

Seroprevalence and Co-infection of Hepatitis A and Hepatitis E Viruses in Children – A Hospital Based Study in Bangladesh

Bodhrun Naher¹, Khondaker Mobasher Ahmed², Rafiqul Islam³,
Wahiduzzaman Mazumder⁴, Rukunuzzaman⁵

Abstract:

Background: Viral hepatitis is a serious health problem globally and in endemic countries like Bangladesh. Viral hepatitis may present as mono-infection or co-infection caused by hepatitis A virus (HAV), hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus (HEV). Enterically transmitted viral agents like Hepatitis A virus (HAV) and Hepatitis E virus (HEV) are common causes of viral hepatitis in developing countries. As the routes of entry are similar double infections by both agents are common. Co-infection with two or more viruses may lead to serious complications and increased mortality. **Objective:** 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. **Methods:** This is a retrospective cross-sectional study of a 2 years duration carried out in the Pediatric

Gastroenterology and Nutrition department of BSMMU, Dhaka. Total 400 cases, presenting with Acute Viral Hepatitis were included in the study. Cases with suggestive history were tested for IgM anti-HAV and IgM anti-HEV respectively. **Results:** Out of 400 samples, 100 samples were positive for HAV and/or HEV infection with an overall prevalence of 24.7%. HAV & HEV seroprevalence in AVH cases were found to be 13.75% (55/400) and 5.75% (23/400), respectively. Dual infection of HAV and HEV was found in 5.25% (21/400) of study subjects. Both year, most of the positive cases are seen in the months of August and September. **Conclusion:** Seroprevalence of HAV was 13.75% , HEV 5.75% and dual infection of HAV & HEV 5.25% in the current study.

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

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1. Dr. Bodhrun Naher, Assistant Professor
Dept. of Pediatric Gastroenterology and Nutrition
Sheikh Russel National Gastroenterology Institute and
Hospital, Dhaka
2. Dr. Khondaker Mobasher Ahmed
Assistant Professor
Dept. of Pediatric Gastroenterology and Nutrition
Comilla Medical College, Cumilla
3. Dr. Md. Rafiqul Islam, Consultant (Pediatrics)
Al Insaaf Diagnostic Centre, Bhola.
4. Dr. Md. Wahiduzzaman Mazumder
Associate Professor
Department of Pediatric Gastroenterology and
Nutrition Bangabandhu Sheikh Mujib Medical
University (BSMMU), Dhaka
5. Dr. Md. Rukunuzzaman, Professor and Chairman
Department of Pediatric Gastroenterology
Bangabandhu Sheikh Mujib Medical University
(BSMMU), Dhaka

Address of correspondence:

Dr. Bodhrun Naher,
Assistant Professor, Department of Pediatric
Gastroenterology and Nutrition, Sheikh Russel
National Gastroenterology Institute & Hospital, Dhaka.
Email: bodhrunnaher@gmail.com,
Contact no: 01712270844

Introduction:

Viral hepatitis is a major public health problem in Bangladesh and worldwide. Cases have been reported throughout the country.¹ Primarily, viral hepatitis is caused by hepatitis A virus (HAV), hepatitis B virus, hepatitis D virus, hepatitis C virus (HCV) and hepatitis E virus (HEV) and dengue virus.^{2,3}

Hepatitis A is caused by HAV that affects liver⁴ and found worldwide. It is a non-enveloped 27-nmRNA virus in the genus Hepatovirus of the family Picornaviridae.⁵ HAV resulted in approximately 1.4 million cases worldwide annually and 27,731 deaths in 2010, according to the World Health Organization (WHO)⁴. Since the introduction of the hepatitis A vaccine and the start of mass vaccination in several countries in the 1980s, hepatitis A incidence has declined substantially, not only among vaccinated children but in the population as a whole^{2,3}. HAV and HEV infections are endemic in many low-income settings. In Asia, many countries have been reported as low, moderate, or high endemic regions for HAV infection^{4,5}. Regions of high endemicity include Bangladesh, as well as India, China, Nepal, Pakistan, Myanmar, and the Philippines⁶.

