Kathmandu University Medical Journal (2006), Vol. 4, No. 4, Issue 16, 530-544

Review Article

Hepatitis E in Nepal

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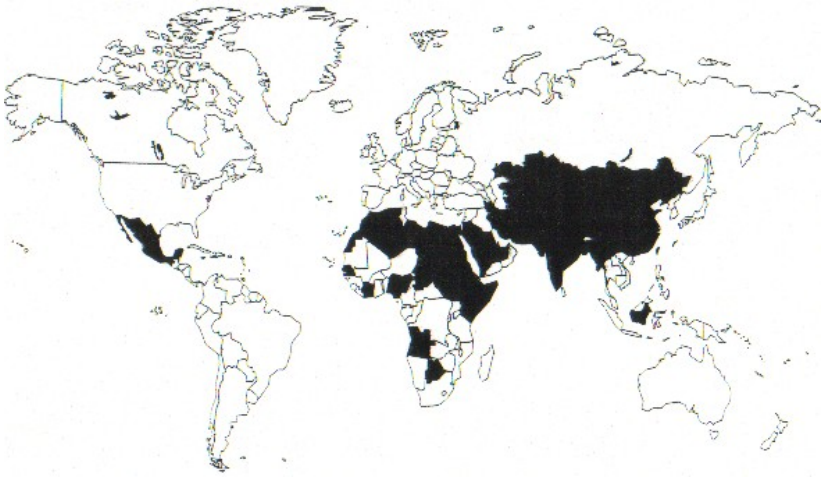
Abstract
Hepatitis E is an acute disease caused by hepatitis E virus that usually manifest as acute jaundice. The hallmark of the disease is its high incidence in young adults, and high mortality in pregnant women from acute hepatic failure. It is a waterborne infection and occurs sporadically or as epidemic outbreaks. Kathmandu valley is a hyper-endemic area for hepatitis E, where during last 30 years three large epidemics and many focal outbreaks have occurred. About 50% of the sporadic cases of acute hepatitis in Kathmandu valley are caused by hepatitis E. This paper describes the epidemiology hepatitis E in Nepal, and its clinical features and management.

Key words: Acute hepatitis in Nepal, Hepatitis E, Hepatitis E in pregnancy

Introduction

Hepatitis E (HE) is an acute self-limiting disease of the liver caused by hepatitis E virus (HEV) that manifest clinically as acute jaundice. Hall-marks of the disease are high attack-rate in young adults and high mortality in pregnant women. It is a fecal-orally transmitted waterborne disease and occurs sporadically or as localized or epidemic outbreaks. The infection is endemic in Asia, Africa and Latin America (Fig 1). It is a common cause of acute hepatic failure in Nepal.

Fig 1: Prevalence of Hepatitis in the World



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History of hepatitis E

Hepatitis E was previously recognized as epidemic or enterically transmitted non-A, non-B hepatitis[1]. The first well documented epidemic of water-borne hepatitis occurred in New Delhi in 1955-1956[2]. In the absence of serological tests for hepatitis it was then believed to be caused by hepatitis A virus (HAV), the only enterically transmitted hepatitis known at that time. When the stored sera from the epidemic were examined 25 years later, these were found negative for serological tests of acute HAV and hepatitis B virus (HBV) infection and the outbreak was labeled as epidemic non-A, non-B hepatitis[3]. In 1980 Khuroo reported a waterborne outbreak of non-A, non-B hepatitis in Kashmir valley[4]. Balayan and colleagues in Moscow in 1983 transmitted the disease to a volunteer who had evidence of prior HAV infection and isolated a spherical 27-30 nm virus-like particles (VLP) from acute phase stool samples by immune-electron microscopy (IEM), thus providing a direct evidence of a distinct etiologic agent of the enteric non-A, non-B hepatitis[5]. Virus like particles isolated from stool of a Nepali patient with non-A, non-B hepatitis during 1981-1982 epidemic was transmitted to marmoset[6]. In 1990, Reyes et al succeeded in molecular cloning of a portion of the genome of this virus, and named the new agent hepatitis E virus[7].

The first documented epidemic hepatitis in Nepal occurred in the Kathmandu valley in 1973 which affected more than 10,000 people, mostly young adults in the age group of 16 to 35 years age[8]. The disease was associated with high incidence of acute hepatic failure and high mortality among pregnant women[9]. Patients with AHF had high incidence of coagulopathy[10]. On the basis of negative serological tests for infections of HBV and ARBO viruses, this epidemic was then assumed to be due to HAV, the only enteric hepatitis known at that time. Another epidemic of hepatitis of similar nature that occurred in the valley in 1981 to 1982 was identified as epidemic non-A, non-B hepatitis. Virus-like particles isolated from the stool samples of a patient was transmitted to marmoset[11,5]. An epidemic of hepatitis of similar epidemiologic and clinical feature reoccurred in the valley in 1987 during which HEV was isolated from stool of a patient with non-A, non-B hepatitis[12]. On the basis of epidemiology and clinical features all epidemics of hepatitis in Kathmandu valley were retrospectively diagnosed as due to HEV[1].

Acute sporadic hepatitis is common in Kathmandu valley. Study done on sporadic hepatitis between 1982 and 1986 showed that 86% (546/638) of the patients were negative for serological markers of HAV and HBV[13]. The non-B hepatitis in these patients was presumed to be due to HEV infection, based on the findings of 27-32 nm VLP particles in stool by immune electron microscopy, and the absence of prolonged or persistent elevation of liver enzymes in these patients[13]. This assumption was supported by the finding of HEV RNA by RT-PCR method in these stool samples that had been stored at -80°C in 2003[14]. The nucleotide sequence of HEV in this sample was found identical with the Nepali strain isolated by Gouvea et al in 1998[15].

Between 1985 and 1986 five localized focal outbreaks of non-A, non-B hepatitis occurred in different institutions like Central jail, police training center, Military hospital and two localities in Kathmandu. These outbreaks were caused by local sewerage contamination of the drinking water[1,16]. Clinical, serological and epidemiological features of these outbreaks were similar to epidemic HE. Hepatitis E, thus, was recognized as the cause of all focal and epidemic outbreaks and the majority of the sporadic hepatitis in Nepal[1].

