ORIGINAL RESEARCH PAPER

Gastroenterology

CLINICAL, HEMATOLOGICAL AND VIROLOGICAL PROFILE OF ACUTE VIRAL HEPATITIS (AVH) IN ADULTS: PROSPECTIVE STUDY FROM EASTERN INDIA

KEY WORDS: HAV-AVH - Hepatitis A virus induced AVH, HBV-AVH - Hepatitis B virus induced AVH, HEV-AVH -Hepatitis E virus induced AVH, HCV-AVH - Hepatitis Cvirus induced AVH. ACLF – Acute on chronic liver failure .

Manjushree Nayak Associate Professor, Pathology, SCB Medical College, Cuttack.

Rajendra Kumar Panda Assistant Professor Pharmacology, SCB Medical College, Cuttack.

Umesh Chandra Patra Professor & Head, Department of Hepatology, SCB Medical College & Hospital Cuttack, Odisha, India -753007

ABSTRACT

Acute viral hepatitis(AVH) is inflammation of the liver caused by infection with one of the five hepatitis viruses[1] .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 where as more than one hepatotrophic 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]. 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[3,4,5]. In India, HEV infection is responsible for 30-70% of cases of acute sporadic hepatitis & the major cause of Acute Liver Failure (ALF)[5]. 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 [6]. There are no published data in Eastern India especially in the State of Odisha. Further 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 hepatotrophic viruses, the present study was undertaken to prospectively evaluate the aetiology of AVH in a tertiary care referral center in Eastern India, especially in the state of Odisha and 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.

MATERIALS &METHOD :

This prospective, observational, hospital based study was conducted in the department of Hepatology, Pathology and Pharmacology at SCB Medical College & Hospital, Cuttack, Odisha after approval from Institutional Ethical Committee The study was conducted from January 2015 to December 2016. Data were collected from patients,those who have attended the Hepatology OPD/IPD diagnosed of Acute Viral Hepatitis. Written informed consent was taken after explaining the details of the study protocol. Acute viral Hepatitis patients were selected as per the inclusion and exclusion criteria of the study

Inclusion Criteria: Consecutive patients diagnosed as AVH and attending the Hepatology department at S.C.B. Medical College & Hospital, Cuttack were included in this study.

Exclusion Criteria: Patients with unreliable history is 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 tenderness of 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: Biochemical tests like Liver function test, Serum bilirubin, Serum transaminase (AST & ALT), Serum protein & albumin, Prothrombin time, Blood urea, serum creatinine, blood glucose, serum electrolytes are tests are routinely done

B Hematological: Tests like Complete Blood Count/Peripheral smear / ESR / Coagulation profile & tests for Malaria Parasite & Leptospira were routinely done

C) Serological: Serum was collected at the time of initial examination to establish the etiological diagnosis of AVH.The following test were done. HBsAg, IgM HAV, IgM HEV, IgM anti-HBc, 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.

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.

STATISTICS: Discrete variables amongst various etiologies of AVH were compared using Chi-square test continuous and rating variables were compared using T test, Wilcoxson rankusum test, and Mann Whitney's test.

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.

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

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 -2 Etiology of AVH (n = 254)

Viral etiology	Isolated infection	Mixed infection	Super infection	Total
HAV	28(11.05)	11	3-	42(16.5%)
HBV	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 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.

Table-3 Etiological distribution of Acute Mixed viral Infection:

Serological markers	No. of Patients	Percent Positivity	
		Of total patients (n=254)	Of mixed infection (n=27)
IgMAnti HBc + lgM Anti HAV	3	1.18%	11.1%
IgMAnti HBc + lgM Anti HEV	10	3.93%	37.0%
IgMAnti HBc + lgM Anti HCV	4	1.5%	14.8%
IgMAnti HAV + lgM Anti HEV	6	2.3%	22.2%
IgMAnti HAV + Anti HEV	2	0.7%	7.4%
IgMAnti HEV + lgM Anti HCV	2	0.7%	7.4%
Total	27(10.6%)		

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 Demographic profile amongst various etiological types of AVH

Demographic Profile-	HAV Alone (n=28)	HBVAlone (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)	19.1 ± 8.8	35.3 ±12.3	30.4 ± 12.3	30.2 ± 18.6	35 ± 9.7	29 ± 11.4
Range	15-42	15-65	15-70	15-77	24-52	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 Surgery	2	5	5	0	3	18

*P= 0.02(when compared with other groups)+P=0.04 remaining parameter were similar between individual groups

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 5-CLINICAL FEATURE AMONG VARIOUS ETIOLOGICAL TYPES OF AVH

Clinical Rrofile	HAV Alone (n=28)	HBV Alone (n=43)	HEV Alone (n=30)	HAV with other viruses (n=ll)	HBV with other viruses (n=17)	Non A-E(n=102) n (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

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

Liver Function	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 AE n=102
Serum bilirubin(mg/dl)						
Mean ± 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)						
Mean ± SD	322 ± 567.8	236 ± 417.2	126.8 ± 254.6	92.6 ± 45.1	111.4 ± 59.5	112.9 ± 72.3
ALT (iu/dl)						
Mean ± SD	322 ± 567.8	298.6 ± 4227	124.7 ± 232.9	217 ± 135.3	130 ± 69.9	173.8 ± 39.3
Alkaline phosphatase (iu/dl)						
Mean ± 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
Total Protein(g/dl)						
Mean ± 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
Serum albumin(g/dl)						
Mean ± 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
Prothrombin Prolongation time over control (Second)						
Mean ± 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 6 outline the various liver function profile amongst the six groups of AVH and it is seen 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 patients 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).

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 Icterus 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

DISCUSSION:

The present study revealed four important events regarding the profile 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 indicate that in India, due to developmental progress certain population pockets are not exposed to sub-clinical HAV infection in childhood. Such observation also indicate 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 [7]. 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 elevation. 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 hepatotrophic 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.

CONCLUSION

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 hepatotrophic 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 pursing 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.

CONFLICTS OF INTEREST :NIL

REFERENCES:

1. Sreenivasan MA, Banerjee K,Pandya PG, Kotak, RR Pandya PM, Desai NJ, et al. Epidemiological investigations of an outbreak of infectious hepatitis in Ahmedabad city during 1975-76. Indian J Med Res 1978;67:197-206.
2. Khuroo MS, Duermeyer W.Zargar, SA, Ahangerr MA, Acute sporadic non-A, non-B hepatitis in India. Am J Epidemiol 1983;118:360-A
3. Fandon BN, Joshi YK jaiff Sk, Gandhi BM, Mathiesen LR, Tandon HD, An epidemic of non-A, non-B hepatitis in north India .India J Med Res 1982;75;739 .
4. Sreenivasan MA, Arankalle VA, Sehgal A, Pavri KM. Non-A, Non-B epidemic hepatitis; visualization of virus likeparticles in the stool by immune electron microscopy Gen Virol 1984;65;1005-7.
5. Acharya SK Panda'Sk, Saxena A, Gupta SD. Acute hepaticfailure in India; A perspective from the east J Gastroenterol Hepatol 2000;15:473-9.
6. Arora NK, Nanda SK, Gulat S, et al -Acute viral hepatitis types E, A & B singly and in combination in acute liver failure in Children in North India, J. Med virology, 1996;48:215-221.
7. Panda SK,Panigrahi AK,Dasarathy S, Achrya SK,Hepatitis G Virus in India, Lancet 1996;348:1319.