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Hepatitis E: Water, water everywhere – Now a Global Disease

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Hepatitis E virus (HEV) is an enterically transmitted virus of 27–34 nm diameter whose genome consists of a poly-adenylated single stranded RNA of 7.2 kb length with 3′ and 5′ non-coding end and three partially overlapping open reading frames (ORFs) [1]. While ORF1 codes for non-structural proteins necessary for its replication, ORF2 and ORF3 code for the viral capsid protein [1]. The genome of HEV has been cloned, sequenced, its structural regions have been expressed *in vitro*, and both serological diagnosis and detection of HEV-RNA in sera, stool, and bile have been established by RT-PCR [1,2].

Due to its enteric route of transmission, it is the most common cause of both acute icteric and anicteric hepatitis in areas with poor sanitation and is known as hepatitis E [1]. Multiple epidemics of hepatitis E involving thousands of people have been reported from developing countries like India, China, Southeast and Central Asia, Northern and Western Africa [2]. The source of HEV in most of these outbreaks has been traced to contaminated drinking water [2]. The virus has been identified, in the faeces of volunteers who ingested faeces of patient having acute hepatitis E, using immune electron microscopy, thereby confirming its faeco-oral enteric route of transmission [3,4]. However, transmission through contaminated food, transmission through infected blood products, and maternal-foetal transmission of HEV have been reported from hyper-endemic regions like the Indian subcontinent [1]. Therefore, HEV remains the most frequent cause of acute hepatitis, acute liver failure, and acute-on-chronic liver failure in hyper-endemic regions and represents an important public health problem [5,6].

Reports from hyper-endemic regions like South Asia have confirmed that pregnant women and patients with chronic liver disease are at an increased risk to contract HEV and subsequently develop severe liver disease leading to liver failure and high mortality rate of around 60–70% [1,5,6]. However, acute hepatitis E in previously healthy individuals is usually self limiting and resolves within 4 to 6 weeks and case fatality rates in most epidemics have been reported to vary between 0.5% to 4% [1,2]. Chronic sequelae among patients during epidemic and sporadic setup have not been documented [7].

In non-endemic regions (Developed Industrialized Nations), where safe water supply has been ascertained, epidemic outbreaks have never been documented and hepatitis E associated deaths have not been recorded in immune competent healthy populations. A few years back, sporadic acute hepatitis E cases from these regions were predominantly documented among exposed travellers returning from HEV hyper-endemic regions. However, in recent years, a small series of cases related to autochthonous transmission of hepatitis E are being reported from developed nations like USA, Europe, Japan, Taiwan, Australia, and Hong Kong [2]. In the present issue of the journal, a long term prospective study from Italy, conducted over 15 years, evaluated the magnitude of acute hepatitis E among patients with acute non A, non C hepatitis ($n = 651$). This study revealed that about one fifth ($n = 134$, 20.6%) of tested patients had acute HEV infection, which was diagnosed by the detection of IgM anti-HEV and/or HEV-RNA in their sera [8]. Among these 134 patients with acute hepatitis E, 81.3% ($n = 109$) developed the disease within 1 to 4 weeks after returning to Italy subsequent to travelling to the Indian subcontinent, Morocco, and other countries that are hyper-endemic for HEV. Three patients (2.3%) were considered to have acquired HEV infection through infra-familial transmission. The remaining 22 (16.4%) were diagnosed as autochthonous acute hepatitis E, because they either (1) did not travel abroad, (2) denied contact with acute hepatitis E patients or people from abroad, (3) were not drug addicts or had transfusion, (4) did not eat raw undercooked shellfish and did not have occupational risks like swine handlers/pig farmers. A proportion of viral isolates ($n = 39$), from patients of acute hepatitis E who travelled to hyper-endemic area, and autochthonous group ($n = 5$), were further analysed for genotyping of the virus using PCR products of ORF2 region which revealed that all isolates of the former group had genotype 1 HEV infection whereas all isolates of autochthonous HEV belonged to genotype 3 [8].

HEV is placed in the Hepevirus genus and is the only member of this family. In 1997, Meng et al. [9] first identified, from swine in Midwestern USA, HEV strains that shared with the Burmese and Mexican (hyper-endemic for HEV) isolates of human HEV [10], 90–92% and 79–83% identity at the amino acid level in the ORF2 and ORF3 regions, respectively. Presence of HEV RNA in faeces and anti-HEV antibodies in sera of domestic swine, cattle, donkeys, deer, mules, and other animals had been reported earlier [11].