On the other side, hepatitis E is caused by the HEV that is a non-enveloped, positive-sense, single-stranded ribonucleic acid virus in the genus *Hepevirus* of the family *Hepeviridae*.⁵ Globally, there are around 20 million hepatitis E infections each year are being reported, over which 3 million cases are symptomatic.⁶ Around 56,600 deaths/year are related to hepatitis E.⁶ 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

Mode of transmission of HAV and HEV is via feco-oral route, mainly through contaminated water. Outbreaks and sporadic cases of hepatitis A and E occur globally but are closely associated with unsafe water, inadequate sanitation, and poor hygiene and health services in resource-limited countries. Hepatitis A and E are usually self-limiting diseases but can develop into fulminant hepatitis (acute liver failure).^{2,4,6}

HAV mainly affects infants and young children in developing countries, whereas HEV primarily affects older children and young adults.^{7,8,9} Clinically, hepatitis A and E infections may present as asymptomatic infection or mild hepatitis or subacute liver failure.^{10,11}

In patient with preexisting chronic liver disease, both HAV and HEV infection can worsen the condition. The clinical course of HEV is more problematic than HAV infection, primarily in pregnant females, contract disease in the second and third trimester. Therefore, HAV-HEV co-infection can lead to serious complications and increased mortality because of acute liver failure in patients in children as well as adults.^{12,13}

Although clinical diagnosis of co-existence of HAV and HEV viruses as a cause of viral hepatitis is difficult and cannot be differentiated with mono-infection, laboratory diagnosis either by serology and polymerase chain reaction (PCR) can be a useful tool in the diagnosis of simultaneous presence of both the viruses.^{11,14}

In our study, we have studied the seroprevalence and co-infection of HAV and HEV infections in various age groups of children. Study on seasonal variation of HAV/HEV infections was also included in the study.

Methods:

This was a retrospective study spanning a period of 2 years (April 2019 to March 2021) which included a

total of 400 patients. Patients of 0-15 years of age attending BSMMU (indoor and outdoor) with a clinical diagnosis of acute viral hepatitis, recorded in register book were included in this study. About 3-5ml serum was collected and were tested for HAV and HEV immunoglobulin M (IgM) antibodies. HAV IgM and HEV IgM antibodies were detected by Enzyme-linked immunosorbent assay (ELISA) kits (DRG International, Inc., USA), according to manufacturer instructions. Data were collected in a Microsoft excel sheet and analyzed by using SPSS version 25. 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 400 samples, 100 samples yielded reactive ELISA, 79 being single agent (HAV or HEV), and 21 mixed (Both HAV and HEV) which was shown in Table 1 and Table 2. Among 100 positive cases of either hepatitis A or hepatitis E or both, 22 cases were <5 years, 53 cases were 6-10 years and 25 were in 11-15 years of age (Table 1).

The overall prevalence of HAV and HEV infection was found 24.7%. The prevalence of HAV infection was found 13.75%, HEV infection 5.7% and HAV/HEV co-infection was 5.2% which was depicted in Table 3. Figure 1 showed the seasonal variation of HAV/HEV positive cases.

Table-I: Age-wise distribution of HAV and HEV positive cases

| Age group | Total cases studied | Only HAV positive | | Only HEV positive | |
|-----------|---------------------|-------------------|--------|-------------------|--------|
| | | Male | Female | Male | Female |
| <5 | 22 | 6 | 6 | 3 | 2 |
| 6-10 | 53 | 18 | 12 | 8 | 5 |
| 11-15 | 25 | 9 | 4 | 3 | 3 |

HAV: Hepatitis A virus, HEV: Hepatitis E virus

Table-II: Age-wise distribution of HAV and HEV co-infected cases

| Age group | Total cases studied | Both HAV positive & HEV positive | |
|-----------|---------------------|----------------------------------|--------|
| | | Male | Female |
| <5 | 22 | 3 | 2 |
| 6-10 | 53 | 5 | 5 |
| 11-15 | 25 | 4 | 2 |

HAV: Hepatitis A virus, HEV: Hepatitis E virus

Table-III: Prevalence of HAV, HEV mono infection and Co-infection by HAV & HEV

| | Number of cases | Prevalence (%) |
|-------------------------|-----------------|----------------|
| HAV positive | 55 | 13.75 |
| HEV positive | 24 | 5.7 |
| HAV & HEV both positive | 21 | 5.2 |

