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Route of Transmission of Infection and Virus Genotype leading to "Viral Hepatitis Outbreak in East Singhbhum"

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Abstract

Background India is an endemic zone for hepatitis E virus (HEV), which is associated with both epidemic and sporadic infections. However, sporadic cases of HEV infection also occur during inter-epidemic periods. This outbreak investigation aimed to detect the cause of viral hepatitis and the source of infection .

Material and methods Blood samples and clinical information were collected from 101 patients of both sexes and different ages with acute viral hepatitis (AVH) at Dadkidih, Jamshedpur during house to house survey. Samples were tested for hepatitis B virus (HBV) surface antigen, anti-hepatitis C virus antibodies, anti-hepatitis A virus IgM, and anti-HEV antibodies (IgM and IgG) by capture ELISA. Water samples; .had been collected from 6 different areas for virological analysis as per the guidelines provided by **the National Institute of Virology, Pune** by molecular detection **Result:** Out of 101 patients, 56 patients were found positive for HEV IgM and 1 for HAV IgM. All were negative for HBsAg and HCV total Ab.Out of 6 water samples collected from different locations HEV and HAV RNA was detected in three samples. The HEV strain found was genotype 1and of HAV it was genotype 3A

Conclusion: To the best of our knowledge, this is the first documented epidemiological study of acute sporadic hepatitis with HEV in the state of Jharkhand, India, indicating that this state is an endemic zone for HEV infection. HEV is the leading cause of non-A, non-B enterically transmitted acute viral hepatitis in this outbreak transmitted through drinking of contaminated water.

INTRODUCTION

Currently five hepatotropic viruses, i.e., hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV) causing viral hepatitis are known till date. Viral hepatitis is a major health problem worldwide and can be caused by any of these 5 different viruses [1]. Hepatitis E virus (HEV) infection is one of the most common public health problems in areas all around the world, resulting large-scale outbreaks of acute hepatitis. HEV of genus *Hepevirus* is a non enveloped RNA virus. It was *firstly* recognized in the early 1980s [2].These viral particles are relatively very stable in the environment and had been recovered from sewage samples [3]. Among all the viruses, HEV is now the major established etiological agent of enterically transmitted non-A, non-B hepatitis. HEV has been classified as the type species of the new genus Hepevirus in the family Hepeviridae. [1]The epidemic in New Delhi of 1955–56 was the first well-documented epidemic of hepatitis E infection in India affecting a total of 29,000 people. Intially Hepatitis A was considered as the virological agent responsible for the outbreak later retrospective study of the stored sera obtained during outbreak, a novel infectious agent was found responsible for the outbreak. [1] which later early in 1990s came to be as known as hepatitis E after identification and sequencing of the novel infectious agent the disease and its agent as hepatitis E virus (HEV).[1] The letter 'E' stands for 'enteric', 'epidemic', or 'endemic', which completely describes the epidemiology of HEV. In pregnant female in the third trimester the fatally rate is around 20% which is a typical pattern of HEV infection. [5,6] .Thus HEV had emerged as major etiological agent of enterically transmitted non-A hepatitis in India. The most of the cases of acute hepatitis in developing countries which leads to self-limiting disease is due to HEV. [7]. There are four different types of HEV genotypes which are mostly found in two different conditions (a) as large epidemics and sporadic cases in the areas where HEV infection is endemic. (genotype 1 [Asia and Africa], genotype 4 [Asia], or genotype 2 [Mexico and Africa]) (b) or as isolated clinical cases occurring among a sizeable group of mostly asymptomatic seropositive residents in developed countries (genotype 3). Till date it had been reported that genotypes 1 and 2 had been found only in humans, whereas genotypes 3 and 4 in animals. [8].Sporadic outbreaks are mostly responsible for the global burden of HEV but epidemic outbreaks are also witnessed. The study done of global burden in 2010 had evaluated 71% of the world's population (around 20.1 million people) were affected with HEV genotypes 1 and 2 in 2005, in nine regions. Part of the affected population which were symptomatic constituted of 3.4 million individuals, 70 000 deaths (included pregnant women),

and 3000 stillbirths. [9]. The death rate was higher among symptomatic pregnant women than symptomatic non-pregnant women. [9]. With the establishment of an efficient cell culture system study of the molecular biology of HEV [10]. and an effective vaccine, [11]. was possible. We still lack a reliable diagnostic procedure. However, anti-HEV antibody assays are widely available in European and Asian countries.

