



Acute Viral Hepatitis with Epidemiological Focus on Hepatitis A Virus Infection and Its Clinical Course in Adults

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Abstract

In this prospective study, two hundred and fifty four patients diagnosed to be having AVH were analyzed with reference to clinical profile & viral markers and statistical analysis was done. Isolated viral infection was documented in 102 (40.1%) patients where as more than one hepatotropic viruses caused AVH in 27(10.6%) patients. Non A-E Virus was the major case of sporadic AVH (40.1%), HBV & HEV were the etiological agent in 23.6% & 25.1% respectively. HAV was detected in 16.5% of the patients and the HCV was incriminated rarely as cause of sporadic AVH. The demographic, clinical and biochemical profile amongst isolated & mixed viral infection were found to be similar. However, HBV-AVH had significant prolonged course ($p < 0.001$) and HAV-AVH was found to have significantly higher number of patients pursuing a course of relapsing hepatitis. However HAV infection amongst adults in the present study was not found to cause severe liver disease except in few cases.

Introduction

Viral Hepatitis, caused by hepatitis viruses A through E, is a major public health problem in India,^[1] since 1955, several epidemics of hepatitis have been reported^[2-8]. Although hepatitis A Virus (HAV) and hepatitis E Virus (HEV) both enterically transmitted are highly endemic in India, HEV has been responsible for most of these epidemics^[2,8,10]. In India, HEV infection is responsible for 30-70% of cases of acute sporadic hepatitis & the major cause of Acute Liver Failure (ALF)^[11]. Amongst children, HAV is the predominant cause of acute hepatitis and dual infection with HAV & HEV have been more frequently reported amongst children with ALF^[12]. There are no published data in Eastern India especially in the State of Odisha.

Further our clinical impression indicates rise in frequency of HAV Infection amongst adults causing severe and atypical form of hepatitis. In view of paucity of data on the aetiology and clinical profile of AVH due to different hepatotropic viruses, the present study was undertaken to prospectively evaluate.

- 1) The aetiology of AVH in a tertiary care referral center in Eastern India, especially in the State of Odisha.
- 2) The clinical course of the HAV induced acute hepatitis amongst adults and to compare the clinical course of AVH due to HAV, HBV, HEV and mixed Infection

Material and Methods

Acute Viral Hepatitis (AVH) was diagnosed if a patient presented with following clinical & biochemical characteristics -

- a) Acute onset clinical symptoms characteristics of AVH such as prodrome followed by onset of overt icterus or biochemical evidence of hepatitis.
- b) Alanine transaminase (ALT) elevation of more than 2.5 times normal documented at least twice during the first two weeks of presentation.
- c) Absence of ingestion of known hepatotoxins such as alcohol, indigenous medicines and known hepatotoxic drugs.
- d) Absence of history suggestive of previous liver disease.

Inclusion Criteria

Consecutive patients diagnosed as AVH and attending the Hepatology department at S.C.B. Medical College & Hospital, Cuttack, Odisha, India from January 2015 to December 2016 were included in this study.

Exclusion Criteria

Patients in whom history is unreliable or alcoholic and patients in whom other diseases like congestive cardiac failure were excluded from the study.

Methods

All patients had a detailed clinical evaluation followed by routine relevant investigations.

Clinical Evaluation

A detailed history with special reference to etiology was taken. Also a complete general and systemic examination was done to look for tender, liver, liver span, splenomegaly and other signs of liver failure.

Investigations

Various biochemical, hematological, serological, microbiological and radiological investigations were undertaken in each patients as an outpatient basis on the first visit and then at regular intervals (10 days to 2 weeks) till recovery.

A) Biochemical

LFT-Serum bilirubin, Serum transaminase (AST & ALT), Serum protein & albumin, Prothrombin time Blood urea, serum creatinine, blood glucose, serum electrolytes.

B) Hematological

CBC/Peripheral smear / ESR / Coagulation profile / Malaria Parasite & Leptospira.

C) Serological:

Serum was collected at the time of initial examination to establish the etiological diagnosis of AVH. The following test were done.

Hepatitis B Surface Antigen (HBsAg)

IgM Antibody to Hepatitis A Virus (IgM HAV)

IgM Antibody to hepatitis E Virus (IgM HEV)

IgM Antibody to hepatitis B Core antigen (IgM anti-HBc)

Anti Hepatitis C virus antibody (Anti HCV)

Markers of autoimmune Hepatitis (ANA, SMA, Anti LKM) were performed only in a selected group of patients diagnosed as non A-E AVH with prolonged course.