Is hepatitis E, that emerged after 1953 in Asia and after 1973 in Nepal a new disease? For last several decades, at least since 1923, hospitals in Nepal, such as Bir, Infectious Disease and Ayurveda had frequent admission of young adults with acute jaundice with high mortality among infected pregnant women[1]. As the adult population of Nepal has solid immunity against HAV (99% has anti-HAV IgG)[17], the common occurrence of acute infectious jaundice mainly affecting adults pointed to the presence of hepatitis E in the country at least since early 20th century. The enterically transmitted outbreaks of hepatitis with high attack rate among young adults and high mortality among infected pregnant women had occurred in Europe and North America during 17th, 18th and 19th centuries[18]. There is evidence that adult European population at that period also had a high degree of immunity against HAV infection[19]. Thus, it appears, hepatitis E was common in Europe before 19th century. With improvement in sanitation and hygiene in Europe and North America the disease after 20th century has become confined to Asia and Africa[20]. Recent findings of the presence of anti-HEV IgG in a very small percentage of indigenous population in industrialized countries (average 1.3%)[21], and in pigs and rats in both endemic and industrialized countries[21-24] indicated that HEV probably has a widespread prevalence in the world beyond tropical countries.

Hepatitis E virus (HEV)

HEV is a round, non-enveloped virus of about 30 nm in size (Fig 2). The genome of the virus is a single-stranded, positive–sense RNA of approximately 7.2 kb. It consists of a short 5' untranslated region (UTR) followed by three partially overlapping open reading frames (ORFs: ORF1, ORF2, and ORF3), and then a short 3'UTR terminated by a poly (A) tract (Fig 3). ORF1 encodes viral non-structural proteins, ORF2 encodes the capsid protein, and ORF3 encodes a small phosphorylated protein. HEV has been classified tentatively into four major genetic groups (genotype 1-4) (Fig 4). Genotype 1 is further segregated into five subgroups, subtypes 1a to 1e. Genome sequencing and phylogentic analysis of HEV isolated from Nepal was first done by Gouvea et al[15, 25]. The predominant HEV genotype seen in Nepal is 1a. Genotype 1c was observed only during 1996 to 1998[14]. Study of 250 HEV isolates from Nepal over ten years period from 1986 to 2006 showed some genetic changes in hepatitis E virus of subtype 1a [26, unreported data].

Fig 2: Hepatitis E virus

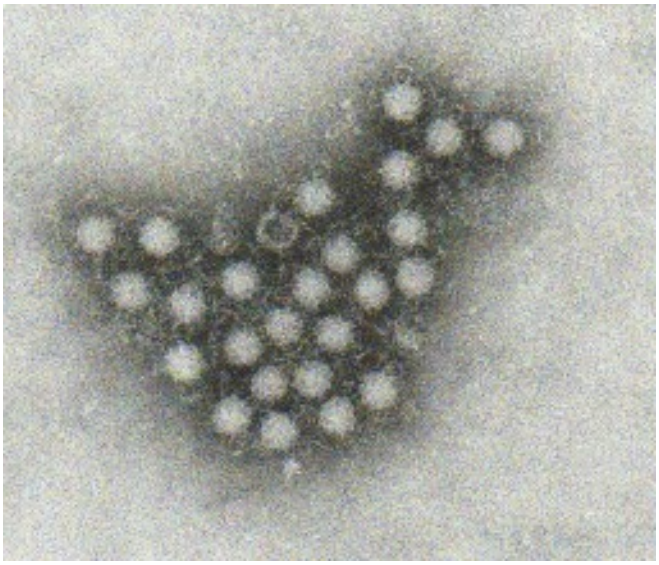


Fig 3: Genomic organization of HEV. There are three open reading frames (ORF 1 to 3). ORF 1 is nonstructural gene and ORF2 is structural gene (size not to scale)

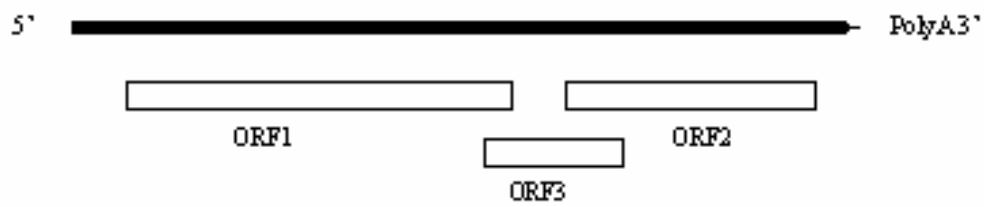
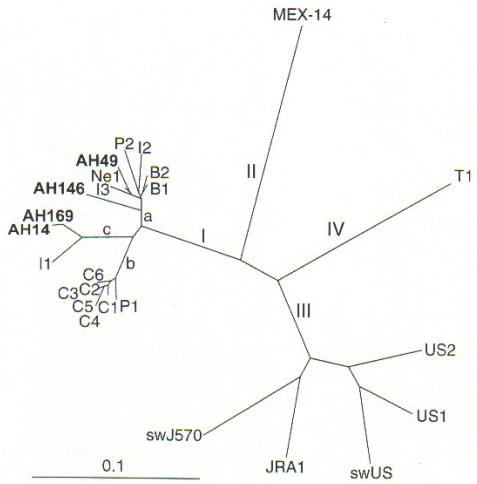
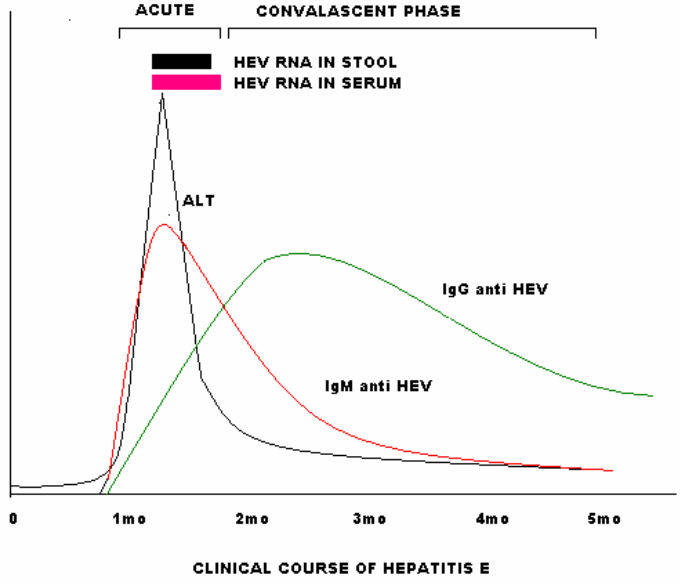


