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PREVALENCE AND CO-INFECTION RATES OF ENTERICALLY TRANSMITTED HEPATITIS A AND E VIRUSES IN ACUTE VIRAL HEPATITIS CASES.

Medical Microbiology

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ABSTRACT

Background: Enterically transmitted Hepatitis A virus (HAV) and Hepatitis E virus (HEV) are both a major public health problem in India. This study aimed to determine incidence of HAV and HEV in patients presenting with acute viral hepatitis (AVH) and the co-infection of HAV and HEV in these patients and the incidence of HEV infection among pregnant women with hepatitis. **Materials and Methods:** It was a retrospective observational study conducted over 3 years at the Department of Microbiology, ESIC Medical College & Hospital, Faridabad from September 2017 to August 2020. A total of 439 serum samples were collected from patients with a clinical diagnosis of AVH. The presence of IgM anti-HAV and IgM anti-HEV antibodies in serum were analyzed by enzyme-linked immunosorbent assay. Data collected was analyzed using Statistical Package for the Social Sciences (SPSS) version 25. **Results:** The seroprevalence of HAV- and HEV-positive patients were 23% and 22%, respectively. The seroprevalence of co-infection of HAV and HEV in patients with acute viral hepatitis was 4.5%. HAV was highest in the age group of 6-10 years and HEV was predominantly seen among young adults. **Conclusion:** Our study showed equal prevalence of HAV and HEV and co-infection rate of 4.5%. This mandates the screening for both enteric viruses across all age groups. High incidence of HEV infection in pregnant women shows the importance of screening symptomatic patients and improving levels of personal hygiene.

KEYWORDS

Viral hepatitis, hepatitis A, hepatitis E, incidence.

INTRODUCTION

Hepatitis A virus and Hepatitis E are predominantly transmitted by the faeco-oral route and are the major cause of several outbreaks of waterborne hepatitis in tropical and subtropical countries and of sporadic cases of viral hepatitis in industrialized countries. As per the global hepatitis report 2017 by the world health organization (WHO), viral hepatitis caused 1.34 million deaths in 2015, which is comparable to deaths caused by tuberculosis and higher than that caused by HIV. Due to the paucity of data, the exact burden of the disease in India is not established.[1]

HEV is a non-enveloped virus with a single-stranded positive-sense RNA in the genus Hepevirus of the family Hepeviridae. To date, four main genotypes of HEV (HEV1-4) have been described. Genotype HEV1 and HEV2 only infect humans, while HEV3 and HEV4 can infect both humans and animals, like pigs, wild boar, deer and rabbits. Hepatitis E infection in developed countries is mostly zoonotic.[2]Pregnant women especially from the Indian subcontinent and Africa are at increased risk of contracting acute HEV infection as well as developing severe complications including acute liver failure.[3]In addition, chronic HEV infections leading to chronic hepatitis and cirrhosis have been described for immunocompromised patients with HEV3.[4]HEV infection can be identified based on the detection of HEV RNA, IgM or at least 4-fold rising of IgG levels. However, IgM offers the highest sensitivity (90.1%) of the three markers and also the antibody persists until early convalescence.[5]The incubation period of HEV infection is estimated to be around 2–9 weeks and during an epidemic of HEV, anicteric hepatitis is more common than icteric hepatitis and clinical hepatitis is seemingly more frequent in adults than in children aged <15 years.[6]

HAV is a non-enveloped 27-nm, heat-, acid-, and ether-resistant RNA virus in the genus Hepatovirus of the family Picornaviridae. Infection by HAV is generally self-limiting and can produce effects that range from mild anicteric hepatitis to fulminant hepatitis. The likelihood of clinically apparent disease associated with HAV infection increases with age. In children <6 years of age, most infections (70%) are non-specific and are usually anicteric.[7]

Anti-HAV IgM antibody can be detected at the time of onset of symptoms in most patients, thus can be used to diagnose acute hepatitis A at the time of clinical symptoms.IgM titers decrease in the weeks after onset and then become undetectable. Recent data shows an increase in prevalence of HAV and HEV infections along with an increase in the rate of coinfection. Hence, the present study was aimed to determine the incidence of HEV and HAV infections in patients with acute viral hepatitis (AVH). The incidence of HEV infection amongst pregnant women with hepatitis was also determined.

MATERIAL AND METHODS

This retrospective study was conducted in the department of microbiology in a teaching hospital which caters to insured industrial workers and their families in north India. This study was conducted over 3 years from September 2017 to August 2020. The study population included 453 patients (out door and hospitalized) between 1 and 59 years of age with clinical features suggestive of hepatitis such as nausea, vomiting, anorexia, jaundice and elevated liver enzymes. The study was approved by the institutional ethics committee. 5 ml of blood was collected in a plain vial from each patient, centrifuged and serum stored at -20°C till further analysis. All samples were tested in duplicate for Ig M anti- HAV and Ig M anti- HEV antibodies using commercially available enzyme- linked immunosorbent assay (ELISA) kits (HAV Ig M ELISA Test, DIA. PRO and HEV Ig M ELISA, DIA.PRO). Each sample was also tested for HBs Ag and IgG anti- hepatitis C virus (HCV) antibodies by ELSIA (VIDAS, Biomerieux) to rule out hepatitis B and HCV infections. 14 patients, who tested positive for HBsAg and anti HCV antibody, were excluded from the study and eventually, data was analyzed for 439 patients. The data collected was analyzed using SPSS version 25 for windows (SPSS, Inc., Chicago, IL< USA). Chi- square test was used for analyzing qualitative variables.