The clinical symptoms of all acute viral hepatitis are indistinguishable. The incubation period varies from 15–60 days, with an average of 40 days [12].The clinical manifestation of Hepatitis E includes with icterus, malaise, anorexia, fever, hepatomegaly, and pruritus. It is also marked with deviated laboratory findings like elevated serum bilirubin levels, liver enzymes, and mild increases in alkaline phosphatase activity. HEV-infected indivisual reflects broad clinical spectrum, ranging from asymptomatic infection to fulminant hepatitis. Studies of nonhuman primates have demonstrated that the clinical presentation, immunological response, severity of symptoms, and biochemical markers of liver damage increase with increasing inoculums. [13]

In a HEV infected patients Anti-HEV immunoglobulin (Ig) M is dectected in the test before the onset of symptoms and disappears between 4– 6 month period [8].Anti-HEV IgG appears in serum of affected individual soon after IgM response appears and may persist up to 12 years after infection In the market there many commercial assays available worldwide but no assay is currently approved by the US Food and Drug Administration (FDA). [14][9].

MATERIAL AND METHODS

Study Area

Dhatkidih is an area densely populated area located in Jamshedpur, Jharkhand. The majority of the population belonged to the Muslim community. The area is marked with overcrowding, open but cemented drains, and closely clustered houses. Residents of the village mainly depend on drinking water on Jusco's intricate network of pipelines run for over 600km and caters to the area. The lab routinely checks quality parameters based on standards set by National Accreditation Board for Testing and Calibration Laboratories.

The study was carried out at the Department of Health and Research Virus Diagnostic and Research Laboratory, Department Of Microbiology, Mahatma Gandhi Memorial Medical College, and Hospital Jamshedpur Jharkhand in August 2018

Study Population

Inhabitants of Dhadkidih

Case definition (as per the ministry of health)

Acute onset of jaundice and severe illness and absence of any known precipitating factors (other common symptoms may include dark urine, anorexia, malaise, extreme fatigue, and right upper quadrant of abdomen tenderness)

Ethical Issues

The Institute Ethics Committee had granted permission for carrying out this research work.

Data Collection

A questionnaire was framed to elicit demographic details of all patients who were suspected of hepatitis infection

Sample Collection

Blood samples were collected by venepuncture by strict aseptic method taking universal precautions. After proper positioning of the arm of the individual, under adequate illumination, the antecubital vein was made prominent by tying a tourniquet upstream of the vein and the area was disinfected using a spirit swab in a centrifugal manner. Around 5 ml whole blood was collected from each patient in a prelabelled sterile plain vacutainer using a disposable sterile needle and 5 ml syringe.

Sample Processing

Blood was allowed to clot for 30 minutes followed by centrifugation at 10000 RCF for 15 minutes to separate serum. Serum was pipette out into properly labeled microcentrifuge tubes.

Sample storage

All serum samples which tested positive for IgM HEV were aliquot into a newly labeled cryovial and stored at 4°C for a week while for long-term storage at -20 °C.

Outbreak Information

By local information it was found significantly, since the last week of July 2018, large number of peoples have been affected by Jaundice in the densely populated Dhatkidih locality, close to posh addresses like Northern Town and Circuit House, prompting the district health department to conduct health camps in the area and Jusco conducting its internal probe into the reason for the outbreak. Contamination of water was suspected with differing claims. Private and government hospitals, stand alone clinics, and pathological labs were witnessing a steady flow of patients with yellow discoloration of the skin, mucous membranes, and the whites of the eyes caused by increased amounts of bilirubin in the blood. One death was also reported suspected due to viral hepatitis which was later confirmed.

Outbreak Investigation

The investigation was carried at Dhadkidih. The investigation team of epidemic surveillance staff was formulated including staff of Integrated Disease Surveillance Program and VRDL consisted of doctors, epidemiologist, research scientists, and technicians who visited the affected areas. The team was escorted by the local doctors and community members to the houses of the reported cases at times. In addition, a door-to-door survey was conducted to identify any unreported cases. In schools, the administrators were informed and active case detection was carried out throughout the school and other organizations.