Fig 4: Phylogenetic Tree of HEV Isolates



HEV enters the host body enterically and infects hepatocytes via portal vein. It multiplies in the cytoplasm of the hepatocytes and is excreted both into blood and bile[27]. Viremia occurs in the first 8 to 10 days of illness. The virus excreted in the bile appears in the stool in the first two weeks of the disease. Protracted viremia (for up to 112 days) and prolonged fecal shedding of virus (for up to 52 days) may occur in a few[28, 29]. HEV infection is associated with marked elevation of ALT level in blood which reaches a peak in first few days of illness and then rapidly declines. HEV infection is associated with development of antibody to HEV. Anti-HEV of classes IgM, IgA and IgG appears in the blood and can be detected by ELISA method. IgM class antibody wane rapidly, but IgG persists for a long period (Fig 5). Anti-HEV IgM and IgA are indicative of acute phase of the infection[30]. Some patients however do not produce an anti-body response to HEV infection[14, 28]. Thus assay of both anti-HEV IgM and HEV RNA may be necessary in the diagnosis of acute HEV infection. Presence of anti-HEV IgG in the absence of antibody of IgM and IgA class indicates past exposure and presence of immunity against HEV infection. HEV is not a cytopathic virus. Hepatitis results from an immunopathologic mechanism caused by host immune response to the presence of infecting agent[31].

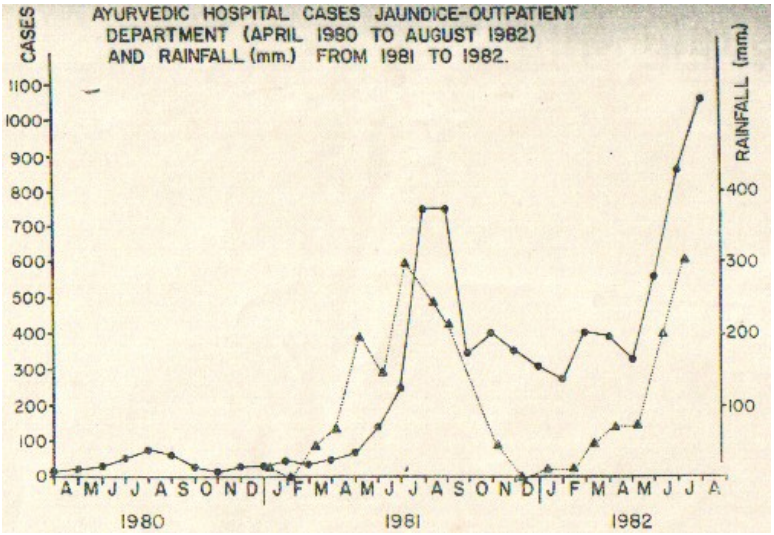
Fig 5: Course of Hepatitis E Infection



Epidemiology of Hepatitis E

Hepatitis E is endemic in South Asia, North Africa and Latin America. It is a disease of urban areas caused by sewerage contamination of drinking water. Two types of hepatitis E epidemics have been described - a short, sharp point source outbreak that last for a few weeks and a prolonged outbreak spread over several months with peak during rainy season. The epidemics in India and the focal outbreaks in Nepal were all short, sharp outbreak caused by a transient heavy sewerage contamination of the drinking water. The New Delhi epidemic of 1955-1956 lasted for six weeks and affected 29,000 people[2]. All epidemics in Kathmandu valley[1] and the epidemic in south Xinjiang in China[32] on the other hand were prolonged outbreaks spread over several months period. The Kathmandu epidemic of 1981-1982 was spread over 17 months and had peaks in the rainy season of both years (Fig 6). Similarly the Xinjiang epidemic lasted for three years from 1986 to 1988 and affected 119,280 people. Besides epidemics, HE also occurs in small focal outbreak and as sporadic cases. About 50% of sporadic hepatitis in endemic areas is caused by hepatitis E.

Fig 6: Hepatitis E Epidemic 1981-1982



Sporadic HE in Nepal

Acute sporadic hepatitis is common in Kathmandu valley. In 1982 to 1986, 86% of the sporadic hepatitis (546/638), 88% in adults and 58% children were presumed to be due to HEV infection[12]. After serological and molecular method of assay for HEV infection became available, Clayson et al in 1995 confirmed that HE indeed accounted for 88% (67/76) acute hepatitis in Kathmandu[21]. Similar study we did on 144 consecutive cases of sporadic acute hepatitis seen in 1997 detected IgM antibodies to HEV (anti-HEV IgM) and HEV RNA in 77 (50%) and 48 (31%), respectively. Consequently, 86 patients (56%) including nine HEV-viremic patients without anti-HEV IgM, were diagnosed hepatitis E[13].

HE remains the most common cause of sporadic hepatitis in the adults in this valley, though its incidence has fluctuated over the years from 10% to 62%. The sporadic form of the disease showed a seasonal pattern with increase in incidence in rainy season, July and August and showed preference for young adults with 70% of cases occurring among ages 16-35 years, and preference for males (75%) and preference for immigrants from other parts of the valley (30%).

Focal outbreaks of hepatitis E in Nepal

Many focal outbreak of hepatitis E have occurred in Kathmandu valley. It occurred in institutions like jails, police or military training centers, and hostel. The outbreaks were precipitated by sewerage contamination of the drinking water commonly caused by breakage of drinking water or sewerage pipes. Five focal outbreak of HE were recorded in Kathmandu in the winter of 1985 and 1986[1]. The outbreak in the police training center was traced to fecal contamination of the well where out of 1000

trainees 150 (attack rate 15%) got acute hepatitis. Sera of 35 patients were examined for evidence of recent (anti-HAV IgM) and past (anti-HAV IgG) infection with hepatitis A and acute hepatitis B (anti-HBc IgM). All had past exposure to HAV as indicated by presence of anti-HAV IgG. Except one patient who had acute hepatitis B (anti-HBc IgM and HBsAg positive), all were negative for serological tests for acute hepatitis A and hepatitis B.