RESULTS

Of 439 samples from cases of AVH, 101 (23%) were positive for Ig M anti-HAV antibodies, 97 (22%) positive for Ig M anti-HEV antibodies and 20 (4.5%) patients were positive for both IgM anti-HAV and IgM anti HEV antibodies indicating HAV-HEV co-infection (Table 1). 49.6% of the patients were positive for AVH. The prevalence of HAV infection in males and females was 50 (28.2%) and 51 (19.4 %) respectively. The prevalence of HEV infection was 41 (23.1%) & 56

(21.3%) respectively. However, such differences in the incidence rates of HAV, HEV and HAV-HEV co-infection between males and females were of no statistical significance (Table 1).

The prevalence of HAV, HEV and co-infection in pregnant women with hepatitis was 2 (1.6 %), 29 (24.5 %) and 1 (0.8 %) respectively. The differences in the incidence rates of HAV, HEV and HAV-HEV co-infection between pregnant and non-pregnant females were statistically significant (Table 2).

In our study, HAV infection was seen in the pediatric age group with highest prevalence in the 6- 10 age group. The prevalence of HAV declined after that. HEV infection was seen among all age group and maximum prevalence was seen in the age between 21-25 years (Fig 1). HAV and HEV infections were prevalent all-round the year with peak of cases with predominance seen towards the end of monsoon and beginning of winters (Fig 2).

DISCUSSION

Enteric hepatitis caused by Hepatitis A and Hepatitis E is an important public health problem in India. Sporadic hepatitis A virus (HAV) and hepatitis E virus (HEV) infections as well as waterborne outbreaks are frequent in the country.[8] Hepatitis A virus exposure typically occurs early in life, when the infection is often subclinical. Serological studies in India have demonstrated a consistent pattern of high HAV exposure during childhood, with more than 80% of children demonstrating antibodies against the virus by age of 10 years.[9] This high exposure to the virus is because of the lack of proper sewage disposal and poor sanitation conditions which lead to contamination of water sources.

In the present study 439 patients were clinically diagnosed with AVH, the seropositivity of AVH was found to be 49.6% (HAV 23%, HEV 22%, coinfection 4.5%)which is as reported in other AVH studies from Mangalore by Joon et al.[10] as 29.9% (HAV 19.3%, HEV 10.54%, coinfection 11.55%), and as 31.5% (HAV 13.3%, HEV 17.3%, coinfection 0.8%) in a study by Radhakrishnan et al. from South India.[11] In a study from Uttarakhand by Kalita et al., 37.6% (HAV 14.7%, HEV 28.0% Combined 5.2%) of the AVH patients had a reactive viral marker.[12] Globally, HAV is considered as the most common cause of viral hepatitis. Studies from different parts of India have identified HEV as the major cause of AVH and more common than HAV.[13] Several studies from India and abroad have reported a varying prevalence ranging from 1.7% to 67% for HAV and 12.6% to 78.6% for HEV.[14-16] Variation in positivity could be due to differences in the study population and living standards. Our study population represents the lower socioeconomic strata of the city. A Co-infection rate of HAV and HEV was 4.5% in our study. Co-infection rates vary from 1.3 to 11.5% in different studies from India. [9,17] It is important to test all viral hepatitis patients for both viruses as co-infection could affect the prognosis of the patient. Co- infection has been reported to cause complications such as hepatic encephalopathy with adverse outcome. [18]The prevalence of HAV infection was 28.2% in males and 19.4% in females in the present study. It was statistically not significant. Some studies have shown male predominance of infectious hepatitis, various others have found equal prevalence of HAV & HEV in both sexes.[9,13]

Among children aged 6-10 years, HAV infection was the highest and was not seen beyond 21 years of age. On the other hand, in age groups of 21-25 years, HEV positivity was higher than that of HAV in our study. A multicentre study by ICMR has reported similar pattern.[9] The HEV infection preferentially reaches teenagers and young adults. With rapid socioeconomic development, the age of acquiring HAV infection in some parts of India has recently undergone epidemiological shift from early childhood to adolescence and young adulthood. However, in our study population, the poor sanitary conditions and non-availability of clean drinking water have led to the exposure of the population in early childhood.