Laboratory Testing

The serum sample was tested with J Mitra HBsAg , J Mitra HCV total antibody ,Diapro HAV and Diapro HEV IgM capture ELISA kit at DHR VRDL NICED Kolkata and water samples were tested at NIV Pune tested with RNA isolation

RESULTS

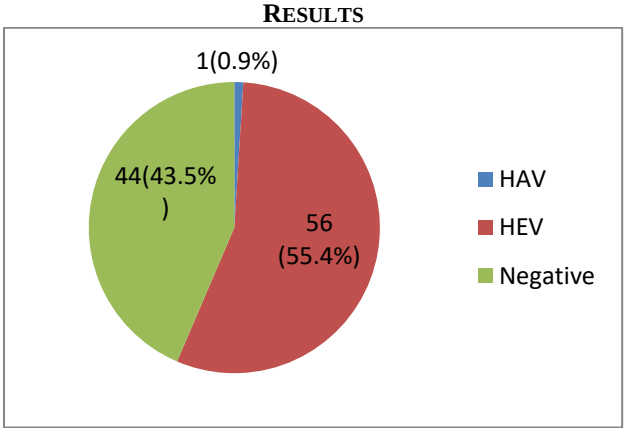

Fig: 1 Part of positive cases of each viral hepatitis

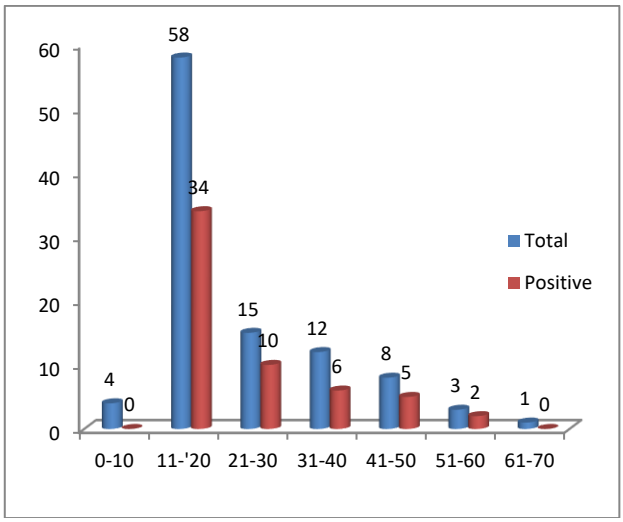

Fig:2 No of positive patients in different age groups.

Samples tested	HBV	HCV
101	0	0

Table: 1 Sample found negative for HAV and HEV were tested for HBV and HCV

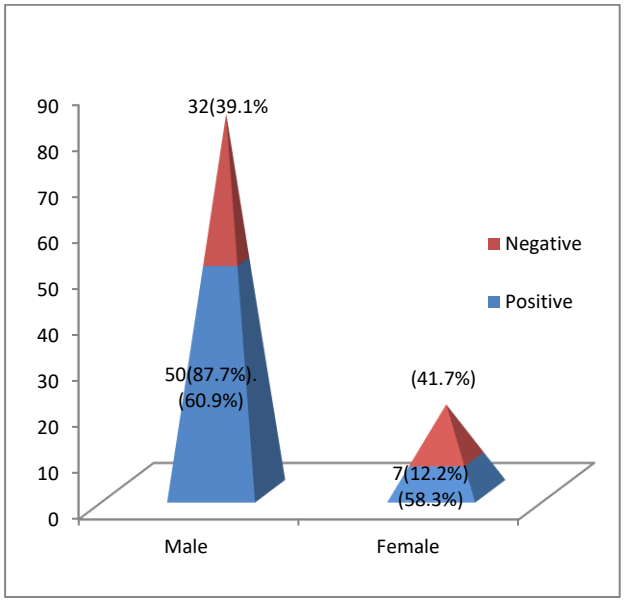

Fig: 3 Gender wise affected population

Detection of HepA and Hep E RNA in water means contamination of the water with. Hepatitis E and hepatitis A virus. Genotyping of the hepatitis A and E viruses was carried out by doing sequencing and phylogenetic analysis .Both HEV positive samples showed presence of Genotype 1 virus while the single HAV positive samples showed the presence of genotype 3 A virus

Table: 2 Water sample report by molecular diagnosis at National Institute of Virology

Sl No	Water sample specimen coolected from different	Hep-A RNA	Hep-E RNA
1	Haroon Iqbal House No 54 Line No 5 ,A Block Dhadkidih	Negative	Negative
2	Md. Safdar House No 29,B Block	Negative	**Positive**
3	Madarsa Faizul Uloom	Negative	**Positive**
4	A Block Line No 4 ,Holding No 16	**Positive**	Negative
5	Holding No 34,Line No 3 ,B Block	Negative	Negative
6	Inlet at Holding No 9 ,Road No 3 ,B Block ,Dhadkidih	Negative	Negative

