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Review

Hepatitis E virus infection in developed countries

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ABSTRACT

Hepatitis E was considered to be endemic infectious disease in developing countries in tropical or subtropical regions with poor sanitary conditions. Large, previously reported outbreaks were mainly due to contaminated water or heavy flooding. Prototype hepatitis E viruses of genotypes I and II were obtained from such endemic cases. In developed countries, in contrast, hepatitis E was rare and diagnosed only in travelers or imported cases. However, the development of accurate diagnostic tests, mainly PCR detection elucidated that autochthonous hepatitis E in developed countries is far more common than previously thought. Although the main route of transmission is food-borne, other routes including blood-borne have been suggested. Recent developments of gene-based diagnostic assays and molecular epidemiology have disclosed the significance of hepatitis E virus infection in developed countries.

Contents

1. Introduction

The presence of water-borne hepatitis associated with viral infection was described in as early as mid 1950s (Melnick, 1957; Viswanathan, 1957). However, it took many years until Balayan et al. (1983) clearly showed that the agent was faecal–orally transmitted. He developed acute hepatitis following self-ingestion of acute phase stool suspensions from a water-borne epidemic of non-A hepatitis in Uzbekistan.

It took another several years until the real breakthrough was brought by the isolation of cDNA from the causative agent of enterically transmitted non-A, non-B hepatitis virus contained in HEV infected Cynomolgus monkey bile (Reyes et al., 1990). The virus contained in the starting material for cloning (bile) was carefully characterized by extensive studies done by Bradley et al. (1987, 1988) and (Bradley and Balayan (1988) and Krawczynski and Bradley, 1989); in particular its infectivity was unequivocally proved by infection experiments in Cynomolgus macaque monkeys.

The virus was designated hepatitis E virus (HEV) and a faecal–orally transmitted non-A, non-B hepatitis agent but has since been classified as HEV. Retrospectively and prospectively, the characteristics of HEV infection became clear: large water-borne outbreaks occur in areas with low sanitary conditions and poor hygiene infrastructure; faecal–oral transmission; highest attack rate among rather young individuals approximately 15–40 years of age; case-fatality rate highest in third trimester pregnant women; low rate of person-to-person transmission; vertical transmission possible; no chronic sequelae (Clayson et al., 1995a; Worm et al., 2002; Emerson and Purcell, 2003; Aggarwal and Naik, 2009).

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2. Hepatitis E in developed countries

The cloning of HEV (Reyes et al., 1990) has accelerated development of assays for detection of HEV antibodies and HEV RNA. The seroepidemiology thereof elucidated the nature of hepatitis E (Bradley, 1992). HEV is the leading cause of enterically transmitted non-A hepatitis worldwide. It is responsible for the major outbreaks of acute hepatitis in developing countries, where outbreaks are usually associated with faecal contamination of drinking water or flooding. It is also an important etiological agent of sporadic acute hepatitis in developing countries. Since then, and up to now, Central and Southeast Asia, Middle East and North Africa are considered to be endemic region of HEV infection in the world (Purcell and Emerson, 2008).

In contrast, hepatitis E in developed countries was sporadic and was not so common. Before HEV was cloned, Margulies et al. (1987) reported that French travelers to Asia and Africa developed fulminant non-A hepatitis. It is noteworthy that they had high fatality rate (70%).

Hepatitis E in travelers to the endemic regions was recognized soon after HEV was identified. Travelers from developed countries to endemic area came back to their own countries and developed diseases; USA to Mexico (Bader et al., 1991), UK to India, Saudi Arabia, Malawi (Skidmore et al., 1991), USA to Pakistan (Dawson et al., 1992), USA to Bangladesh (Roberts and Whitlock, 1992), USA to Mexico, India, Pakistan, Nepal (CDC, 1993), Netherlands to Bangladesh, Somalia, Middle East (Zaaijer et al., 1993), Australia to Nepal (Fletcher, 1993), Norway to Burma, Nepal, Bangladesh (Skaug et al., 1994), Japan to China (Ishikawa et al., 1995), Sweden to Turkey (Johansson et al., 1995), Canada to India (Weiss et al., 1995), Canada to Nepal, Thailand, India (Akai et al., 1995), UK to Pakistan (Abid et al., 1997), USA to Mexico, Pakistan (Ooi et al., 1999), Israel to Nepal, India (Schwartz et al., 1999), Korea to India (Kim et al., 2004). These reports published in 1990s are mainly brief case reports with fragmental information, but described clinical features are basically similar to those in endemic countries. Higher mortality rate and a higher fatality rate (~20%) in pregnant women should be noted.

