

Simultaneous infection of Hepatitis A and Hepatitis E viruses amongst acute viral hepatitis patients: A hospital-based study from Uttarakhand

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ABSTRACT

Background: Enterically transmitted viral agents like Hepatitis A virus (HAV) and Hepatitis E virus (HEV) are common causes of viral hepatitis in developing countries. Double infections by both agents, as their routes of entry are similar, are common. Overall this is a major health issue for our country. This study was carried out to learn about the seroprevalence of HAV & HEV (and double infections if any) infections in acute viral hepatitis (AVH) cases attending our hospital. **Materials and Methods:** This is a retrospective cross-sectional study of a 2-years duration carried out in the serology lab of Dept. of Microbiology, AIIMS Rishikesh. Continuously collected samples totaling 617 cases, presenting with Acute Viral Hepatitis was included in the study. Cases with suggestive history were tested for IgM anti-HAV and IgM anti-HEV respectively. Commercially available ELISA kits were put into use. Standard Statistical Package (SPSS 23) was put to use for statistical analysis. **Results:** HAV & HEV seroprevalence in AVH cases were found to be 14.7% (91/617) and 28.04% (173/617), respectively. Dual infection of HAV and HEV was found in 5.9% (32/617) of study subjects. The prevalence of HAV and HEV among males were 14.2% and 34.26%, respectively while that in female were 15.36% and 21.16%, respectively. Infection was predominantly found in young adults. Distinct seasonal variation was observed, period towards the end of monsoon, and beginning of winter recorded more cases. Both year, most of the positive cases are seen in the months of August and September. **Conclusion:** The infection rate of HEV is higher than HAV amongst AVH cases. This and relatively high co-infection rate (5.9%) is significant in terms of the need for regular screening of HEV in pregnant women as well as the urgent need to improve hygiene amongst the population. This data will help in future vaccine strategies and sanitation programs in this part of the country.

Keywords: Acute viral hepatitis, enterically transmitted hepatitis, feco-orally transmitted hepatitis, HAV and HEV co-infection

Introduction

Feco-orally transmitted Hepatitis is still one of the major communicable diseases in India and it is an indicator of poor sanitization, especially in rural and semi-urban localities. The

government of India too recognized this issue and launched the National Viral Hepatitis Control Program which includes hepatitis Virus (HAV) and Hepatitis E Virus, besides other agents.^[1] HAV is one of the major feco-orally transmitted agents and responsible for 1.4 million new cases per year.^[2,3] HAV is an RNA virus belonging to the genus Hepatovirus and family Picornaviridae. Anti-HAV antibodies in human sera are detectable in acute illness as serum liver enzyme level reaches a high level and fecal HAV shedding is still going on. IgM class antibody elevates initially persisting for a few months (6-12 months usually). In

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the later stage (convalescence) IgG class of anti-HAV emerges predominantly. HAV is a self-limiting infection without any chronic sequelae.^[4] From the early 1990s, a safe and effective vaccine became available against HAV infection.

Similar to HAV, Hepatitis E virus (HEV) is another agent transmitted feco-orally and predominantly found in Asia, parts of Africa, and in core Central America. It is an RNA virus falling under the genus Hepevirus of the family Hepeviridae. The anti-HEV IgM antibody appears soon after an acute infection and falls to a very low level within 6 months of infection.^[5] HEV is reported to be the agent of 20-60% of cases of sporadic acute hepatitis with fulminant liver failure.^[5] HEV infection is observed to be higher amongst the pregnant women than seen amongst non-pregnant ladies with AVH.^[5]

Acute Hepatitis (Jaundice) is one of the commonest conditions seen in day to day general practice/family medicine practice in India and as per one survey released by CDC-Morbidity and mortality weekly report, in India, 7.4% of acute hepatitis cases could be of hepatitis A and 10.4% of hepatitis E virus.^[6] One large Indian study on acute hepatitis, found 12.6% HAV, 16.1% HEV, and 1.3% combined infection.^[7] A recent outbreak of acute hepatitis in Chandigarh (published in 2020) had HEV and HAV as the principal etiological agents.^[8] HAV-HEV co-infection is common and can lead to serious complications and increased mortality due to the high risk of acute liver failure in both children and adults.^[9,10] As mentioned above Hepatitis E Virus infection in pregnancy is considered high risk due to enhanced mortality.^[5] Also, a proper understanding of the extent/epidemiology of both the infections will go a long way in implementing preventive measures like vaccine planning/strategy, etc., which can be very crucial in a resource scant set up like our state.

A trend of high HAV and HEV co-infection perceived by authors in our local set up stimulated this study. This study was planned primarily to check the infection rate of HAV and HEV and their co-infection in AVH cases in our hospital.

