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Hepatitis E: Epidemiology, Clinical Course: Paediatric Population North India

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Abstract

Objective: Hepatitis E virus is a hepatotropic virus,endemic in the developing world. It causes outbreaks and sporadic cases due to fecal contamination of water supplies, genotype 1 and 2 being responsible. Symptomatic disease in endemic hotspots is commonly seen in young adults (15-40 years). Asymptomatic/mild infection is common in children and in majority cases, disease goes unnoticed. With this background in mind, this study was designed to estimate the prevalence of HEV in a dedicated children's hospital and to describe the clinical profile of HEV positive patients.

MATERIAL AND METHODS: The prevalence of HEV in children was analysed between 2015 and 2020. Clinical and laboratory parameters of all patients who were admitted between this time frame were scrutinised.

RESULTS: A total of 19,147 samples were received for IgM HEV in 6 years. Fifty four HEV positive children required hospitalisation between 2015 and 2020. Thirty one of these were males(57%). Maximum admissions were seen in those aged more than 5 years of age(81%). Fever was the most common presenting complaint. Acute hepatitis was seen in 28 patients and fulminant hepatitis in 6 patients. Hepatitis A virus was the most common co-infection seen in these patients(20%) followed by enteric fever(9%).Immune deficiency was an underlying factor in 5 patients. Majority of the patients recovered from the illness(>90%).

CONCLUSIONS: HEV is more common in children aged above 5 years of age. It causes asymptomatic/mild illness in majority of the cases. Associated infection with other hepatotropic viruses like HAV may be seen in some cases. Progression to chronic liver disease may be seen in immune deficient children, hence follow up is necessary and vaccination should be introduced in this group of patients.

Keywords: Hepatitis E, Anti HEV IgM, hepatitis, hospitalisation, Hepatitis A virus

INTRODUCTION

Hepatitis E virus (HEV) belongs to the *Hepeviridae* family and isan important common cause of acute viral hepatitis worldwide [(1-3)]. Infection in humans is caused by 4 genotypes, type 1 and 2 are anthropotropic, prevalent in endemic countries and type 3 and 4 are zoonotic, found in developed parts of the world.The incidence of disease is higher in age group 15-26 years, when caused by genotype 1 and 2 while in the developed world it mainly affects individuals who are more than 50 years of age.[(4)] In the clinical perspective, HEV infections have diverse clinical manifestations, majority of infections being asymptomatic due to spontaneous clearance of the virus. Other varied presentations include acute and self-limiting hepatitis, acute-on-chronic liver disease, chronic hepatitis, cirrhosis, and liver failure. The classical clinical presentation of acute hepatitis in HEV infected patients includes jaundice, fever, flu-like symptoms, abdominal pain, vomiting, anorexia, and hepatomegaly. However, chronicity has been observed in immunosuppressed hosts and fulminant infection with mortality rates of around 25% are seen in pregnant women.[(5)]Additionally, HEV-associated extrahepatic manifestations involving various organs have been reported, although the causal link for many of them still needs to be proven.[(6,7,8,9)]

The incubation period of HEV infection is usually 2-6 weeks. [10] At the time of diagnosis, HEV RNA and anti-HEV IgM can be detected, followed by anti-HEV IgG antibodies. Anti-HEV IgM antibodies have a positivity for a short period of time (approximately 3-4 months), but sometimes it persists for a year.[11] HEV RNA can be detected in the blood after 3 weeks of exposure, and viral shedding lasts approximately 4-6 weeks in stool.[12]

In majority of children it causes an asymptomatic/mild illness. The data on clinico-demographic profile of HEV infected children requiring hospitalisation is limited. Hence, this study was designed to understand the demographic profile, clinical picture and disease outcome of hepatitis E infected paediatric population requiring hospital in-patient admission in North India.

METHODOLOGY

In this retrospective study, children infected with Hepatitis E virus from January 2015 to December 2020 were reviewed from the hospital data base. Clinical case records were accessed to evaluate relevant demographic details (age stratified as <1 year, 1-5years, >5 years, gender), clinical presentation (clinical features, presence of any underlying chronic condition/immune deficient state,association with other hepatotropic viruses, presence of any co-infection)and disease outcome (improved and discharged, referral to higher centre and death).

Anti-HEV IgM was detected in serum using solid phase capture ELISA (Bioneovan Co Ltd.) following the manufacturer's instructions. The levels of transaminases in the liver function tests were noted to determine the percentage of patients presenting with acute hepatitis. According to the American College of Gastroenterology, acute hepatitis was defined as severe elevation in transaminases (>15 times the upper limit,i.e., >250 U/L for SGPT and >125 U/L for SGOT). Co-infections namely, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus and Leptospirosis were also detected.