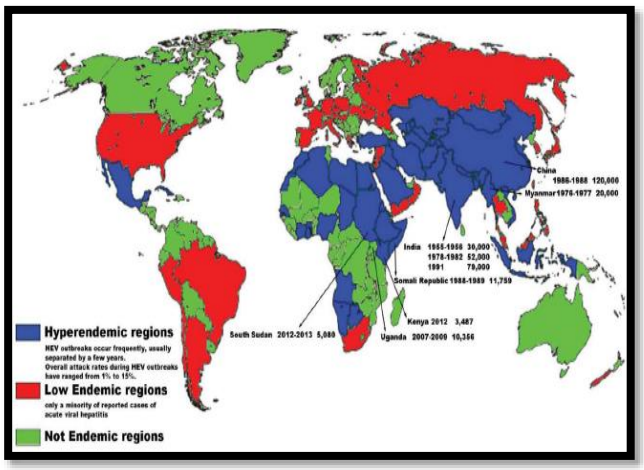

Fig: 4 Endemicity of HEV all over the world

Fig 5 Distribution of cases by area ,Dhatkidih, East Singhnhum, Jhatkhand March –Aug 2018 (Quaterly newsletter from NCDC)

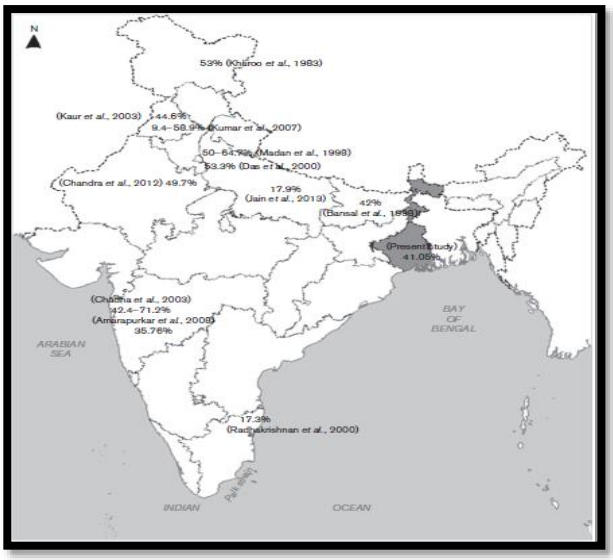

Fig: 6 HEV outbreaks were reported in different regions of India at different times. .

(Prevalence of Hepatitis E Virus Infection in West Bengal, Eastern India: A Hospital Based Study. Journal of Medical Microbiology May 2014 DOI: 10.1099/jmm.0.072249-0 · Source: PubMed)

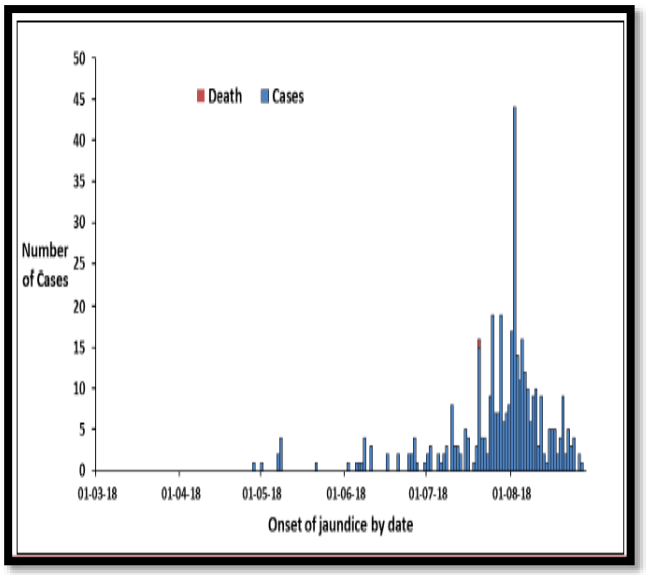

Fig : 7 Distribution of cases by date of onset Dhatkidih, East singhnhum,Jhatkhand March Aug 2018(Quaterly newsletter from NCDC)

Fig: 8 Water pipelines leakage and connection stealing (Quaterly newsletter from NCDC)

