidemic hepatitis. These are described below, in some detail : The disease primarily affected adults, only 2·9 per cent of the patients being below 12 yr of age. Khuroo[3] also reported, in a house-to-house survey only 12 per cent of the patients below 10 yr of age. In contrast, virus A epidemics are known to predominantly affect children[5].

The pre-icteric phase of illness was severe and prolonged, the symptoms of the pre-icteric phase extending for 4-5 days in the icteric phase. Pre-icteric phase in virus A epidemics is on an average six days. All the major symptoms of this phase subside when the jaundice appears. In the present epidemic, fever, fatigue, nausea and anorexia continued for nearly a week after the appearance of icterus and the patients were more ill and bed-ridden than usually observed with virus A hepatitis in which the patients are ambulatory and afebrile, after the appearance of icterus. This observation is in contrast to the report[3] of Srinagar epidemic, where the mean duration of pre-icteric symptoms was only 3·5 days[4]. The cholestatic features were recorded in this study only in 10 per cent patients as compared to 20 per cent reported by Khuroo[3].

Contact spread was noted to be very significant in this study, close contacts and family being recorded in 70 per cent of the patients. This contact spread could have been an important factor for the persistence of the epidemic for nearly 9 months. This phenomenon was not observed in the epidemic at Kashmir[3]. Contact spread has not been reported also in post-transfusion non-A non-B hepatitis.

The mortality of hospital registered patients in this epidemic was 12 per cent with a higher mortality in females (20%) particularly in pregnant women (39%). The predominance of females in the ratio of 2 : 1 for fulminant hepatitis, leading to high fatality in an epidemic due to NANB as also high mortality in pregnancy have been reported by others[3].

Despite the fact that the mortality rate was higher and the prodromal phase was severe, the icteric phase was milder and clinical recovery was complete within 4 to 6 wk of illness.

The liver function tests were only moderately abnormal.

Five hundred persons including all the hospital staff and pregnant women in the community were administered 3 ml of 10 per cent gammaglobulin. None of these persons reported with clinical features of hepatitis during two months of observation, although during the same period, patients of hepatitis

were being admitted from among the general population. The prophylactic value of gammaglobulin in post-transfusion NANB hepatitis has been reported[12].

The clinical profile, biochemical alterations and the prognosis of NANB hepatitis in this epidemic were different from the post-transfusion NANB hepatitis which has the typical characteristics[1] of insidious onset, higher proportion of anicteric cases, less severe icteric phase, intermittent elevation of transaminases with a high proportion of patients having persistently elevated transaminase levels for more than 6 months.

Sporadic NANB hepatitis reported from Costa Rica has a clinical profile much similar to virus A hepatitis with mild clinical features and a very good prognosis[13]. The epidemic of NANB hepatitis reported here and earlier by Khuroo[3] of considerable public health importance in India.

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