Common occurrence of asymptomatic cases in hepatitis E was documented in a focal outbreak in Central Jail in November 1985 (15). Of the 33 patients with symptoms 27 had acute hepatitis. But marked elevation of ALT with normal serum bilirubin was detected in 16 out of 49 individuals without symptoms who volunteered for examination. Forty two of the 43 patients with acute hepatitis had non-A, non-B hepatitis (negative for anti-HAV IgM, HBsAg and anti-HBc IgM). All were positive for anti-HAV IgG- indicating past exposure to HAV. Among the jail inmates 120 were from Kathmandu valley and 980 were from outside the valley. Acute non-a, non-B hepatitis however was observed only among those from outside the valley. The attack rate in male was 4.1% and in female 1.0%. The attack rate in different age groups were as follows: 0% (0/15) below <15 years, 5.1% (36/705) among 16-45 years and 1.5% (6/380) in those above 45 years.

Though the disease is common in urban area, occurrence of fecal contamination of drinking water may result in an outbreak of the disease in rural areas also as shown by an outbreak in Jitpur village at the outskirt of Kathmandu in November 1997. Though in the past outbreaks of HE was reported only from Kathmandu valley, the Birganj outbreak that occurred in 2005-2006 has sent a warning signal that outbreak of HE may occur in other towns in Nepal if proper attention is not paid to drinking water supply system and sewage disposal.

Epidemics in Nepal

1973 epidemic[7-9]: The first recorded epidemic of hepatitis E in Nepal occurred in 1973 in Kathmandu valley. This epidemic was spread over a 10 month period from January to October, and reached a sharp peak during July and August monsoon rains. It affected 2.4% of the population, and caused more than 10,000 cases of acute icteric hepatitis, of which 70% were among young adults in the age group 16 to 35 years. At the peak of the epidemic, 118 pregnant women were hospitalized with acute hepatitis, of which 41 developed acute hepatic failure (AHF). The mortality among infected pregnant women was 25.4% (30/118) and fetal loss was 62%. On the basis of its epidemiology the 1973 epidemic was retrospectively attributed to hepatitis E[1].

1981-1982 epidemic[10, 11]: Five years later another epidemic occurred in the Kathmandu valley in 1981. This outbreak began in May 1981 and continued till September 1982, and had peaks in the rainy season of both years (Fig 6). It affected 7.6% of the households and 1.4% of the population of the valley and caused more than 12,000 cases of acute jaundice. As in previous epidemic, it predominantly affected young adults in the age group 16-35 years (70%) of which 70% were male. Twenty-five out of 119 pregnant women admitted to the hospital died of acute hepatic failure (mortality 21%). The epidemic was labeled as non-A, non-B hepatitis based on negative serology for acute hepatitis A and hepatitis B. A 27 nm virus like particles (VLP) was recovered from a patient's stool, which was transmitted to marmosets.

1987 Epidemic[32]: After a gap five years another epidemic occurred again in the Kathmandu valley in 1987. It lasted for a whole year with sharp peak in July and August. During this outbreak increase in the number of the cases of jaundice was observed in all hospitals in the valley except the Kanti Children Hospital. Of 7,405 patients seen in the hospitals 49.6% were recent immigrants to the valley from other areas of the country. Serological tests done in 393 patients showed that 10 (2.3%) had hepatitis A, 13 (3.1%) hepatitis B, and the reminder 370 (88.7%) non-A, non-B hepatitis. Spherical 32 nm VLP were recovered from stool samples in 3.

Sero-epidemiology of HEV in Nepal

Presence of anti-HEV IgG in the absence of anti-HEV IgM indicates past exposure to HEV. The seroepidemiology study done in 1999-2000 showed that the average prevalence of anti-HEV IgG among normal population in Nepal is 38% (Fig 7). It is about 16% in the age group of 1-9 years and gradually rises to 42% at 40-49 years and then decline. There is however a marked geographical difference in the prevalence of this infection in Nepal. It is more common in Kathmandu valley (38%), intermediate in major urban areas like Pokhara and Birganj (23%) and very low in rural areas, almost none in remote hilly areas like Myagdi and Taplejung (0%). Within the valley, 75% (186/249) local residents of Patan were positive compared to 38% (209/555) mixed floating population of Kathmandu (Fig 8). Based on the seroepidemiology study, Kathmandu valley is designated as the hyper-endemic area, other urban areas endemic and rural areas as non-endemic area for hepatitis E.