DISCUSSION

In India, 30%–60% of all sporadic cases of hepatitis are due to HEV infection. However, in cases in non-endemic regions and sporadic cases in endemic regions, it is often not possible to establish the route of acquisition of infection. Distinct patterns of epidemiology have been seen in the geographical regions where hepatitis E is endemic compared to where it is non-endemic. In areas of endemic disease, epidemics of hepatitis E are more frequent and are usually separated by a few years. Such outbreaks have been observed in China, the Indian subcontinent, southeast, central Asia, the Middle East, northern and western parts of Africa. These outbreaks are usually large, and several hundred to several thousand persons are affected. [15] A hospital-based investigation in West Bengal revealed the detection of anti-HEV IgG in 41.8% ie such a big percentage of the population under study had been exposed to HEV infection previously[16] However, in Egypt—where the prevalence of anti- HEV antibody in the rural population is high, compared with in other countries—severe cases of hepatitis E have never been reported [17]. This suggests little understanding of the role of viral-host factors in disease development following exposure to HEV. In our study, the outbreak was recorded from March 2018 to October 2018. A more variable incubation period of 2–10 weeks has been reported during hepatitis E outbreaks. Research among non-human primates has shown a direct association between infective dose and disease severity, but an inverse relationship to the incubation period.[15]

In our study total of 101 samples were collected within 2 days as representative testing samples to find out the reason for the outbreak. It was found 55.4 % (56) of people are affected with HEV infection and only 0.9% (1) were found affected with HAV infection. Rest 43.5 % cases were found negative. As per NCDC reports they identified 293 suspect cases, 53 probable cases and 56 laboratory confirmed cases of hepatitis E and one for hepatitis A and one death. Highest attack rate was observed in Madrasa area. (Fig: 5) .As per IDSP, India report (2018), from 2013 to 2018 an aggregate of 22671 cases of HEV have been reported, and out of these 152 deaths were reported. Similarly, 1667 cases of suspected hepatitis have additionally been reported with 1 death. [18]. None of the dual infection was found. Duel infection of hepatitis E and B were accounted in Delhi for the first time, and 26 patients with double infections showed that hepatitis B virus (HBV) infected chronic carriers patients were secondarily infected with HEV and resulted in acute hepatitis [19]. Chronic infection with HEV is rare, although chronic carriage may be more frequent in HIV-infected persons [20].None of such dual infection was reported in our study and none of the patient was suffering from chronic liver disease. Chronic liver disease following acute infection has not been documented in countries where HEV is endemic. However, there are anecdotal reports and case series of chronic hepatitis. E among indigenously acquired cases of hepatitis E in developed countries, especially among transplant recipients [21–24] and other patients who were severely immunocompromised [25, 26]. Other notable large outbreaks, resulting in significant morbidity, include outbreaks in India and China that resulted in 79,000 cases [27] and 119,000 cases [28, 29] , respectively. In endemic areas most commonly pregnant females are affected due to viral hepatitis In studies 37% of cases of acute viral hepatitis and 81% of cases of fulminant hepatitis was reported in pregnant females [30].Out of total affected females one fourth possessed obstetric complications, such as premature rupture of membranes and intrauterine growth restriction [30, 31].Death due to fulminant hepatitis or obstetric complications is the common cause in third trimester of pregnancy. Cause for such severity is still unknown [32] Morbidity and mortality of infants is also common due to vertical transmission of HEV infection [33]. Case-fatality rates range from 0.2% to 4%, but in pregnant women especially during third trimester it may range from 10%-25%[34] .In our study, no pregnant case was reported.