RESULTS

Over a period of six years (2015-2020), 10,451 serum samples were received from children (2months-12 years) visiting our OPD and IPD services for viral hepatitis testing. A total of 5.8%cases (610)were found to be seropositive for IgM HEV ELISA. Of the 610 IgM HEV seropositive cases, 93.6% (571) and 6.3% (39) were from children attending our out-patient and in-patient services respectively. A sharp decline in number of cases was observed from 2015 to 2016, which was followed by a gradual decline in 2017. The prevalence of HEV infection increased marginally in 2018. A peculiar finding was seen in 2019 when the number of patients requiring hospitalisation increased but the total number of patients infected with HEV decreased. The falling trend in prevalence continued in 2020, both for inpatients and outpatients (figure1).

Complete demographic and clinical records were analysed for 39 inpatient admitted cases with HEV infection. The distribution of HEV infection among children <1 year, 1-5 years, >5 years was 5%, 10% and 85% respectively.Majority of infection occurred among >5year age-group children with youngest being 2months old. Seropositive males (54%) outnumbered the females with male: female ratio being 1.16:1. The clinical profile, pre-disposing factors and clinical outcome of infected children were evaluated (Table1).

Fever >39ºC was seen in 80% of patients; it was of intermittent pattern and had duration of 1-2 weeks. Vomiting, yellow discolorations of skin, loose stools were other common manifestations noted. Acute hepatic injury with raised liver enzymes was observed in 57%(20) cases. Behavioural changes, altered sensorium and hepatic encephalopathy were observed as few of the neurological complications. Extra-hepatic manifestations such as acute pancreatitis, Henoch-Schonlein purpura, immune haemolysis and thrombocytopenia were seenin 20%(7) patients. Most common co-infections noted were Hepatitis A in 28% (11) patients followed by Enteric fever in 7.7 % (3) cases.

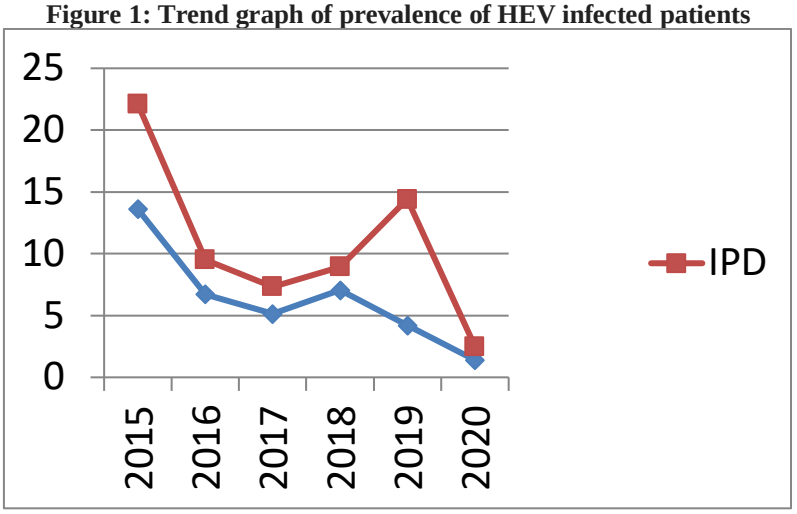
Average length of stay observed in the study population was 8.7days. 75% patients (30)were discharged without any complications while three were referred to higher centres for further management of complications. Unfavourable outcome due to hepatic failure was observed in two cases.

Table 1: Demographic and clinical profile of HIV infected IPD patients

Characterstic or Outcome	**No of HEV infected Children (n=39)**	**(%)**
Age		(5%)
<1year	2	(10%)
1-5 years	4	(85%)
>5 years	34	
Sex		54%
Male	21	46%

Female	18	
Predisposing Condition (n=35)		**Outcome**
Disseminated Koch's	1	Improved and discharged
Type 1 Diabetes Mellitus	1	Referred to AIIMS for evaluation
Acute Lymphoid Leukemia	1	Improved and discharged
Nephrotic Syndrome	1	Improved and discharged
Congenital hypothyroidism	1	Improved and discharged
CLINICAL PRESENTATION (n=35)		**%**
Fever	28	80
Vomiting	16	46
Yellowish discoloration of skin/sclera/urine	15	43
Pain abdomen	9	26
Loose stool	7	20
Weakness	3	9
Abdominal distention	2	5
Abnormal behaviour and altered sensorium	2	5
Nasal bleeding	3	9
Generalised swelling	3	9
Cough	2	5
Ecchymotic patches	1	2.8
Hepatic Encephalopathy	2	5
Extra-hepatic presentation Acute pancreatitis, Immune hemolysis and Thrombocytopenia; and Henoch-Schonlein purpura nephritis	7	20
Elevated liver enzymes (>250 U/L for SGPT and >125 U/L for SGOT): Defined as acute hepatic injury	20	57
Co-infection (n=35)		**%**
HEPATITIS A HEPATITIS B HEPATITIS C LEPTOSPIROSIS ENTERIC FEVER	11 1 0 1 3	(28%) (2.5) (2.5) (7.7)
Disease Outcome(n=35)		**%**
Improved and discharged	30	(75)
Referred to higher centre	3	(7.5)
Death: Mortality was seen due to hepatic failure in a six month old infant; and 11 year old girl presenting with hepatic encephalopathy	2	. (5)
Details missing	4	(10)
Average Length of stay	8.7 days	