Fig 7: Anti-HEV IgG in Nepal

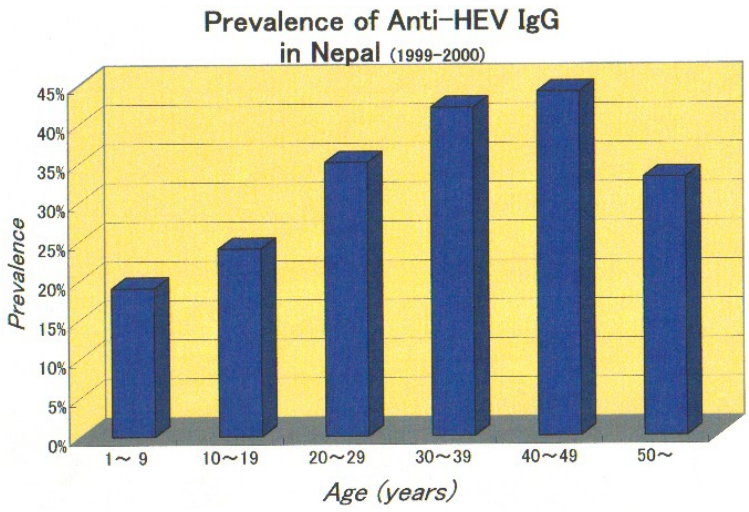
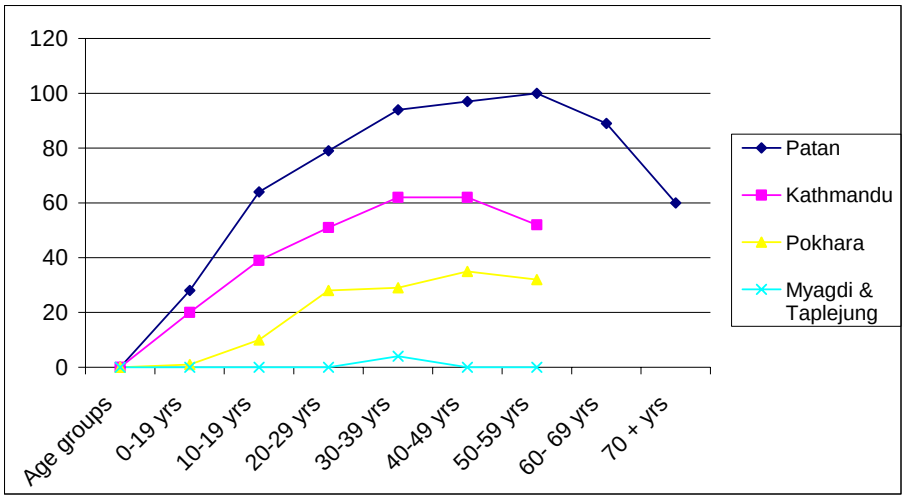


Fig 8: Anti-HEV IgG prevalence in different parts of Nepal



Factors responsible for spread of hepatitis E in endemic areas

Hepatitis E is essentially an ecologically determined disease of urban areas caused by fecal contamination of the drinking water. The following factors helps in the spread of the disease: (i) leaky water-pipes with intermittent flow that runs through polluted soil or in proximity of sewerage pipes, (ii) diversion of sewage into water pipes during road or house repair work, (iii) failure of the chlorination of drinking water at the treatment station and, (iv) diversion of sewage into water pumping station following flooding or heavy rains, and (v) crowded living conditions with unsafe water supply and disposal of human wastes.

What is the cause of recurrent epidemics of HE in the Kathmandu valley?

Hepatitis E is the sole cause of all focal and epidemic outbreaks in Nepal. There are two patterns of outbreak of HE in the valley. The focal outbreaks had compressed unimodal type of curve, where a large number of cases occurred within a few days or weeks, and was associated with sewerage contamination of drinking water due to broken sewage and or water pipes. In contrast the large epidemics were prolonged outbreaks that lasted for several months with peak in rainy season. There is no evidence that the Kathmandu epidemics were caused by unusual heavy rains or diversion of sewerage to water pumping station as it happened in India e.g. in the New Delhi epidemic of 1955-1956 or Kanpur epidemic of 1997. The drinking water in Kathmandu

valley however, showed widespread and all most continuous fecal contamination that increased during rainy season[33, 34]. Thus occurrence of massive water pollution was not found to be the cause of reoccurrence of epidemics. Pollution of drinking water in Kathmandu valley occurred equally both at epidemic and inter-epidemic periods. The pattern of acute hepatitis[12] and the seasonal distribution of cases during epidemics were similar to sporadic cases, with peak in the rainy season. Thus epidemics in Kathmandu valley were more like an exacerbation of the endemic state.

The proportion of patients with acute hepatitis and HE attending our clinic in last 10 years from 1996 to 2006 showed that it varied from 72 to 170 cases and 10% to 62% respectively. The incidence of AH and HE cases were highest in 1997 and 2003 and 2005 and the lowest in the years 1999 to 2001. The incidence of HE, thus increased from time to time and at intervals of about 5- 8 years it took an epidemic form like it happened in 1973, 1981-1982 and 1987.

What is the cause for the recurrence of epidemics of hepatitis E in the Kathmandu valley? For an outbreak of infection to re-occur in the same community either the population of the susceptible has to increase to a level sufficient to maintain an outbreak or the virulence of the virus has to change. Outbreaks of hepatitis E would occur in the valley (i) if the immunity following the infection is transient, or (ii) if the proportion of the susceptible population increases due to migration of non-immune population, or (iii) if the virus mutates and takes a virulent form from time to time.

Immunity following HEV infection: There is evidence that immunity following HEV infection is not short lived. Second attack of hepatitis E in the same person have been document only in a few, and occurred mostly after 5 to 10 years. Anti-HEV IgG was found to persist for 10 to 15 years after the infection in some patient we studied. Other investigators also detected long-lived protective antibody levels following acute infection with HEV[35].

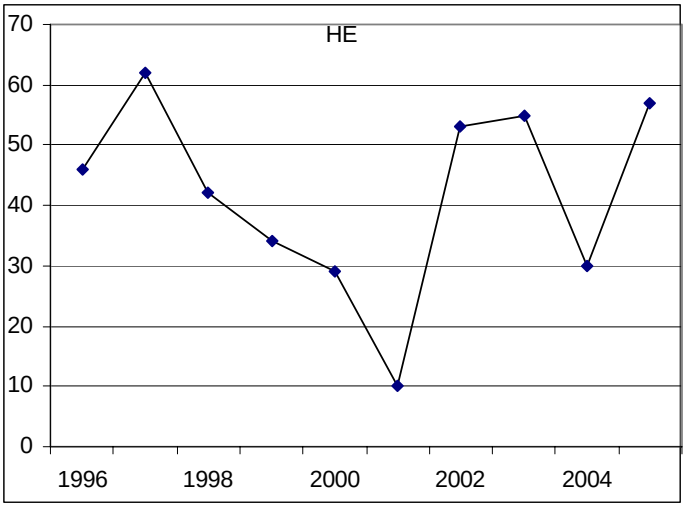
Genetic change in the HEV virus: There is evidence that HEV outbreaks are not caused by the introduction of a new strain of HEV in the community, either. Study of genetic changes of more than 259 HEV isolates from Nepal from 1996 to 2005 showed that all the isolates belonged to genotype 1, and except of 1996-1998 all belonged to subgroup 1a[26 unpublished information]. Minor genetic changes but no significant mutation was noted. The epidemics were thus not related to change in the virulence of the virus.