Transmission

Transmission in developing countries

In developing countries initially HEV infection was defined as a waterborne disease, transmitted orally through drinking fecal contaminated water. (Table 1) but in recent investigations fecal contaminated water had not been traced only to be the possible route of transmission .Thus other modes of transmission could be to the level of population immunity, sanitary conditions, living conditions, and other factors.[27,28] Till date four major routes of transmission of HEV infection had been justified are as follows (1) fecal-oral transmission due to contamination of drinking water supplies; (2) food borne transmission; (3) transfusion of infected blood products; and (4) vertical transmission. Currently person to person transmission evidence is also growing. HEV can be transmitted from person to person, even though this mode of transmission was not thought to contribute significantly to morbidity in epidemics. In a recent outbreak in northern Uganda, waves of secondary cases of hepatitis E followed primary cases within households, providing, for the first time, credible evidence of person-to-person transmission. But of all drinking contaminated water is the commonest route. The primary mode of transmission of HEV is fecal-oral which had been associated with several outbreaks in India. [26] In our study it was the same. The drinking water samples were collected from 6 different sites and send to the National Institute of Virology, Pune. The Real-time PCR of the water samples was done as well as sequenced. The result showed two of the sample of the site was contaminated with HEV virus and one with HAV virus. (Table 2) which depicted the contamination of drinking water. Overcrowding and refugee camps also worsen the situations.[29] In our study retrieval of drinking water with short handle from containers and hand-washing without soap before eating was found to be significantly associated with illness on analysis. Environmental investigations revealed that there were multiple sewage points which were leaking and water pipeline connection stealing. (Fig 8) In countries with substandard or poor quality sanitary conditions, HEV is the single most important cause of sporadic and epidemic hepatitis. In susceptible populations, high attack rates have been observed [26] In India many reports had been found of viral hepatitis outbreak due to contaminated water , poverty and lack of sanitation source e.g. in Bathinda city, Punjab (64.19% cases of HEV) ; in Nanital, Uttrakhand ; Two suburban (Nawanshahar and Palsora) of Punjab were suspected of viral hepatitis Fig . Vertical transmission of HEV at the rate of 78.9% (based on IgM, IgG anti-HEV, and HEV RNA positive) was confirmed in newly conceived babies 35. (Fig:6)

Transmission in developed countries

The sterile and clean conditions are unable to justify the locally-acquired cases of water-borne fecal-oral transmission hepatitis E in developed countries. In such areas the zoonotic transmission via ingestion of uncooked meat are the principal cause of HEV infection [35,36].The role of zoonotic transmission of HEV in endemic regions remains unclear. Recent research by different groups also suggests that food borne HEV transmission is possible concerning the ingestion of raw or undercooked meat and offal from swine.[37,38] In some countries like Japan people dietary habits of eating raw or undercooked pig livers has been associated with high seropositivity of HEV [39,40] High seropositivity is also associated with being a swine worker [41,42,43]; and with wild boar consumption in Germany [44].Many packaged commercial pig livers in US groceries had been found infected with HEV. [45]. But

pork consumption cannot be considered as one factors for raised seropositivity in countries like Japan and Germany [46]as they are more into these industries (packaged commercial pig livers) and its consumption while rarely in United States .It is very uncommon in most of the European countries .HEV in developed countries cannot be addressed to pork consumption. Thus this exposure alone cannot account for the high seroprevalence observed in many developed countries. Secondarily, data from NHANES in the United States did not find any statistically significant between association of persons consuming pork and pork products and persons who had not, such as vegetarians, orthodox Jews, and Muslims with HEV seropositivity but data from NHANES described that HEV seropositivity were significantly associated with other exposures, none of the (adjusted) odds ratios was 11.5. [47]. A report from China suggest the prevalence of anti-HEV IgG in the general human population around 32% among individuals who had frequent contact with swine while 21% among individuals who were in rare contact with swine. [48] .In a study of USA, a significant association was found between individuals and animal contact (pets in the home.) in HEV seropositive patients. [49,50]. Again this does not rule out the fact that pet owners did not had exposure to environmental contamination from different sources, including human waste. Thus above study cannot be taken under considerations.

. Similarly **person-to-person transmission** of HEV is very uncommon. but few cases had been reported [51] An anti-HEV IgG prevalence rate ranging from of 7.8% to 45% had been found in blood donors in endemic countries while in industrialized countries the prevalence ranged from 1–4% [52] HEV presence in plasma fractionation pools was reported in Sweden, Germany, and the USA.[53].Sexual mode of transmission had been also suggested in few of the studies eg HEV reported in homosexual men. [54, 55] In north Indian village hepatitis E was found in an active group of male homosexuals [56]

Seasonal variation

In our study the significant cases started in the month of May and took peak in the month of August. (Fig; 7) Outbreaks occur most frequently during the rainy season, due to overflowing drains and the use of contaminated water for drinking [57]. In a first systematic review on the seasonal variation of human viral hepatitis it was found there was no definite and consistent seasonal pattern but most of the time spring and summer peak was observed.[58] In south India , there was 94% to 100% HEV RNA nucleotide sequence similarity between HEV strains isolated from the sporadic hepatitis cases and strains isolated from sewage during the summer (81.2%) than the monsoon season (14.5%) ($P < 0.001$). [59] The cases of HAV and HEV infections were mostly diagnosed in winter months of January and February, followed by monsoons (August). Fecal contamination drinking water may have been the reason for outbreaks in winter months due to leakage in water pipelines. During the rainy season heavy run off during rains causes contamination of water leading to excess of HAV and HEV infections. Many outbreaks had been reported by other researchers during rainy season [60, 61]

