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EDITORIAL

Subclinical hepatitis E virus genotype 1 infection: The concept of "dynamic human reservoir"

Ananta Shrestha, Suresh Basnet, Sudhamshu KC

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Abstract

Hepatitis E virus (HEV) is hyperendemic in South Asia and Africa accounting for half of total Global HEV burden. There are eight genotypes of HEV. Among them, the four common ones known to infect humans, genotypes 1 and 2 are prevalent in the developing world and genotypes 3 and 4 are causing challenge in the industrialized world. Asymptomatic HEV viremia in the general population, especially among blood donors, has been reported in the literature worldwide. The clinical implications related to this asymptomatic viremia are unclear and need further exploration. Detection of viremia due to HEV genotype 1 infection, apparently among healthy blood donors is also reported without much knowledge about its infection rate. Similarly, while HEV genotype 3 is known to be transmitted *via* blood transfusion in humans and has been subjected to screening in many European nations, instances of transmission have also been documented albeit without significant clinical consequences. Epidemiology of HEV genotype 1 in endemic areas often show waxing and waning pattern. Occasional sporadic occurrence of HEV infection interrupted by outbreaks have been frequently seen. In absence of known animal reservoir, where HEV exists in between outbreak is a mystery that needs further exploration. However, occurrence of asymptomatic HEV viremia due to HEV genotype 1 during epidemiologically quiescent period may explain that this phenomenon may act as a dynamic reservoir. Since HEV genotype 1 infection cannot cause chronicity, subclinical transient infection and transmission of virus might be the reason it sustains in interepidemic period. This might be the similar phenomenon with SARS COVID-19 corona virus infection which is circulating worldwide in distinct phases with peaks and plateaus despite vaccination against it. In view of existing evidence, we propose the concept of "Dynamic Human Reservoir." Quiescent subclinical infection of HEV without any

clinical consequences and subsequent transmission may contribute to the existence of the virus in a community. The potential for transmitting HEV infection by asymptomatic HEV infected individuals by fecal shedding of virus has not been reported in literature. This missing link may be a key to Pandora's box in understanding epidemiology of HEV infection in genotype 1 predominant region.

Key Words: Hepatitis E; Viral hepatitis; Genotype 1; Dynamic human reservoir; Subclinical infection

Core Tip: Epidemiology of hepatitis E virus (HEV) is yet to be known and unraveled. HEV genotype 1 outbreaks tend to reoccur in periodic fashion in certain endemic areas. The virus often disappears even during conducible seasons and living conditions in between these outbreaks. There are no known animal reservoirs for human HEV genotype 1. Occurrence of asymptomatic viremia and transmission during epidemic quiescence in endemic areas may show humans acting as transient reservoir keeping the virus viable in the community. We propose this phenomenon as "Dynamic Human Reservoir" and emphasize the need for further research and data on this area for better understanding of HEV epidemiology.

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INTRODUCTION

Hepatitis E virus (HEV) infection is a global health concern that leads to 20 million infections, 3.3 million symptomatic cases, and 44000 deaths annually[1]. There is a dichotomy in the distribution of its genotypes and subsequent clinical manifestation worldwide. Previously considered a disease of developing and underdeveloped countries where poor sanitation and water hygiene prevail, is now being progressively recognized as an equally important public health problem in the industrialized world[2]. HEV genotype 1 and 2 is transmitted through contaminated drinking water, limited to humans only, and is prevalent in developing countries of Asia and Africa. It is known to manifest as a spectrum starting from asymptomatic infection, uncomplicated acute hepatitis, acute liver failure, especially among pregnant women, acute on chronic liver failure, and other extrahepatic manifestations. Genotypes 3 and 4 are initially zoonotic diseases that have crossed the species barrier and infected humans. It is endemic in industrialized nations of Asia and Europe, transmitted by undercooked meat products[3,4]. Its manifestations are less dramatic, with only a milder form of illness, but can potentially lead to chronic infection in immunocompromised hosts, culminating in the form of chronic liver disease[5-7]. Considering this dichotomy and completely distinct epidemiology of genotypes 1 and 2 from genotypes 3 and 4, this manuscript intends to discuss the former.

EPIDEMIOLOGY

The epidemiology of HEV genotypes 1 and 2 is heterogeneous across the region. While young adults are more affected in the Asian population, Egyptians experience more severe disease and high infection rates among children[8]. Similarly, the Global Burden of Disease (GBD) due to HEV is difficult to estimate due to data gaps in understanding its epidemiology. While symptomatic cases of HEV are easy to confirm and report, asymptomatic HEV infection is challenging to detect. Data on what proportion of HEV infection results in symptomatic infections is lacking, even in GBD estimation of HEV, extrapolation from the natural history of HAV infection, which may not truly reflect the behavior of HEV[9]. The actual burden of asymptomatic HEV viremia and its significance in the context of HEV genotype 1 and 2 is yet to be explored and understood.