Material and Methods

This was a retrospective study spanning a period of 2 years (January 2018 to December 2019) which included a total of 617 patients. Institutional Ethics Committee permission was obtained vide letter no. AIIMS/IEC/20/642-dt26/9/20. Patients attending AIIMS Rishikesh (indoor and outdoor) with a clinical diagnosis of acute viral hepatitis were included in this study, irrespective of age and sex.^[4] About 3-5 ml serum was collected and stored in lab freezer before testing. Commercial ELISA kit for anti-HAV [HAV IgM capture Immune assay (ELISA) for determination of IgM class antibodies to Hepatitis A Virus in human plasma or sera by DIA.PRO Diagnostic Bioprobes Srl, San Giovanni (Milano) – Italy] and anti HEV [HEV IgM capture Immune assay (ELISA) for determination of IgM class antibodies to Hepatitis A Virus in human plasma or sera by DIA.PRO Diagnostic Bioprobes Srl, San Giovanni (Milano) – Italy] were

used to test strictly as per the kit insert provided. Euroimmune seven plate walkaway automated ELISA system was utilized to run the assays. Data were collected in a Microsoft excel sheet and analyzed by using SPSS version 23. The Chi-square (χ^2) and Fisher's exact test were put to use to check statistically significant associations between various demographic factors with HAV and HEV results.

Results

Out of a total of 617 samples, 232 samples yielded reactive ELISA, 200 being single agent (HAV or HEV), and 32 mixed (Both HAV and HEV). Table 1 shows the baseline data of the study population as well as the ELISA result.

Discussion

The infection rate of HAV and HEV and their co-infection status were analyzed in this study.

In the present study, 37.6% (HAV 14.7%, HEV 28.0% Combined 5.2%) of the AVH patients had a reactive viral marker. This reactive rate is lower to Al-Naimy *et al.*'s 43%.^[11] But Joon *et al.* from India reported a viral (HAV, HEV) infection rate of 29.9% with HAV & HEV being 19.31% and 10.54%, respectively. The co-infection rate in this study was 11.5% compared to 5.2% in our study.^[12] Varde *et al.* described an HAV rate of 5.1% and HEV 13.1% in a hospital-based study on acute hepatitis cases of a predominantly male adult population from Jabalpur, India.^[13] In a large nationwide study carried out in Bangladesh 19% HAV and 10% HEV cases were detected with a median age of 12 and 25 years respectively. HAV was found more in females while HEV attacked males dominantly. A clear seasonal variation for both infections with a higher number of cases in July to September period was observed.^[14] Samadar *et al.* observed a higher seroprevalence of HEV (9.63%) compared to HAV (6.96%) with a coinfection rate of 2.07% in a population of acute hepatitis.^[15] In this population 9.6% of pregnant ladies had HEV. A seasonal trend was observed with a higher incidence in May to September (summer and rainy season).^[15] In recent a

Table 1: Baseline data and ELISA result

	Anti HAV IgM reactive	Anti HEV IgM reactive	Mixed+
Total Sample: 617			
Male :Female Ratio- (324:293)			
Positive	91	173	32
Male	46	111	21
Female	45	62	11
Mean Age (Standard deviation)	20.07 (16.2)	35.34 (17.4)	20.27 (14.8)
Median Age (IQR)	16.33	28.1	19.33
Pregnancy positive	2	7	-
Fulminant hepatitis	0	4	0
Death	0	1	0
Presence of other illness	22	52	10

community based acute hepatitis outbreak surveillance from Chandigarh, Kankaria *et al.* reported predominantly (85.1%) HEV followed by 12.8% HAV and 2.1% combined infection.^[8] More males were infected and food and water were considered likely sources.^[8] Malhotra *et al.* also reported a recent rise of HEV (all by genotype IA) in a locality within the Jaipur region, mainly attributable to poor hygiene and sanitary condition.^[16]

In a Cuban study by Rodríguez Lay Lde *et al.* 36.4% of subjects were positive for HAV (IgM), 21.2% for HEV (IgM) while a whopping 42.4% had IgM antibody to both HAV & HEV.^[17] A Japanese study by Takahashi *et al.* on the other hand found 100% positivity to HAV in the adult population (23-86 years group) while anti HEV was found in 11% only.^[18]

Radhakrishnan *et al.* found that prognosis after symptomatic treatment is unaffected by the presence of one or two infections.^[19] But other report says that co-infection can lead to severe conditions like hepatic encephalopathy etc.^[20] Generally, HAV cases are linked to socioeconomic factors, sanitation, and hygiene.