HBsAg, IgM anti HBc, IgM anti HAV and anti HEV tests were performed using commercial Elisa kits (Organon Teknika, Netherlands) according to manufacturers instruction.

Criteria for etiological diagnosis of AVH:

HAV - AVH - IgM anti HAV +Ve

HBV - AVH - IgM anti HBc +Ve

HEV - AVH - IgM anti HEV +Ve

HCV - AVH - anti HCV +Ve

Non A-Non-E - AVH - Absence of all above markers in the sera.

D) Radiological:

Chest X-ray was done in few cases to evaluate their clinical and biochemical improvement. Ultrasonography & MR cholangiography was done in selected and complicated cases.

Follow-Up:

Patients were followed up every 10 days to two weeks to evaluate their clinical and biochemical improvement.

Cholestatic hepatitis is used to refer to a clinical picture, in which the course of the disease and the laboratory finding simulate those associated with mechanical obstruction of the bile- ducts. It is also used to describe the characteristic set of histological findings in the liver.

Prolonged viral hepatitis refers to rare cases of viral hepatitis that are atypically lengthy, laboratory abnormalities persist and symptoms and physical findings continue for more than 16 weeks.

Relapsing hepatitis refers to an illness in which the patient who has apparently had complete recovery after an acute episode of viral hepatitis manifests a recurrence of the original symptoms and finding on one or more occasions usually within six months of the original illness.

Statistics

Discrete variables amongst various etiologies of AVH were compared using Chi-square test continuous and rating variables were compared using Ltest, Wilcoxon ranksum test, and Mann Whitney's test.

Table 1: Liver Function Profile (n = 254)

Liver Function	± Mean SD	Range
S Bilirubin(mg/dl)	7.9±8.6	0.3-41.9
ALT (iu/dl)	207.2 ±389.9	100-2130
AST (iu/dl)	155.1 ± 277.2	80-1900
SAP (iu/dl)	333.3 ± 211.5	23-1360
T. Pr. (g/dl)	7.4 + 0.9	4.4-11.8
S. Alb(g/dl)	3.8 ± 1.1	0.5-5.7
Proth. Time Prolongation over control in seconds	1.2 ± 2.9	0-24

Table 2: Etiology of AVH (n = 254)

Viral etiology	Isolated infection	Mixed infection	Super infection	Total
HAV	28(11.05)	11	3-	42(16.5%)
HB.V	43(16.92%)	17	-	60(23.6%)
HEV	30(11.8%)	18	16	64(25.1%)
HCV	1 (0.3%)	8	4	13(5.1%)
Total	102(40.1%)		23(9.0%)	

No viral marker 102(40.1%), 22 had only HBsAg.

Under each etiology few patients had been common viz. acute HAV+HEV infection has been included both under HAV with another viral infection and HEV with another viral infection. Mixed viral infection occurred in 27(10.6%) patients.

Table 3: Etiological distribution of Acute Mixed viral infection

Serological markers	No. of Patients	Of mixed infection (n=27)
IgMAnti HBc + IgM Anti HAV	3	11.1%
IgMAnti HBc + IgM Anti HEV	10	37.0%
IgMAnti HBc + IgM Anti HCV	4	14.8%
IgMAnti HAV + IgM Anti HEV	6	22.2%
IgMAnti HAV + Anti HEV	2	7.4%
IgMAnti HEV + IgM Anti HCV	2	7.4%
Total	27(10.6%)	

Table 4: Demographic profile amongst various etiological types of AVH

Demographic Profile-	HAV Alone (n=28)	HBV Alone (n=43)	HEV Alone (n=30)	HAV with other viruses (n=11)	HBV with other viruses (n=17)	Non A-E (n=102)
Age (Mean Yrs ±SD) Range	19.1 ± 8.8 15-42	35.3 ± 12.3 15-65	30.4 ± 12.3 15-70	30.2 ± 18.6 15-77	35 ± 9.7 24-52	29 ± 11. 4 16-65
Sex M:F	14:14	29:14	20:10	5:4	7:5	71:31
Transfusion	1	7*	1	0	2	0
Needle Pricks	2	8+	0	2	0	-
H/O of	2	5	5	0	3	18
Surgery						