HEV OUTBREAKS AND PERIOD OF QUIESCENCE

At least forty-four major outbreaks of HEV have been reported in Asia and Africa between 2011-2022[10]. Each of these significant outbreaks has witnessed thousands of symptomatic infections and a fair number of deaths, especially among the pregnant women. Except for recurrent outbreaks seen in Kathmandu Valley (Nepal), other outbreaks are temporally and spatially separated. It is not well understood why these large outbreaks occur interspersed by a period of inactivity or low level of sporadic cases. Having documented at least 4 significant outbreaks since 1973, we have taken Kathmandu Valley as a model for our discussion[11]. HEV once used to account for nearly half of the sporadic acute hepatitis among adults in 1997[12]. After a large outbreak of HEV between 2007-2008 in Kathmandu valley, HEV infection went into

dormancy. It is now rare to see acute HEV hepatitis in Kathmandu Valley other than occasional cases, which are more likely to be imported based on their travel history. After the 2015 mega earthquake, it created a perfect humanitarian setting due to internal displacement of people in Nepal, prediction of outbreak was anticipated[13]. However, HEV defied the prediction and remains a rare entity in Kathmandu Valley, once known as the epicenter of HEV.

SUBCLINICAL VIREMIA IN ENDEMIC AREAS

During our investigation among residents of Kathmandu, to our surprise, we detected viremia among asymptomatic healthy blood donors amid quiescence of HEV[14]. Out of 581 blood donors evaluated in 2014, HEV RNA was isolated in eight subjects (1.5%), all belonging to genotype 1a. Rate of anti-HEV IgM and anti-HEV IgG detection were 3.6% and 8.3%, respectively. Serum transaminase levels were normal in all the subjects and majority of these viremic subjects did not have any serological evidence of infection[14]. Similar reports have been published from other genotype 1 predominant regions, and some of the studies have even shown the possibility of transfusion transmitted HEV[15-17]. However, these infections were milder, subclinical, and of unknown significance, hence classifying this as an unimportant route of transmission.

HEV viremia among healthy asymptomatic blood donors has been reported in several studies from India. Arankalle *et al*[15] reported HEV RNA detection among 3 out of 200 healthy blood donors with Anti HEV IgM antibody in only one case. Similarly, Khuroo *et al*[17] found HEV viremia among 0.8%-3.7% of healthy controls and evidence that blood transfusion can transmit HEV infection. Occurrences of subclinical infection during an outbreak have also been well documented[18,19].

IMPLICATIONS OF SUBCLINICAL HEV VIREMIA

These findings indicate that subclinical HEV viremia is frequent in endemic areas both during an outbreak and even in the absence of sporadic cases or an outbreak. One may assume that without sporadic outbreaks of HEV in a community, contamination of the drinking water supply may not occur. However, these findings refute such assumptions. Even during quiescence of HEV infection, subclinical infection, subsequent fecal shedding, and contamination of water sources might keep the virus transmitting in the community. Now, there is evidence in both experimental animal models as well as humans that asymptomatic viremic subjects can shed HEV in feces[18,20]. Unlike in symptomatic subjects, where both viremia and fecal shedding occur for a short duration and until symptomatic and biochemical resolution, the duration of viremia in asymptomatic subjects is unknown. However, it is unlikely that asymptomatic subjects can shed the virus protractedly.

Why some individuals with HEV infection do not develop clinical hepatitis is unknown. One may speculate that for any symptomatic infection, there could be asymptomatic infections, but the proportion is yet to be determined. There is preliminary data to suggest that inoculum size may be an essential factor in determining the severity of HEV infection, and for that matter, low inoculum size may be the reason individuals do not develop disease despite viremia[21]. There is evidence that patients with subclinical infections during outbreak setting have lower viral load than those with clinical acute hepatitis[19]. Lower dose of inoculum at infection leading to low viral load may result in subclinical infection, but this association is yet to be proven. Fecal shedding of HEV from subclinical infection causing low-grade to modest contamination of drinking water sources could be the reason HEV keeps circulating in the community as subclinical viremia even when clinical HEV is nonexistent in the community. These subclinical human infections might function as transient reservoirs or "dynamic human reservoirs" and have a strong implication in understanding the epidemiology of HEV.

Another essential characteristic of subclinical infection is the frequent absence of IgM and IgG antibodies against HEV [14,15,17]. Low viral load of HEV in subclinical infections may be the reason for lower immune response leading to the absence or short-lived IgM and IgG in these cases. This might as well explain the reason for the low prevalence of anti-HEV IgG among blood donors despite subclinical viremia being common and may indicate subclinical infection and circulation may not provide immunity against future infections. Contrary to these observations, Egyptian children have a high seroconversion rate despite acquiring asymptomatic infections. Our observations cannot explain this phenomenon, but despite frequent subclinical infections in children, significant outbreaks have not been observed in Egypt, and adverse maternal outcomes due to HEV infection during pregnancy are less frequent[22]. Antibody response due to early subclinical infection in childhood could have prevented both outbreaks and adverse outcomes in pregnancy in Egypt.

CONCLUSION

Hepatitis E Virus infection is an enigma. Heterogeneity, even within genotype 1 infection in terms of epidemiological and clinical manifestation, has stood as a barrier to proper understanding of this disease. Frequent detection of HEV viremia in asymptomatic healthy subjects during periods of low incidence of clinical acute hepatitis in the community argues towards possible transient human reservoirs. In view of limited available data, more studies to characterize these subclinical infections and to better understand their clinical significance are warranted.

FOOTNOTES

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