Increase in susceptible population by migration of non-immune population Hepatitis E is predominantly an urban disease and occurred rarely in rural areas. Sero-epidemiology study showed that the infection is highly endemic in Kathmandu valley but almost not existent in rural areas[36]. The vast rural population of Nepal is non-immune to HE. In 1987 epidemic, nearly half of the patients (49.6%) were recent immigrants to the valley from other areas[30]. In the 1985 Central jail outbreak it was noted that the infection spared those that belonged to Kathmandu valley and affected only those from outside the valley[16]. And those affected in outbreaks in police and military training centers were new recruits coming from outside the valley. Besides, it was noted that about 30% of the patients with sporadic HE in Kathmandu valley in last several years have from outside who had immigrated into the valley within last few years.

The internal migration of people in Nepal occurred mainly (81%) from rural to urban area[37]. Kathmandu, being the capital city with more facilities, has been a natural place for young adults from rural areas to come to for education, employment and opportunities since decades. Internal migration to the Kathmandu valley increased during Maoist insurgency which began in February 1996[38,39]. In last ten years the internal displacement induced by conflict became a significant social phenomenon in Nepal. However there is no reliable statistics on the number of conflict induced displacement in the country. But it is estimated that the number of internally displaced persons could be between 100,000 and 200,000[40]. The first wave of conflict induced displacement occurred at the onset of conflict in Feb 1996, and the second wave occurred with the escalation of the conflict after the imposition of 'state of emergency' in November 2001[39, 40].

The trend in the incidence of hepatitis E in the Kathmandu valley as monitored by Liver Foundation Nepal showed increase in the cases in 1996-1998 with peak in 1997, which declined till 2001 then peaked again in 2002 and 2003 (Fig 9). The trend in the prevalence of HE in the valley coincided with the waves of internal displacement following insurgency.

Fig 9: Prevalence of Hepatitis E (in percentage) among patient with Acute Hepatitis in Kathmandu valley from 1996 to 2005.



The high prevalence and frequent occurrence of outbreaks of hepatitis E in the Kathmandu valley thus appeared to be influenced by migration into the valley of the non-immune population from the rural areas. The high endemicity of hepatitis E in the valley is thus caused by combination of two factors, (i) the perpetual widespread contamination of drinking water in the valley and (ii) the increase in the susceptible population by internal immigration from other parts of the country.

Mode of transmission of Hepatitis E Virus:

In endemic areas hepatitis E is spread predominantly by contaminated water. But there is a possibility of other mode of spread for HEV also. About 25% rodents, dogs and swine, and over 10% of chickens and ducks in the Kathmandu valley have anti-HEV IgG (41). Some domestic and peri-domestic animals in Kathmandu valley thus may act as reservoir for the virus and there may be some opportunity for zoonotic spread of the virus in Nepal. There is evidence that hepatitis E is also a zoonotic disease[42]. Food-borne transmission of HEV through ingestion of raw or undercooked meat including liver and intestine from infected swine, dear or boar has been reported from Japan[43]. As HEV infection is associated with viremia and a substantial proportion of the patients with this infection are asymptomatic[16], there will also be opportunity for the spread of infection through blood transfusion.

Difference in the epidemiology of two fecal-orally transmitted hepatitis viruses, HAV and HEV:

Both hepatitis A and E are infectious hepatitis spread by fecal-oral route. While hepatitis A is highly infectious and almost all the Nepalese acquire the infection by the age of 5 years and develops life-long immunity against the infection[17], hepatitis E is less infectious, and in Nepal it is spread mainly by contaminated drinking water, and it is predominantly a disease of the young adults. Though hepatitis A transmission occurs very frequently in Nepal and is the common cause of hepatitis among foreign visitors from Japan and the West, it rarely causes disease in Nepalese adults[44]. The reason for this difference in the epidemiology of HAV and HEV may be due to the fact that HAV is very stable and hardy virus compared to HEV which is fragile and easily destroyed even by ordinary laboratory manipulation like freezing and thawing[45].

Clinical features of Hepatitis E

Incubation period of hepatitis E is about 4 to 6 weeks. HEV infection has a wide spectrum of presentation and it includes asymptomatic, an-icteric, acute icteric illness, cholestatic hepatitis, sub-acute hepatic failure and acute hepatic failure.

Acute Icteric illness: Majority of the patients with hepatitis E presents with acute jaundice. Other features of the disease are lethargy, dark urine, anorexia, nausea, and vomiting. Some has mild fever for initial a few days and mild upper abdomen discomfort and itching. Hepatomegaly is uncommon in hepatitis E. There is mild to moderate elevation of serum bilirubin, moderate to marked elevation of ALT (5 to 30 times above the upper limit of normal) and mild elevation of alkaline phosphatase (1.5 to 2.5 times above the upper limit of the normal) . Acute symptoms last for a few weeks. Serum bilirubin and ALT returns to normal usually within a month.

Cholestatic hepatitis: It is characterized by prolonged often deep jaundice with light colored stool and itching. This condition was frequently observed in male above the age of 40 years (Table 1). Though cholestatic hepatitis in some patient becomes very distressing causing insomnia, its prognosis is not bad. Cholestatic hepatitis needs to be differentiated from obstructive jaundice due to other causes of intra- and extra-hepatic billiary obstruction like ampullary carcinoma. Extra-hepatic bile obstruction is commonly associated with hepatomegaly, normal or mild elevation of ALT with marked elevation of AP and ultrasound evidence of intrahepatic bile ducts dilatation, whereas patient with cholestatic hepatitis E is usually not associated with hepatomegaly and has marked to moderate elevation of ALT and mild elevation of AP.

Table 1: Age groups of patients with cholestatic features-1987 epidemic

Age group	Number of patients	Number with Cholestasis	%
16-35 years	297	14	4.7
36-55 years	41	10	24.4
56 + years	12	5	41.7

(From: Shrestha SM - Enteric non-A, non-B hepatitis in Nepal: clinical and epidemiological observations. In: Shikata T, Purcell RH Uchida T - Viral hepatitis C,D and E, eds, Amsterdam, Elsevier Science Publishers 1991.)