In addition to these travel returnees, hepatitis A and E were predominant among tourists and foreigners in Nepal (Clayson et al., 1995b). Hepatitis E outbreaks among soldiers dispatched to endemic areas were frequently reported (Tsega et al., 1991; Coursaget et al., 1993; Buisson et al., 1994). Diplomats and foreign aid workers are also exposed to HEV infection (Burans et al., 1994; Taylor et al., 2008).

It has long been noted that other than imported cases from endemic countries, especially in developed countries, more than half patients were non-travelers. The presence of indigenous HEV strain and autochthonous hepatitis E has been strongly suggested (Aggarwal and Krawczynski, 2000).

Studies to explore other potential reservoirs and animal hosts of HEV were carried out in non-endemic countries, and a novel swine virus closely related to human HEV was incidentally discovered. This finding was extraordinarily important to the understanding of the epidemiology of disease and the diversity of HEV genotypes (Meng et al., 1997). The swine virus was found to be in the same genotype group of HEV obtained from a hepatitis E patient in the USA who had no history of travel to an endemic area (Schlauder et al., 1998). Meng et al. (1999) further studied the prevalence of anti-HEV in pigs and found pigs are highly infected. After this observation, extensive studies were performed to study HEV prevalence in different countries (reviewed by Goens and Perdue, 2004 and more recently by Pavio et al., 2010). All these studies, either by anti-HEV antibodies or PCR detection of viral RNA, indicated a very wide distribution of HEV in swine herds in the world.

This observation immediately prompted the examination of HEV transmission from swine to humans. Anti-HEV was tested in high risk population (swine herd workers, veterinarians, etc.). Results were varied, but showed a high prevalence in such population in the USA (Drobeniuc et al., 2001; Meng et al., 2002). Recent studies showed that higher prevalence by anti-HEV or PCR were observed in pig handlers in many countries (Withers et al., 2002; Olsen et al., 2006; Galiana et al., 2008, 2010; Eker et al., 2009; Meader et al., 2010). However, in Sardinia, Italy, a low prevalence value was found in swine workers at zoonotic risk (Masia et al., 2009). This discrepant result may be due to different anti-HEV assays and/or selection of population tested. Even though anti-HEV or HEV RNA was positive among such "high risk" population, distinct clinical cases have not been heretofore reported. In most of the cases, infection may be inapparent. Establishment of an internationally standardized and sensitive anti-HEV assay system is thus expected (FitzSimons et al., 2010; Teshale et al., 2010).

As described above, it is now clear that pigs are a reservoir of HEV. Recently, commercially sold pig meat and pig products are reported to contain HEV (Bouwknegt et al., 2007; Feagins et al., 2007; Kulkarni and Arankalle, 2008; Colson et al., 2010). Feagins et al. (2008) suggested that HEV in contaminated commercial pig meet and livers can be effectively inactivated if cooked properly. However, Yazaki et al. (2003) reported that among sporadic or fulminant hepatitis E patients in Hokkaido, a northern island of Japan, 90% had histories of consuming not well grilled or undercooked pig liver 2–8 weeks before the disease onset.

Successful production of virus like particle (VLP) of HEV played an important role for the seroepidemiology of HEV infection (Li et al., 1997). Truncated ORF2 gene of HEV genotype 1 (Uchida et al., 1992) was efficiently expressed in insect cells by a recombinant baculovirus. Using the VLPs, they established a sensitive but simple antibody detection system (Li et al., 2000) and found that there was autochthonous, indigenous HEV infection in Japan. Using this system, it was further shown that HEV has been constantly circulating in Japan at low level (Tanaka et al., 2001, 2005).