In our study, HAV and HEV infections were prevalent all-round the year with peak of cases with predominance seen towards the end of monsoon and beginning of winters. Earlier studies have shown higher positivity during June to November, compared with the period from December to May. However, HEV exhibited less seasonal variation throughout the year.[9]

In the present study, the prevalence of HAV, HEV and co- infection amongst pregnant women was 1.6%, 24.5% and 0.8% respectively. Statistical significance was observed between pregnancy and HEV infection. Khuroo et al reported high prevalence of HEV in pregnant women and also increased severity of disease.[19] Similar findings were reported in other study by Bansal Y et al[20]. Pregnant females constituted 14.3% of the HEV cases which is consistent with data from a previous study from India.[12] HEV is known to cause pregnancy-related complications in up to 30% of infected females Pregnant women with jaundice and acute viral hepatitis caused by HEV infection had a higher maternal mortality rate and worse obstetric and fetal outcomes like abortion, preterm labor, still births, low birth weight, than did pregnant women with jaundice and acute viral hepatitis caused by other types of viral hepatitis.[21]

A high prevalence of HEV and HAV together with co infection rate of 4.5 % mandates the screening for both viruses in all suspected cases of AVH. The clinical presentation of HEV infection is similar to hepatitis A virus (HAV) infection, with most cases being subclinical. However, HEV differs from HAV in that infectivity is lower though chronicity is known to occur in some pediatric solid organ transplant recipients with HEV infection. There is a need for long-term protection, which can be achieved through available hepatitis A vaccination. High level of personal hygiene, food hygiene, safe drinking water together with safe sewage disposal is the key requirement for prevention of enteric infections in our country.

Limitations Of The Study

1. Only the patients having ESI card were included in the study.
2. Clinical outcome of pregnant women with HEV could not be followed in this study.

Table 1. Prevalence Of Hepatitis A Virus, Hepatitis E Virus And Co-infection In Males And Females With Acute Viral Hepatitis

Infection	MALE (n=177), n (%)	FEMALE (n=262)	Total (n=439)	P value
IgM anti- HAV	50 (28.2)	51 (19.4)	101 (23)	0.43
IgM anti-HEV	41 (23.1)	56 (21.3)	97(22)	0.64
Co-infection	9 (5)	11 (4.1)	20 (4.5)	0.22
Total cases of AVH	100 (56.4)	118 (45)	218 (49.6)	0.59

Table 2. Prevalence Of Hepatitis A, Hepatitis E Virus And Co-infection In Pregnant Women With Acute Viral Hepatitis

Infection	Pregnant (n=118), n (%)	Non Pregnant (n=144), n (%)	Total (n=262), n (%)	P value
IgM anti-HAV	2 (1.6)	48 (33.3)	51 (19.4)	0.001
IgM anti-HEV	29 (24.5)	27(18.7)	56(21.3)	0.001
Co-infection	1 (0.8)	10 (6.9)	11(4.1)	0.001
Total cases of AVH	32 (27.1)	85 (59.0)	118 (81.9)	0.001

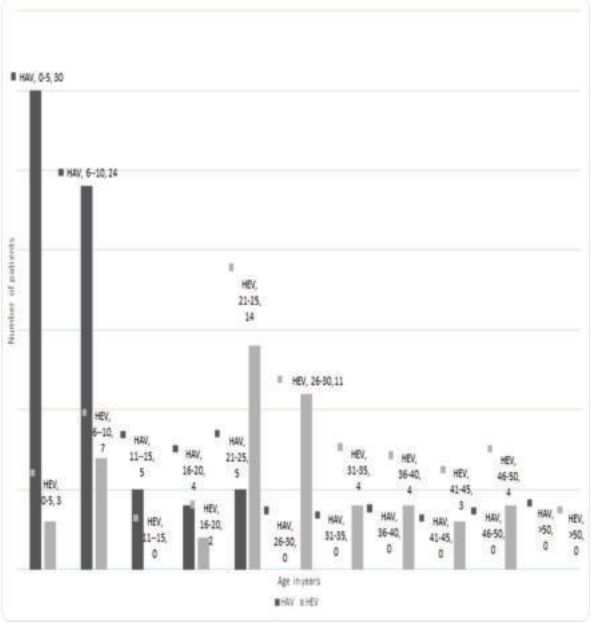

Fig 1: Age Dependent Prevalence Of HAV And HEV Serological Markers

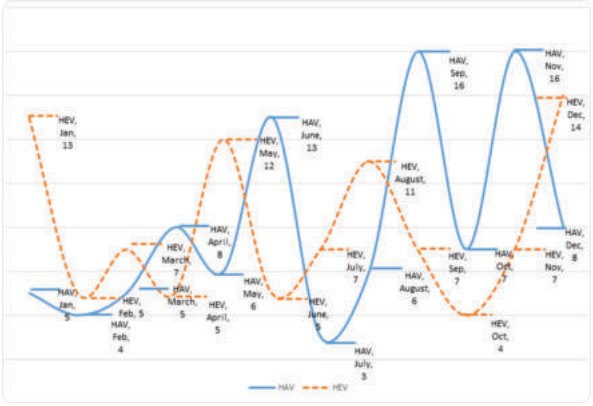

Fig 2: Seasonal Distribution Of HAV And HEV

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