*P=0.02 (when compared with other groups)

P=0.04 Remaining parameter were similar between each individual groups

Table 5: Clinical feature among various etiological types of AVH

Clinical Profile	HAV Alone (n=28)	HBV Alone	HEV Alone (n=30)	HAV with other viruses (n=11)	HBV with other viruses (n=17)	Non A-E (n=102)
Types. Of prodrome						
Fever	26	34	26	8	10	87
Anorexia & Nausea	27	38	29	8	12	95
Abd. Pain	5	4	11	1	5	14
Arthralgia	4	14	0	0	1	8
Duration of prodromme (days)						
Means ± SD	5.4 ± 3	6.2 ± 4.6	6.6 ± 8.2	4.6 ± 2.3	5.2 ± 4.4	7.5 ± 7.3
Range	1-14	1-22	2-24	1-7	1-17	1-36
Duration of icterus (Days)						
Means ± SD	39.2 ± 34	68.9 ± 42.4	44.3 ± 40.6	60.1 ± 60.2	60.9 ± 55.9	42.3 ± 36.9
Range	2-135	11-180	U-180	13-210	13-233	15-180
Hepatomegaly (cm)						
Means + SD	2.4 ± 1.2	2.2 ± 1.1	3.3 ± 1.7	2.5 ± 0.5	3.1 ± 1.5	2.5 ± 1.3
Range	0-5	0-6	0-7	0-3	0-5	0-8

None of the above parameters were significantly different from each other (P>0.1)

Table 6: Liver function profile amongst various etiological types of AVH

Liver' Function	HAV Alone (n=28Y)	HBV Alone (n=43)	HEV Alone (n=30)	HAV with other viruses	HBV with other viruses (n=17)	Non A-E (n=102)
S. Bil (mg/dl)						
Means ± SD	7.5 ± 7.4	12.6 ± 11.3	8.7 ± 8.2	4.1 ± 3.4	6.6 ± 3.1	6.1 ± 7.1
AST(iu/dl)						
Means ± SD	322 ± 567.8	236 ± 417.2	126.8 ± 254.6	92.6 ± 45.1	111.4 ± 59.5	1129 ± 172.3
ALT (iu/dl)						
Means ± SD	322 ± 567.8	298.6 ± 4227	124.7 ± 232.9	217 ± 135.3	130 ± 69.9	173.8 ± 39.3
Alk. phos (iu/dl)						
Means ± SD	373.3 ± 231.5	325.8 ± 214.9	194.7 ± 125.8	362.7 ± 152.8	383.8 ± 311.6	329.9 ± 214.5
T.Protein(g/dl)						
Means ± SD	7.5 ± 0.7	7.7 ± 0.8	7.3 ± 1.1	8.0 ± 0.6	6.9 ± 1.1	7.2 ± 1.0
S.albumin(g/dl)						
Means ± SD	4.1 ± 0.7	3.9 ± 0.8	3.8 ± 0.8	3.3 ± 0.6	3.6 ± 2.1	3.8 ± 1.3
Pro-time prolongation over control (Second)						
Means ± SD	0.6 ± 1.1	1.7 ± 3.7	0.4 ± 1.0	0.1 ± 0.3	0.6 ± 1.7	1.5 ± 3.3

Table 7: Unusual characteristics amongst various etiological types of AVH

Characteristics	HAV Alone (n=28)	HBV Alone (n=43)	HEV Alone (n=30)	HAV with other viruses (n=11)	HBV with other viruses (n=17)	Non A-E (n=102)
Duration of Citrus more Than 6 wks	8(28.5)	30(69.7%)*	10(33.3%)	3(27.2%)	7(41.1%)	32(31.3%)
Two peaks of ALT	3+	1	0	2+	0	5
Proth. Time Prolongation of >20 seconds	0.	3	0	0	0	2

*P<0.001 (Significantly higher proportion of HBV-AVH had prolonged course of AVH than any other groups of AVH).

Results

Two hundred and fifty-four consecutive patients over the age of 15 years diagnosed as AVH attending the Hepatology department at SCB Medical College & Hospital, Cuttack, Odisha from January 2015 to December 2016 were included in the present study. Their mean age was 29.7 ± 12.4 with a male: female ratio of 1.8:1. All the patients had distinct prodrome, hepatitic phase and convalescence. There were only 11 (4.3%) anicteric hepatitis and the remaining patients (n=243) had overt jaundice. There liver function profile has been depicted in Table 1. This depicted liver function profile indicated the value at the time of maximum level of serum biliurbin in individual patients.