Genotyping HEV strains and correlation between genotypes and transmission

Genotyping of HEV should be undertaken. The source of drinking water was considered the reservoir of infection. To confirm the fact as many people reported poor water quality supply the samples from different locations were picked and send for HEV PCR and genotyping. The result obtained after sequencing and phylogenetic analysis described that the water sample from two site were contaminated with HEV strain of genotype 1 E and one spot with HAV strain genotype 3A (Table: 2).HEV genotyping trend became common in 1990s which helped to conclude that outbreaks in developing countries infection, include those travelling to HEV endemic areas, living in overcrowded refugee camps, suffering from chronic liver disease and those handling non-human primates [62],the primarily responsible strain is HEV genotype 1, while genotype 2 in Mexico and western Africa {63,64] and sporadic cases in Asia spotted by genotype 4 [65].,HEV genotype 1 infection has been considered a waterborne infection transmitted through the drinking of fecally contaminated water [66,67]. In our study we were not able to sequence the patient samples but the water samples sequence were found carrying HEV genotype 1 strain. (Table: 2).The best way to confirm the source and infected host responsible is to find identicalness between strains of source and host .For example, in Hokkaido, Japan, HEV strains in the livers of infected pigs sold at one local grocery store had some variation from the HEV strains found in porcine organs identical to HEV genotype 3 and 4 strains recovered from the local human cases after genetic analysis [68]. One more study showed similar results of transmission of infection in a family and friend due to eating undercooked dear meat since both human and meat source shared similar RNA sequences .[69] . Genotypes 1 and 3 is associated with transfusion based transmission of hepatitis E [70, 71]. Human HEV genotypes 1 and 2 in developing countries has shown cross-species can be transmitted to nonhuman primates but not to other animals. In developed counties like Europe and the United States HEV genotype 3 are in zoonotic reservoirs and HEV genotype 4 in China and Japan [72,73] testing of pigs and other animals near outbreaks have not supported zoonotic transfer to humans [74,75].Research on neurological sequelae due to HEV infection is scarce, and reports come mainly from the Indian subcontinent, where genotype 1 infection is predominant. The role played by other genotypes in industrialized countries is unknown.

Affected Age group and Sex

In most of the HEV outbreaks overall attack rates ranges from 1% to 15%, generally with males at higher side than females**.**In our study age group 11-20yrs was in maximum affected and coming next was 21-30yrs age group while other groups were also affected.[Fig 2].It had been noted

that in some populations, HEV appears to be easily transmissible up to 76% of population among 1-20 years having serological evidence of being infected in past but not suffered from significant disease [76].Seroepidemiological evidence of HEV infection in developing countries, as determined by detection of anti-HEV IgG, has consistently shown that seroprevalence increases in direct proportion with increasing age eg survey in Pune, India, HEV prevalence increased with age and peaked at ~20 years of age [77]. Interestingly, studies in North Africa have shown a high prevalence of anti-HEV antibody in hospitalized children [78], but non hospitalized children had an anti-HEV antibody prevalence comparable to that in children of a similar age group from other countries. During outbreaks of hepatitis E, the disease attack rates are the highest among adolescents and young adults in the age group of 15–40 years. Infection with HEV in young children is less likely to lead to disease. The disease appears to be somewhat more common among men than among women. [27, 12]

Diagnosis

The onset of clinical symptoms in hepatitis E infection is marked by abnormalities in liver enzyme and liver function tests, such as elevated serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and gamma-glutamyltransferase. The enzyme levels are deranged due to severe hepatic synthetic defect and extensive hepatocellular necrosis..Histopathological changes are also observed in the liver during acute infection like focal necrosis and modest inflammation.

The cases of hepatitis E are indistinguishable from other acute viral hepatitis thus it is diagnosed by detecting elevated HEV antibody levels in the blood. Both IgM and IgG antibody response is elicited after HEV infection. The IgM anti-HEV response is rapid, within a month after infection and rising on the onset of biochemical abnormalities or symptoms.. Clinicians should promply consider hepatitis E in the differential diagnosis of unexplained jaundice since the window for HEV diagnosis may be a narrow, particularly among elderly persons, men, solid-organ transplant recipients, and those with compromised immune systems when there is lack of evidence for other causes of abnormal liver enzymes, [79].