Acute hepatic failure: Acute hepatic failure (AHF) in hepatitis E is characterized by sudden onset of encephalopathy within 4 weeks of the onset of illness. HE is the common cause of AHF in Nepal. This should be suspected if patient with HE becomes drowsy or develops abnormal behavior or altered sleep rhythm or suddenly become unconscious. Some patient develops coma, even before the onset of jaundice. AHF should be considered in the differential diagnosis of sudden onset coma in young people especially during HE outbreak, and look for jaundice and elevated ALT level. AHF is associated with very high mortality. Without intensive care management 90% of patient dies.

Subacute hepatic failure: Subacute hepatic failure (SHF) is another condition seen in patients with HE that is associated with high mortality. The condition is diagnosed when jaundice becomes deep and develops features of liver failure like ascites or encephalopathy between 4 to 24 weeks after the onset of illness. Development of deep jaundice in spite of declining ALT level and development of ascites has been found in HE patient with super added bacterial infection. Ultrasound examination in these patients showed thrombophlebitis of the hepatic portion of the inferior vena cava, the acute hepatic vena cava disease. Ascites in this condition is commonly associated with Gram-negative bacterial peritonitis. Early recognition and treatment of bacterial infection improves survival. So patients with SHF should have immediate culture of blood and ascitic fluid for aerobic organism, and ascitic fluid examination for total and differential WBC count.

Incidence of clinical profile of hepatitis E: Of the 370 patients seen during 1987 epidemic, 87% had acute icteric illness, 7.8% had cholestatic features, 1.6% subacute hepatic failure and 3.5% an-icteric illness. Acute hepatic failure was common among pregnant women. Of the total 310 pregnant women with acute hepatitis admitted to hospital during three epidemics in Kathmandu, 1973, 1981-1982 and 1987, 23.6% died of acute hepatic failure. Hepatitis E does not cause chronic liver disease. The pattern of clinical disease seen in HEV infection, their predilection to certain categories people like acute icteric illness in young adults, cholestatic features and SHF in male above 40 years of age, AHF in pregnant women, probably indicates that the outcome of this infection is determined by the host factors rather than by the dose or the virulence of the virus. Experimental study in animals also indicates that the hepatic damage in HEV infection is immune-mediated rather than direct cytopathic[31].

Hepatitis E in Pregnancy[1,9,10]

High incidence of death from acute hepatic failure in pregnant women is recognized as a distinct characteristic feature of hepatitis E. This was however noticed mainly during epidemic periods. AHF occurs in sporadic cases also, but in sporadic setting AHF may be due to HE or hepatitis non- A to E, and it occurs equally among male and non-pregnant women.

Pregnant women are not found to be more prone to HE, but the incidence of AHF is higher among pregnant women during the epidemics. During 1973 epidemic, out of 118 pregnant women with AH 41 (34.7%) developed acute hepatic failure. AHF

occurred within 4 weeks, mostly (63%) within 10 days of the onset of illness. It was more common in 3rd trimester (41%), compared to 1st trimester (20%) or 2nds trimester (26%). Majority of patients with AHF were young (78% were aged below 25 years age) and prime-gravida (70%) and came from rural background and were poor (93%) and were engaged in heavy manual work as farming at the time of the onset of AHF.

The common complications noted among the patients with AHF during 1973 epidemic were coagulopathy with bleeding tendency (75.6%), hypoglycemia (41%), hyperventilation (17%), cerebral edema and edema of legs. Though intravascular coagulation occurred it did not influenced the mortality. WBC count of at or above 12000 was noted in 34 out of 41 patients with AHF (83%) compared to 22% (17/77) without AHF. Of the 34 patient with high WBC count 43% had count above 20,000/cu mm. There was suggestion that probably 83% of the patients with AHF had bacterial infection. Study of immune response during HEV infection in pregnancy demonstrated an increase in CD8 T cell activation, upregulation of type 2 and a down-regulation of type 1 cytokine responses[46].

Table 2: Mortality in infected pregnant women during epidemics of hepatitis E in Kathmandu valley

Kathmandu epidemic	Total number persons with AH	Pregnant woman admitted with AH to hospital	Death in pregnancy	
			Number	%
1973	10,000	118	30	25.4
1981-1982	12,000	119	25	21.0
1987	7,405	73	18	24.6
Total		310	73	23.5

Mortality was 23.5% among a total of 310 pregnant women admitted to hospital in last three epidemics of HE[1]. Mortality correlated with the period of gestation. There was no death in first trimester. The mortality in 2nd and 3rd trimesters was 16.6% 32.4% respectively. Highest incidence of death occurred in the immediate postpartum period. Fetal loss among the infected pregnant women, which included abortion, stillbirth and maternal death before delivery was 60%, compared to4.2% among 893 deliveries in non-infected women in the same hospital during that period.

Postmortem examination done in six cases showed that the liver was considerably shrunken, pale and flabby and had wrinkled capsule. The histology showed massive necrosis of the liver cells. One showed pneumonic changes and microthrombi and hemorrhage in the lung. The kidney, suprarenals, heart and brain showed normal histology.

Acute hepatic failure in hepatitis E is common among pregnant women during epidemic period and occurred more frequently in 3rd trimester. It is common in prime belonging to poor socio-economic group and those engaged in heavy manual work. In the majority it is associated with bacterial infection.

Diagnosis of HEV Infection

HE is a common cause of acute hepatitis in young adults in developing countries. Persons presenting with acute jaundice or illness associated with malaise and anorexia or vomiting should have blood tests for serum bilirubin, ALT, AP and total and differential WBC count and anti-HEV IgM. Patients with HE have mild to moderate elevation of serum bilirubin, moderate to marked elevation of ALT level (5 to 30 times above the upper limit of normal), AP normal or mildly elevated (1.5 to 2.5 times above normal) and are positive for anti-HEV IgM. Diagnosis of acute hepatitis E is based on seropositivity for anti-HEV IgM or HEV RNA. Anti-HEV IgA also has equal diagnostic value[47].