Very clear evidence of an outbreak of hepatitis E was shown in Japan by Mishiro group. They described unequivocal HEV infection in two families that shared several meals consisting of raw venison from wild sika deer. Only meat eaters developed typical hepatitis E in a dose dependent manner (Tei et al., 2003, 2004). The HEV RNA sequence obtained from the patients was identical with those from the precious sika meat that was frozen in a refrigerator until testing. This work is extremely important because it, for the first time, showed direct evidence that HEV can be transmitted through uncooked meat. The study undoubtedly revealed well-defined autochthonous, non-traveler's HEV infection in a developed country. They furthermore showed that the HEV genome derived from one of the outbreak cases was almost identical to that originating from a deer caught in the nearby countryside (Takahashi et al., 2004). After Mishiro report, many cases from wild deer and wild boar (Matsuda et al., 2003; Tamada et al., 2004; Li et al., 2005; Masuda et al., 2005) were reported, raising the paper price in Tokyo. From wild boars and deer in Japan, HEV RNA was detected (Sonoda et al., 2004; Nishizawa et al., 2005; Yano, 2007; Michitaka et al., 2007; Sakano et al., 2009). Li et al. organized all-Japan sero- and stool-surveys in wild sika deer and boars using ELISA and PCR assays. Prevalence of anti-HEV IgG in sika deer was lower than those in pigs and wild boars. Furthermore, no HEV RNA was detected in sera, stool and liver tissues from wild deer obtained different parts of Japan. Wild deer may not be a reservoir of HEV in Japan (Matsuura et al., 2007). Detection of HEV RNA in wild boars was confirmed in Germany, Italy, France, Spain and Netherlands (Kaci et al., 2008; Wichmann et al., 2008; de Deus et al., 2008; Martelli et al., 2008; Schielke et al., 2009; Rutjes et al., 2010; Kaba et al., 2010). In endemic country, Hungary wild boar and deer liver was positive by PCR (Reuter et al., 2009; Pavio et al., 2010). It is of particular noteworthy that

all HEV from developed countries are genotype 3 or 4 (Lu et al., 2005).

After all, HEV infection in developed countries is not restricted to imported cases. Incubation and clinical manifestation in individuals in developed countries seems to be similar to that from endemic regions. However, the mortality rates are higher, ranging from 8% to 11% in spite of their better treatment. Causative HEV are either genotype 3 or 4 (Okamoto et al., 2003; Ijaz et al., 2005; Borgen et al., 2008; Peron et al., 2006a; Dalton et al., 2008).

3. HEV infection in Japan

In Japan, Shikata et al. started pioneer studies of enterically transmitted non-A, non-B hepatitis designed to identify its causative agent as early as in 1980s. The group chased down the infectious agent using stool samples from Myanmar patients by macaque transmission experiments (Soe et al., 1989). Uchida et al. (1992) finally cloned HEV cDNA (genotype 1 Myanmar strain) totally independently from Reyes and Bradley (Aye et al., 1993). The results were derived from close collaboration with Myanmar scientists using clinical materials from Myanmar patients. Since HEV infection has been long considered as endemic only in undeveloped countries, such international collaboration is important, in particular for the evaluation and standardization of antibody assay systems.

The clone was the prototype of HEV genotype 1 from Myanmar and widely used in thereafter studies in Japan. Li et al. (1997) efficiently produced HEV VLP from this clone and established a sensitive antibody detection system. They, for the first time, showed the prevalence of IgG in healthy Japanese sera kept in the blood bank. It varied from 1.9% to 14.1% depending on the region (Li et al., 2000). Surprisingly, the overall IgG positive rate was equivalent to or even higher than the rate observed in India, where HEV is endemic (Arankalle et al., 1995). This observation suggested the presence of autochthonous HEV infection in Japan. Thenceforth, many studies on HEV prevalence either by Li's- or other ELISA system (or even HEV RNA detection system) were carried out (Tanaka et al., 2001, 2005; Fukuda et al., 2004; Sakata et al., 2008; Takahashi M. et al., 2010). The positive rate is rather high (nearly 10% in over 40 years of age). There is a clear regional difference (north > south and east > west) and male > female. Among these serological surveys, Tanaka's observation is particularly noteworthy. They investigated anti-HEV as well as anti-HAV positivity in sera collected in 1974, 1984 and 1994 in Japan. Age specific profiles of anti-HEV remained constant with peaks at 40–49 years, while those of anti-HAV changed strikingly (peak at 20–29 years in 1974, at 30–39 years in 1984 and at 40–49 in 1994). This result suggested that a silent HEV infection was ongoing in the last 20 years in Japan (Tanaka et al., 2005). This was soon followed by Gotanda et al. (2007) and Fukuda et al. (2007) in their respective studies among blood donors with elevated alanine aminotransferase in Japan.