The etiological distribution of AVH has been depicted in table 2. Isolated viral infection was documented in 102 (40.1%) patients. Mixed acute viral infection was documented in 27 (10.6%) patients and super infection of one of the hepatotrophic viral infection over hepatitis B virus carrier was documented in 23(9.0%) of the patients. Non A-E viral hepatitis (patients without any of known hepatotrophic viral marker) was documented in 102 (40.1%) of the patients and 22 (21.5%) of these non A-E patients were HBV carriers. The over all frequency of HAV, HBV, HCV and HEV amongst these patients was 42(16.5%), 60(23.6%), 13(5.1%) and 64(25.1%) respectively. Isolated HAV, HBV, HCV and HEV infection was documented in 28(11%), 43(16.9%) 1(0.3%) and 30(11.8%) patients respectively. Amongst 23(9.0%) patients of HBV carrier with super infection, HEV was super infecting agent in 16 patients.

Table 3 depicts the details of acute mixed viral infection (co-infection) amongst patients with AVH. The commonest form of acute mixed viral infection was due to Hepatitis B+E & Hepatitis A+E Co-infection.

To detect the difference in clinical and biochemical dynamics amongst various etiological agent induced AVH, they were grouped into following six groups.

- Group - I: Isolated HAV Infection (n=28).
- Group - II: Isolated HBV infection (n=43).
- Group - III: Isolated HEV Infection (n=30).
- Group - IV: HAV with HBV or HEV or HCV (n=11).
- Group - V: HBV with HEV & HCV (n=17).
- Group - VI: Non A-E AVH (n=102).

Isolated HCV infection was documented only in one patient and hence was not taken as separate Group. The remaining 12 patients with HCV Infection were associated with another viral infection which was included in either group IV & group V Twenty two patients (87.5%) in group I, 34(79%) in Group-II, 24(80%) in group-in, 6(54.5%) in group IV, 10(58.82%) in group V and 78(76.4%) in group VI could be followed up till they had complete clinical & biochemical recovery.

Table 4 depicts the demographic profile of AVH amongst various etiological group. The frequency of blood transfusion and needle prick amongst HBV-AVH was significantly (P<0.05) higher

than other group of AVH. The age and sex distribution however was similar amongst the groups.

Table 5 denotes the important clinical features amongst various group of AVH. However the types of prodrome, duration of prodrome, duration of icterus & degree of hepatomegaly were similar amongst various groups. Table 6 outline the various liver function profile amongst the six groups of AVH. It is obvious that the mean (± SD) and ranges of the various liver functions were similar amongst the different groups of AVH. HBV-AVH in comparison to other types of AVH due to HBV had significantly prolonged course (table 7). About 70% of patients with AVH-B had icteric hepatitis more than 6 weeks where as only about 30% of AVH due to other etiologies had icteric hepatitis of more than 6 weeks.

Two peaks of ALT could be documented amongst about 14% of HAV-AVH (Table-7) where as similar phenomenon was rarely observed amongst AVH patients due to other etiologies. Severe prolongation of prothrombine time was not a usual feature in any types AVH. Only two of the 254 patients developed complication in the form of fulminant hepatitis. One patient belonged to non A-E AVH and the other belonged to HAV-AVH. 4(four) patients developed acute on chronic liver failure(ACLF) (HBV-2, Non A-E -2).

Discussion

The present study revealed four important events regarding the etiology of AVH in one of the large tertiary care centre in Eastern India in the State of Odisha. First the major etiological agents of sporadic AVH was found to be HEV (25.1%) as well as HBV (23.6%) and hepatitis C virus is an infrequent cause of sporadic AVH (Table-2). This is in sharp contrast to developed nations where HEV is unusual and HBV as well as HCV constitutes the major viral etiologies of sporadic AVH. In the present study, none of our patients with sporadic HCV-AVH which can be termed as community acquired HCV-AVH had history of any identifiable parenteral exposure such as blood transfusion or needle prick. None of them were drug addicts, alcoholic and neither had multiple sex partners. The source of such HCV infection needs evaluation further.