Table-IV: Comparative evaluation of HAV-HEV co-infection in different studies

| Study | HAV and HEV co infection |
|---------------------|--------------------------|
| Das et al. [21] | 5.31% |
| Sarguna et al. [22] | 5.31% |
| Jain et al. [23] | 8.61% (23 cases) |
| Arora et al. [24] | 7.5% (5 cases) |
| Poddar et al. [25] | 7 per cent (12 cases) |
| Our study | 5.2% (21 cases) |

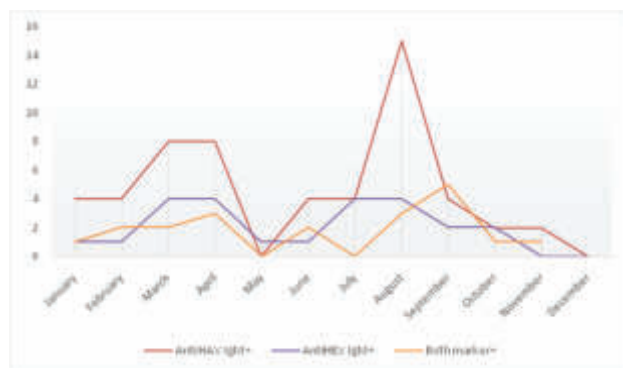


Figure-1: Seasonal variation of HAV/HEV positive cases

Discussion:

Globally, HAV is found common cause of viral hepatitis^{15,16}. In the present study, 24.7% (HAV 13.75%, HEV 5.75% and both 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% which is similar to our study.¹² 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 A seasonal trend was observed with a higher incidence in May to September (summer and rainy season).¹⁵ 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

Age-wise distribution of HAV and HEV IgM positive cases is depicted in Table 1. Age-wise distribution of HAV and HEV co-infected cases is illustrated in Table 2. Probability of lower HEV infection rates in children may be due to: (1) Anicteric HEV infections, therefore, children can go unnoticed.¹⁹ (2) Subclinical HEV infections in the endemic area make children more immune and adult more vulnerable for HEV infection.^{13,20}

Co-infection with HAV and HEV was found in 21 cases with the seroprevalence of 5.2%. It is similar in various other studies also^{21,22,23,24,25} shown in Table 4. Co-infection with HAV and HEV does not affect the prognosis of the patient much as these cases usually resolve with conservative treatment but in rare cases may lead to acute liver failure or hepatic encephalopathy.^{12,13,22} Although it is always a difficult to diagnose HAV/HEV co-infection clinically and by biochemical analysis, serology and PCR may help in timely diagnosis and identification of causative agent and support in prevention and management of acute liver failure in children in Bangladesh.

Seasonal variation of HAV and HEV was also studied as depicted in Figure 1. Cases were reported throughout the year as these infections are endemic in Bangladesh, with the peak of maximum number in August that is the rainy season. It is possible that cross contamination of drinking water with sewage could be more common during rainy season.²⁶ Both HAV and HEV prevalence were detected higher in males than in females which

had correlated well with another study. Outdoor and social activities of males may make them more vulnerable for the exposure than females.²⁷ HAV and HEV infections are enterically transmitted and have similar risk factors, therefore the most effective method to control viral hepatitis is to prevent infection. That can be done by interrupting the route of transmission and focusing on proper sanitary condition, hygiene, and public education.²

Simultaneously vaccines can be used as a preventive strategy. Although HAV vaccine is in the market but not easily accessible and extremely high prevalence of anti-HAV antibody in the general population make it less cost effective for mass immunization in country like Bangladesh, can be used in risk population like during onset of epidemics, chronic liver disease patients, travelers visiting endemic areas, etc. As HAV infection is common in younger children, inclusion of single dose inactivated HAV vaccine in immunization schedule of children can be useful.^{2,3,11}

No specific treatment is available, complete rest following infection is important for recovery. Infection resolves without any sequel most of the time but in rare case of acute viral hepatitis or fulminant liver failure, liver transplantation is the end treatment.^{3,13}

Conclusion:

Seroprevalence of HAV in pediatric AVH in the present study was 13.75%, HEV 5.75% and dual infection of HAV & HEV 5.25%.

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