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Editorial

Table 1
Hepatitis E virus: Genotypes, geographical prevalence, viral and disease characteristics.

Genotype	Reservoir	Animal to human transmission	Water borne transmission	Geographical distribution	Severity	Chronicity	Relation to pregnancy	Causes ACLF	Epidemics
1	Human	No	Yes	South Asia, Central Asia, China, Sub-Saharan Africa	Yes	No	Cause severe disease	Yes	Yes
2	Human	No	Yes	Mexico, Nigeria	Yes	No	NK	NK	Yes
3	Swine	Yes	NK	Industrialized countries, USA, Europe, Japan	No	Yes	NK	NK	No
4	Swine	Yes	Yes	Taiwan, Japan, China	No	NK	NK	NK	No

NK, Not Known.

However, initial reports from the USA, on acute hepatitis E [10,12,13] in human and HEV isolates from patients showing nucleotide and amino acid heterogeneity similar to human isolates of Burmese and Mexican strains, prompted further investigation and the search for sources of HEV reservoirs in industrialized countries. HEV has mainly been found in pigs from all parts of the world, irrespective of HEV endemicity and the frequency of acute hepatitis E in respective human populations [1,2]. It has also been found that swine HEV naturally infects pigs, causing viremia and an antibody response that cross-reacts with human strains [2]. Furthermore, zoonotic human HEV infection, particularly in industrialized and developed nations, was first suspected after the detection of closely similar HEV isolates in two autochthonous cases in regions of the USA with locally prevalent swine HEV isolates [10,12,13]. The zoonotic transmission of HEV was then confirmed by a Japanese case series of acute hepatitis E where patients consumed inadequately cooked deer meat a few weeks before the illness declared itself, and HEV isolated from these patients were akin to the HEV isolates detected from the frozen left over deer meat [14]. Various additional evidences have supported the existence of zoonotic transmission in non-endemic region [15].

By now, multiple reports on the presence of autochthonous acute hepatitis E in non-endemic, industrialized countries like USA, France, Spain, Italy, Greece, Netherlands, UK and non-endemic developed Asian-Pacific countries like Australia, Japan and Taiwan have appeared in the English literature [2], and isolates from these patients with acute hepatitis E have been analysed and genotyped [2]. Despite the lack of consensus regarding the genotyping process, genotyping of HEV isolates is presently performed based on the ORF2 region and genotypes are defined as viruses having a nucleotide divergence of not more than 20% [16].

Based on genome sequence analysis, human and swine HEV isolates have been categorized into four distinct genotypes 1–4 (Table 1). Each genotype has several subtypes but all genotypes have common serotypes [1,2,15]. As indicated earlier, it is clear that acute autochthonous hepatitis E is being reported with increasing frequency in developed and industrialized country, thus confirming HEV as a cause of acute hepatitis all over the world. However, while genotype 1 and 2 are prevalent in hyper-endemic regions where the reservoir for HEV seems to be human (continuous subclinical infection [17]), genotype 3 and 4 are prevalent in USA, Europe, and Japan where the reservoir seems to be represented by pigs, and the zoonotic transmission is considered to be the cause of infection of human beings, leading to autochthonous acute HEV. Genotype 4 has been identified in both swine and human patients with acute hepatitis E in China, Taiwan and Japan, but in the Indian subcontinent, even though swine HEV belongs to genotype 4, all human cases to date had genotype 1 infection [2]. All swine isolates belong to genotype 3 and 4 and no animal isolates to date belong to genotype 1 and 2. This may indicate that genotype 1 and 2 may not be capable of crossing the species barrier whereas genotype 3 and 4 can do so. On the other hand, genotype 1 and 2 cause severe liver disease whereas genotype 3 and 4 cause milder disease [1,2]. It is further evident by the observation that the seroprevalence of anti-HEV in populations belonging to developed nations varies from 5–21% [18], indicating frequent exposure but epidemic outbreaks and the low frequency of autochthonous hepatitis would suggest that these viruses may be more benign than those prevalent in hyper-endemic region. Despite increasing reports on the occurrence of autochthonous acute hepatitis E in industrialized nations, acute liver failure and acute-on-chronic liver failure, due to autochthonous acute hepatitis E belonging to genotype 3 and 4, have not yet been documented.