Secondly, it was seen that about one tenth (10.6%) of our patients had serological evidence of acute infection due to more than one hepatotrophic viruses. The commonest type of mixed infection encountered was due to hepatitis B+E and hepatitis A+E (Table-3). Such high frequency of mixed infection has not been reported previously from any part of the country and dual infection amongst sporadic AVH in developed nation is extremely rare and in English literature such reports are lacking. However despite having multiple hepatotrophic viral infection, their demographic (Table-4), clinical (Table-5), liver function profile (Table-6) was similar to isolated viral infection. None of these multiple viral infected AVH developed severe acute hepatitis in the form of fulminant and acute on chronic liver failure(ACLF). This factor

emphasizes that host factor possibly plays a major role in determining the severity of acute hepatitic illness.

Third important fact noted in the present study was the frequency of HAV-AVH amongst adult (>15yrs). In the present study about 15% of the adults AVH were due to HAV. This fact assumes importance particularly in India because India is supposed to be endemic for HAV and by the age of 15 yrs 90% of population are reported to be protected against HAV due to sub-clinical exposure to HAV in childhood resulting in development of protective antibody against HAV in them^[13].

This observation indicates that in India, due to developmental progress certain population pockets are not exposed to sub-clinical HAV infection in childhood. Such observation also indicates the need to re-evaluate the seroepidemiology of HAV infection in population to identify the high risk group to develop HAV infection. Such information may influence vaccination strategy for HAV in this country. Further a recent report indicate that combined infection of HAV & HEV, amongst children was responsible for 40% of fulminant hepatitis in this Country^[14]. Both these studies may be indicating a serious problem due to Hepatitis A Virus that this country may face in the ensuing decade.

Fourthly the previous reports on sporadic AVH indicated non-A, non B, as the etiological agent in about 60% of the patients. In the present study, however non-A-E Virus was found to be the cause in 40% of patient. Obviously, this reduction in frequency of unidentified viral etiology of AVH is due to identification of HEV & HCV Further it also indicates the possibility of existence of more than one non-A-E viruses. In 1995 hepatitis G virus has been identified as the third major non A, non B virus, however its role in causation of acute sporadic AVH is yet to be evaluated. Recently it has been reported regarding the presence of HGV in one patient in acute liver failure^[15]. Evaluation for presence of HGV among these sporadic non A-E patients may provide beneficial information.

The clinical and liver function profiles of isolated hepatotropic viral infection and acute mixed viral infection was found to be similar in the present study. However, patients with Hepatitis A virus infection were not infrequently found to have two peak ALT elevations. Recently in the Western country two forms of clinical course was described amongst patients with HAV infection viz. Cholestatic hepatitis and relapsing hepatitis (two peak ALT elevation). Even though we documented relapsing hepatitis amongst 15% of our HAV-AVH patients the frequency of prolonged hepatitis amongst HAV patients was similar to HEV-AVH & mixed viral infection. In contrast HBV-AVH in the present study frequently had prolonged course (table-7).

Unlike Western report clinical course of adult HAV-AVH in the present study was relatively benign and severe form of hepatitic illness was encountered in few cases only. We will like to conclude that non A-E followed by HBV & HEV are the major etiological agents of AVH at our centre. Despite endemicity of HAV in this country 15% of the adults AVH are due to HAV infection. More than one hepatotropic viral infection was encountered in about 10% of the patients. Fifteen percent of HAV-AVH had relapsing Hepatitis. The demographic clinical and liver function profile of isolated & mixed viral infection was similar. HBV-AVH patient however had much more prolonged course than all other etiological types of AVH.

Summary

In this prospective study two hundred and fifty-four patients diagnosed to be having AVH were analyzed with reference to clinical profile & viral markers. Isolated viral infection was

documented in 102 (40.1%) patients whereas more than one hepatotropic viruses caused AVH in 27(10.6%) patients. Non-A-E Virus was the major case of sporadic AVH (40.1%), HBV & HEV were the etiological agent in 23.6% & 25.1% respectively. HAV was detected in 16.5% of the patients and the HCV was incriminated rarely as cause of sporadic AVH. The demographic, clinical and biochemical profile amongst isolated & mixed viral infection were found to be similar. However, HBV-AVH had significant prolonged course ($p<0.001$) and HAV-AVH was found to have significantly higher number of patients pursuing a course of relapsing hepatitis. However, HAV infection amongst adults in the present study was not found to cause severe liver disease except in few cases.

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