Table 2 and Figure 1 depict a distinct relationship of age with HAV & HEV infections. A low prevalence of HEV compared to HAV in children is very clear and it may be attributed to lack of exposure.^[18] But HEV seems to afflict teenagers and young people much more than HAV. This finding corroborates well with other studies.^[13,18,14] Takahashi *et al.* reported that in HEV, risk and severity of AVH enhance with age.^[18] A relevant point to note here is that HEV infection is mostly manifested without icterus and hence missed in children.^[21,22] In a Mongolian study, the prevalence of HAV was significantly higher than HEV infection across the adult study population.^[23]

Out of 7 HEV cases in pregnancy, 4 went to develop fulminant hepatitis and one of them expired. Detail nature of pregnancy was not available. A correlation could not be established due to the small number of cases. But there are reports of increased mortality with HEV infection during pregnancy.^[19] Overall it is clear from Table 1, that males were more affected than females (esp. for HEV) which corroborates well with other studies and attributable to the fact that males are more exposed due to professional and social activities.^[8,11,13,21]

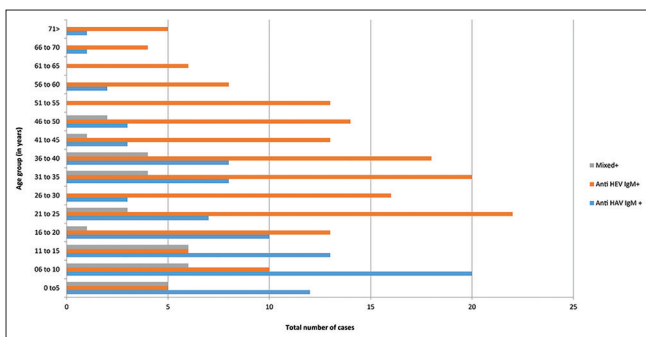


Figure 1: Age-dependent prevalence of HAV and HEV serological markers

As depicted in Figure 2 and Table 3, both HAV & HEV were prevalent throughout the year with peaking between May to November for both the infection (with minor differences). Maximum increase was observed between August and October/November (end of monsoons and beginning of winters) for both the viruses. These findings complied with similar findings in other studies.^[12,14,15]

The current study detects a high infection rate of HEV (28%) and HAV (14.7%) in acute hepatitis cases presenting to our hospital. Likely similar (high) rate in the community can be anticipated. A significant co-infection (HAV and HEV) rate was observed at 5.2% which indicates a possibility of severe acute hepatitis/complication in 1 in 20 cases as co-infection may associate with complications. High infection rates associated with double the rate of HEV infection compared to HAV infection implies, the need for accurate virological diagnosis (laboratory diagnosis), especially in a high-risk group like pregnancy, symptomatic children, etc., A marked seasonal pattern of both the type of viral infections was witnessed. There was a higher infection rate in late monsoon to early winter, a finding which can help in planning preventive measures, including vaccination strategies economically and effectively. Given the common route of transmission (fecal-oral) and current stress on personal and food hygiene in society, periodic surveillance of HAV & HEV

Age range	Anti HAV IgM+	Anti HEV IgM+	Mixed+
0-5	12	5	5
6-10	20	10	6
11-15	13	6	6
16-20	10	13	1
21-25	7	22	3
26-30	3	16	-
31-35	8	20	4
36-40	8	18	4
41-45	3	13	1
46-50	3	14	2
51-55	-	13	-
56-60	2	8	-
61-65	-	6	-
66-70	1	4	-
71>	1	5	-

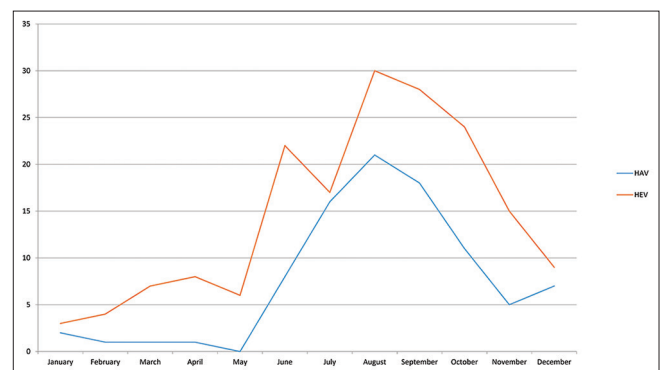


Figure 2: Seasonal distribution of HAV and HEV

Table 3: Seasonality

Months	1 st year		2 nd year	
	Anti HAV IgM reactive	Anti HEV IgM reactive	Anti HAV IgM reactive	Anti HEV IgM reactive
January	1	2	1	1
February	1	1	-	3
March	1	4	-	3
April	1	-	-	8
May	-	1	-	5
June	1	5	7	17
July	-	6	16	11
August	-	8	21	22
September	3	6	15	22
October	2	6	9	18
November	-	5	5	10
December	1	3	6	6

exposure pattern needs to be carried out. Safe water supply and sewage disposal are of great essence.

Conclusion

HEV infection is higher than HAV with the former predominating in relatively older patients compared to younger subjects of the latter infection. The co-infection rate is also not negligible at 5.9%.

Routine HEV screening of pregnant ladies as well as improvement of hygiene and sanitation is most essential. Regular testing for HAV and HEV may be useful in our cohort of AVH subjects, which is not routinely performed in all cases otherwise, especially during the period spanning late monsoon and early winter here.

Abbreviation

HAV = Hepatitis A Virus, HEV = Hepatitis E Virus, IgM = Immunoglobulin M, IgG = Immunoglobulin G, AVH = Acute Viral hepatitis

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Conflicts of interest

There are no conflicts of interest.

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