In Nepal, during epidemics nearly 30% of the HE patients have super-infection with Gram-negative bacteria and its presence is associated with complications and increased mortality, so blood culture for aerobic organism is suggested. Prolonged prothrombin time indicates severity of AH. PT estimation has prognostic significance in acute hepatitis.

Management of Hepatitis E

Hepatitis E is a self limiting disease. With rest and good diet many recover completely and do not develop chronic liver disease. Some however, during early period of illness develop fatal complications like AHF or SHF. SHF was common in elderly male and diabetics. AHF is common in women with advanced pregnancy. Both these complications occurred more frequently in patients with bacterial super-infection. Patients with bacterial infection also commonly develop acute hepatic vena cava disease which may lead to development of chronic liver disease.

Management of Acute Icteric Illness: Patient is given palatable food and advised to maintain good nutrition with frequent intake of carbohydrate foods and fruits. Attention to hygiene of food and drinking water is emphasized to prevent bacterial infection. Strenuous physical exertion and use of alcohol and hepato-toxic drugs should be avoided. Vitamin supplement is given. Anti-emetic drugs like domperidone or metoclopramide are used as necessary. If there is evidence of or suspicion of bacterial super-infection antibiotic like ofloxacin is given orally. Anti-viral drug therapy is not indicated.

Patient is advised to take thing easy. HE patients need not be routinely hospitalized. Bed rest is recommended only if symptoms are marked. Patient who can not retain food due to persistent vomit; and those with impending AHF, like patient in full term pregnancy or those who develop abnormal behavior or change in sleep rhythm should be admitted to the hospital with intensive care facility.

Cholestatic Hepatitis: Management of severe prolonged itching is difficult. Cholestyramine (4 g) or colestipol (5 g) in water or fruit juice three times a day may help. It absorbs bile acids in large gut and relieves pruritis. Vitamin K supplement should be given to those receiving cholestyramine. Opioid antagonists (eg, naltrexone, 50mg/d by mouth or naloxone, 0.2 μg/kg/min intravenous) may be necessary in severe cases of pruritis. Anti-histamin like terfenadrine may provide some relief. Because of lack of toxicity and its beneficial effect in primary biliary cirrhosis, ursodeoxycholic acid (10-15 mg/kg/d in one or two doses) is sometime used. Corticosteroid, however, has no benefit in patient with deep jaundice or acute hepatic failure and should not be used.

Subacute hepatic failure: Patients, who develop ascites, should have an ultrasound examination for evidence of hepatic vena cava disease (HVD) and a diagnostic tap of the ascites. As concomitant bacterial peritonitis is common, the ascitic fluid is examined for total and differential WBC count, level of protein and albumin and for culture of aerobic organism. Early and adequate treatment of the bacterial infection improves survival. Patients with HVD and bacterial peritonitis need prolonged antibiotic treatment for 6 to 8 weeks[48].

Acute Hepatic failure: Acute hepatic failure is one of the most dramatic and challenging syndrome in medicine and without ICU treatment 90% of the patient dies. These patients develop serious complications like infection, coagulopathy with bleeding tendency, hypoglycemia, cerebral edema, and electrolyte and acid base disturbance. Patient with AHF requires immediate hospitalization. They are treated in intensive care unit whose staffs are familiar with the management of AHF. Policy of aggressive intensive care management is adopted where patients are monitored for likely complications and are treated immediately as they arise.

Mortality from Hepatitis E

Mortality in hepatitis E is related to development of complications like acute hepatic failure and subacute hepatic failure. Cholestatic hepatitis does no carry bad prognosis. But death has occurred in patient with prolonged jaundice treated with dietary restriction and herbal preparation that causes persistent diarrhea. Overall mortality in hepatitis E is 0.4%[1]. But mortality in infected pregnant women varies from 10 to 25%.

Economic impact of Hepatitis E in Nepal

Hepatitis E is common in the Kathmandu valley where it affects about 2% of the population annually. Persons with acute hepatitis E are sick for an average of one month and each incurs a treatment cost of about Rs.2516. Kathmandu valley with a population of 1.2 million has a large HE clinical burden. Annual economic loss for Nepal from hepatitis E-has been estimated to be about Rs.80 million.

Prevention of Hepatitis E

In the endemic areas HEV is a predominantly a waterborne infection, spread by sewerage contamination of drinking water. Provision of safe drinking water in urban areas in developing countries is a challenging task. Efficient chlorination of the water at the treatment sites should be insured. Care should be taken to prevent contamination of drinking water supply system from sewerage during construction of road and house.

Kathmandu valley is an area of water scarcity (50% less during dry season and 25% less in rainy season of the total estimated daily demand in the valley of 21 caror 44 lakh liter and nearly 37% leakage). As such water supply in the pipe is only intermittent, for a few hours daily or on alternated days. Intermittent supply in leaky drinking-water pipes that runs close to sewerage systems, leads to sucking in of fecal contamination material. Sewerage contamination of the drinking water is very high during rainy season. In the present condition the only reliable option for safety of drinking water appears to be to pasteurize it by boiling or by use of SODIS (solar water disinfection) procedure[49]. SODIS procedure is probably a convenient and affordable procedure for the prevention of hepatitis E in Nepal. Because of water scarcity especially during dry season, people pay less attention to the quality of the water. In Kathmandu valley, pregnant women and immigrants from other parts of the country are especially advised to use only drinking water that has been pasteurized by SODIS procedure or by boiling.

Strategy for control of hepatitis E in Nepal thus should include immediate measures such as creating awareness about the disease and use of SODIS procedure for sterilization drinking water; and long term measures like renovation of pipe system to prevent leakage and improve the water supply to provide constant flow in the pipe. Prevention of further epidemics of hepatitis E in the Kathmandu valley however requires not only good management drinking water supply system, but also adoption of measures to prevent accumulation of non-immune population like political solution to insurgency and creating job opportunities in rural areas.

Conclusion

In conclusion hepatitis E, a water-borne disease is an important cause of morbidity and mortality in young adults in Nepal. It is an easily preventable disease. Prevention however, depends upon our awareness of the disease and the priority we give to proper management of drinking water, as an individual and as a nation.

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