Treatment and control strategy

Keystone of the prevention of the infection is to block the predominant mode of transmission which is proper treatment and safe disposal of human excreta, provision for safe drinking water supply, and personal hygiene improvement .Secondarily person-to-person transmission of HEV could be reduced again by good personal hygiene practice such as handwashing with soap will reduce transmission. .

Intervention can be done by developing vaccine [80] Many unsuccessful attempts for producing HEV vaccine was done .The attempt of administering normal immunoglobulin from plasma purified from populations of endemic region which was failure [81] probably due to low prevalence and low anti HEV titer. or results were uncertainAs the populations in regions where HEV is endemic have a relatively low prevalence and titer of anti-HEV, thus may not contain protective quantities of anti-HEV antibodies. [82].

Several recombinant proteins (HEV capsid protein) induce specific antibodies in animals.[83] Human HEV vaccine, a 56 kDa truncated HEV ORF2 protein had been produced from a recombinant baculovirus .The vaccine underwent the efficacy study in different phases .This vaccine has undergone safety and efficacy studies in humans. In phase I trial the healthy volunteers were dosed with recombinant protein in an alum-adjuvant formulation to induce the production of anti-HEV among healthy volunteers in a dose-dependent manner.[83] In the later phase II–III efficacy trials, nearly 2000 Nepalese Army who lacked detectable anti-HEV antibodies were indulged as volunteers and given 20 mg of alum adjuvant recombinant HEV protein or a matched placebo in three doses (at 0, 1, and 6 months) and they were followed up for more than 2 years.64.The vaccine efficacy rate of 95% was found .A efficacy rate reduced to 86% after administration of only two doses of the vaccine. Later in the follow up it was found the titers of anti-HEV had declined significantly below protective titre in 44% of subjects .Thus, further studies are needed to determine the duration of protection afforded by this vaccine. Unfortunately, this vaccine has not yet reached the market. Moreover cost of production is also a important point to be taken under consideration [84]. . Recently, a Chinese group prepared a new hepatitis E vaccine was developed by expressing truncated HEV capsid protein (corresponding to amino acids 376–606) expressed in Escherichia coli and was HEV 239 vaccine. All the volunteers were administered with three doses(20 mg each at 0, 1, and 6 months, respectively) who lacked anti-HEV seroconverted within a month .After complete dosage HEV infections were less frequent in the vaccine recipients than in the control subjects, indicating that the vaccine had a protective effect. A phase III trial is currently in progress. [85]

In-depth studies are required to be done to study the safety of the vaccine in pregnant women, children, and certain other groups, such as persons with chronic liver disease. The knowledge obtained till date is only on clinical disease rates not on HEV infection rate; thus it remains unclear whether the use of the vaccine will reduce rates of transmission of HEV in a community.The exact role of the HEV vaccines remains unclear. Vaccine would be useful for people travelling from non-endemic regions to endemic area, while in endemic areas a vaccine would be useful for pregnant women and persons suffering from chronic liver infections susceptible to HEV infection

None of the vaccine had been approved by the FDA or by any international regulatory agency. The major barriers to commercial production by international manufacturer hepatitis E vaccine candidate is the longest standing published data on efficacy, the start-up costs and apparent lack of market profitability. Trials for vaccine efficacy is still underway in several countries, including large efficacy trial in China, and perhaps these trials will

encourage further vaccine candidate development and eventual implementation in susceptible populations.

Action Taken

The IDSP and VRDL team examined the filtration and disinfection process at the central water tower. Thereafter, the team visited the lab and scrutinized water test reports. An intricate network of pipelines runs over the area and caters to many people. The team also toured Dhatkidih and checked the water supply. It showed how tapping from the main supply line had led to leaks and contamination.

CONCLUSION

HEV infection is majorly transmitted through fecal contamination of drinking water but there are many other transmission modes which somehow reflect the affecting genotype though it has only one serotype .It majorily affects young adults and mostly males .It is diagnosed by HEV IgM presence in blood .Raising sanitation and personal hygiene standards are the only way to reduce the transmission. We don't have yet any FDA approved diagnostic kits and vaccines.

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