In the paper reported in this issue [8], 96 (71.6%) patients with acute hepatitis E were viremic, as shown by the presence of HEV RNA. Even though the paper did not provide the exact frequency of viremia among autochthonous cases, many of them would presumably be viremic. It may be relevant to these populations where autoimmune hepatitis (AIH) is more prevalent and corticosteroid therapy is the mainstay of treatment. AIH in these parts of the world is frequently diagnosed by excluding known causes of viral hepatitis, and autoimmune markers may be absent in about 30–40% of such cases. Therefore, it seems that a serological test for HEV may be relevant for such patients, before embarking upon an immunosuppressive therapy. With the increasing prevalence of non-alcoholic fatty liver disease and alcoholic liver disease, HEV super-infection might be a cause of deterioration in patients who have never been investigated. HEV super-infection in such patients has already been documented to cause rapid decompensation [5,6]. However, these reports have emanated from the Indian subcontinent which is hyper-endemic for HEV where human disease is caused by HEV genotype 1 [2]. Whether HEV genotype 3 and 4 super-infection would cause such sequel is unclear and needs prospective evaluation. A prototype example is a recent report on drug induced hepatitis (DH) in the UK [19]. In this report, in 13% of patients DH was due to acute hepatitis E, as diagnosed by a later analysis of their stored sera.

Data on HEV in the developed world is inadequate because of the belief that HEV prevalence and transmission is extremely infrequent in these areas. The seroprevalence studies from these countries had used ELISA assays, to detect IgG anti-HEV antibody, manufactured by either GeneLabs (Singapore) or/and Abbott, (Germany) which uses truncated recombinant peptides of ORF2 and ORF3 regions from the Burmese and Mexican prototype sequences [20]. A recent study showed that the above mentioned ELISA assays may be less sensitive to detect IgG anti-HEV antibody in the sera [21]. A recently developed, more sensitive ELISA (IgG EIA kit, Wantai, Beijing, China) with a lower limit of detection for IgG anti-HEV (0.25 WHO unit/ml) was compared with the frequently used GeneLab IgG anti-HEV kit that has a higher limit of detection for IgG anti-HEV (2.5 WHO unit/ml) [21]. Both these assays were used for the analysis of stored sera of known acute hepatitis E and donor blood from the UK. The Wantai kit was positive in more sera of proven cases as compared to the GeneLab kit (98% vs 56%) and resulted in a markedly higher estimate of seroprevalence in blood donors (16.2% vs 3.6%). Therefore, the actual seroprevalence might have been underestimated in most of the industrialized countries due to the use of less sensitive assays. Furthermore, IgM anti-HEV antibody in autochthonous acute hepatitis E may not be detectable by less sensitive assays and diagnosis has been ascertained by detection of HEV-RNA in the sera or stool [22]. It may be relevant to reassess the sero-epidemiology of HEV in the developed nations, and identify the other sources of HEV transmission in view of the increasing number of reports on acute hepatitis E, as documented by the paper in this issue of the journal. In addition to zoonotic transmission, contaminated water, as a source of acute hepatitis E, has been reported from France [23]. During a 13 month duration, the evaluation of consecutive patients with acute hepatitis in South Hampshire, UK, revealed that acute hepatitis E was more frequent than acute hepatitis A and B and none of the patients had a history of travel abroad or had consumed any raw meat in the recent past, raising the suspicion of transmission through contaminated water or food [24].

It is evident that HEV is endemic in most part of the developed and industrialized nations indicating its global prevalence. While HEV genotype 1 is hyper-endemic in Asia and Africa, where it causes outbreaks, sporadic acute hepatitis, acute liver failure, and acute-on chronic liver failure; HEV genotype 3 and 4 are prevalent in the industrialized and developed nations and increasing reports on autochothonous acute hepatitis E due to these viruses are being identified. The reservoir for genotype 1 has been identified to be human whereas the reservoir for the genotype 3 and 4 seems to be pigs, and therefore zoonotic transmission is more prevalent in these regions. However, the latter viruses have not been implicated in causing severe liver disease and more studies are needed to further clarify this observation. (Table 1). Genotype 2 like genotype 1 has been reported from Mexico and Nigeria with similar epidemiological and sporadic features. Due to the global prevalence of HEV, an effective vaccine with long lasting immunity is urgently needed to protect people throughout the world and therefore it is time that HEV associated diseases are not considered as a disease of the developing world where sanitation is inadequate. HEV, indeed, is prevalent globally and is of public health importance, which requires the attention of public health experts, academia, and the health authorities throughout the world in order to reduce the morbidity and mortality caused by it.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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