Figure 1: Trend graph of prevalence of HEV infected patients



DISCUSSION

The data from present study demonstrates that infants and young children are susceptible to HEV infection. During the study period serological evidence of recent infection (HEV IgM ELISA) was observed in in 5.83% children aged 2months -12years. These rates are comparatively higher than 0.75%, as reported in children aged less than 10 years, from a study in South Indiaand comparable to a study from North India stating a prevalence of 9.79% .[13,14]

The literature on clinical presentation of HEV in children requiring hospitalisation is scarce, hence we tried to describe out the demographic profile, clinical picture and disease outcome in HEV infected children. A declining trend in overall prevalence from 2015(13.6%) to 2017 (5.13%) was observed which was followed by a rise in 2018(7.05%); a decline was noticed again till 2020(1.4%). This can be attributed to the varying infectivity of the predominant strain/genotype prevalent in East Delhi. A downswing in the prevalence of HEV in the year 2020 may be due to the ongoing COVID-19 pandemic that led to implementation of stringent precautions like hand washing, social distancing and avoiding social gatherings.

The profile of symptoms observed in our patients corresponds with the classical presentation described in literature.[15,16,17]Hepatic manifestations including fever,jaundice, flu-like symptoms, abdominal pain, vomiting and loose stools were present as predominant symptoms. Hepatocellular injury leading to acute hepatitis was evidenced in 57% patients. This is a little lower in comparison to 70% which has been described in a systematic review on HEV in children. [18]

Extrahepatic manifestations in the form of Guillain-Barré syndrome, meningoencephalitis, acute pancreatitis, severe thrombocytopenia, hemolytic anemia, and hemophagocytic syndrome, membranoproliferative glomerulonephritis, membranous glomerulonephritis, or nephrotic syndrome have been associated commonly with HEV genotype 3 infection.[6,7,19]Acute pancreatitis, when observed, has been associated with genotype 1 majorly as it has tropism for pancreatic cells, although reports due to genotype 3 have also been published.[6, 20]Extrahepatic manifestations as thrombocytopenia, meningoencephalitis and acute pancreatitiswere observed in 20% patients which are concordant with published data. Of note, in our study renal manifestations in form of HSP nephritis and nephrotic syndrome were also observed in 5.8%cases. Published studies on prevalent genotypes have found Genotype 1 to predominate in North India.[21] Life threatening disease in the form of hepatic encephalopathy is extremely rare in children and was seen in 2 patients. Neurological complications like encephalopathy are associated with genotype 3 and genotype 4. [4]

Thus, these varied presentations of HEVwarrant the need for a study to find the predominant genotype of HEV responsible for symptomatic infections in our geographical area.

Fulminant hepatic failure is rare inHEV infected children. Though, it has been described to cause acute decompensation in children with chronic liver disease.[22]In our study death due to hepatic failure was noted in two cases, but pre-existing chronic liver disease could not be ruled out.

Co-infections observed in the study were Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, enteric fever and leptospirosis. Dual positivity with Anti HAV IgM was seen in 28% of IgM HEV seropositive cases Hence,in our Indian settings, in a suspected outbreak of acute viral hepatitis , children should be tested for both, HAV and HEV infections.
Chronic HEV infection and cirrhosis has been described in immunodeficient children, especially solid organ transplant recipients.[23] Four of our patients had an underlying immunodeficient state and such patients need to be followed up to look for the development of a chronic state. Further studies are required to access the chronicity of infection in HEV

infected paediatric population requiring inpatient admission. Progression to chronic liver disease may be seen in immune deficient children, hence follow up is necessary and vaccination should be introduced in this group of patients. Studies ascertaining the predominating genotype of HEV circulating in paediatric population are also imperative to understand the varied disease presentation in children.

CONCLUSION

The prevalence of HEV in less than 15 years of age remains low. Symptomatic disease is more common in >5 years of age and has hepatic and extrahepatic manifestations as described for adults. Outcome is favourable in majority of cases. Associated infection with other hepatotropic viruses like HAV may be seen in some cases. Progression to chronic liver disease may be seen in immune deficient children, hence follow up is necessary and vaccination should be introduced in this group of patients.

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