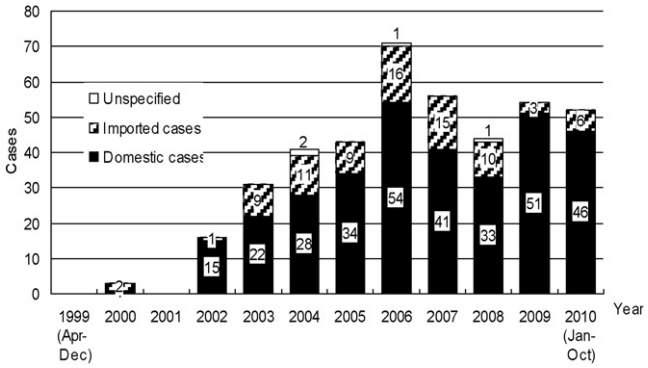

Fig. 1. Annual number of hepatitis E cases in Japan, 1999–2010.

Clinical courses and symptoms of HEV infection in Japan are well summarized by Okamoto et al. (2003). He described a course of HEV infection that seems to be rather severe in Japan compared to other developed countries. Fulminant cases were also reported (Suzuki et al., 2002; Ohnishi et al., 2003; Yazaki et al., 2003).

In Japan, reporting of hepatitis E has been mandatory within 7 days after diagnosis by physicians as an "acute viral hepatitis" (notifiable infectious disease category IV), under the National Epidemiological Surveillance of Infectious Diseases (NESID) based on the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Disease Control Law, implemented in April 1999). Subsequently, in accordance with the law amendment in November 2003, "hepatitis E" became an independent category IV (together with hepatitis A) notifiable infectious disease, with notification being required immediately after diagnosis. Fig. 1 illustrates reported annual numbers of confirmed HEV cases in Japan from 1999 to 2010. Although this numbers may be underestimated, significant numbers of HEV infection has been reported. Recently observed high rate of local HEV infections may be related to improved sensitivity of laboratory diagnosis (HEV RNA detection by RT-PCR and IgM anti-HEV detection). Seasonal difference is not apparent but males are overwhelmingly outnumbers females among both domestic and imported cases. Most of the domestic cases are of middle or advanced ages, with peaks in the latter half of 50s for males and the

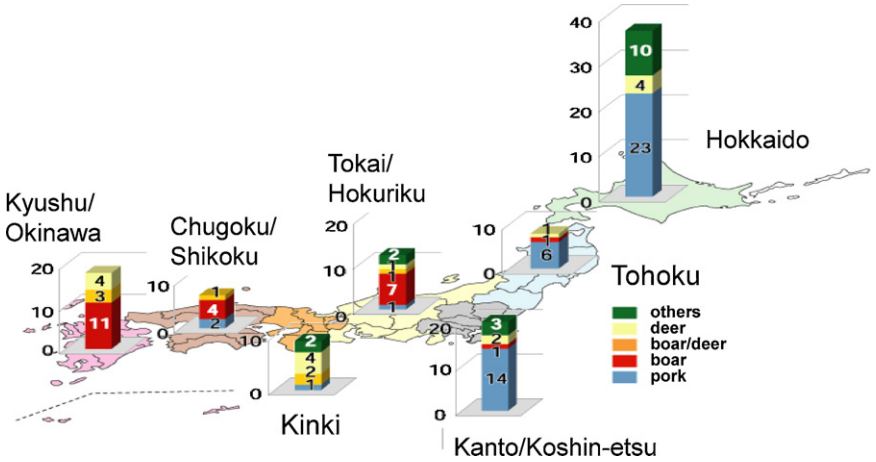

Fig. 2. Food source of infection of domestic hepatitis E cases by region, Japan, April 2006–June 2008 (n = 111: cases with suspected food source).

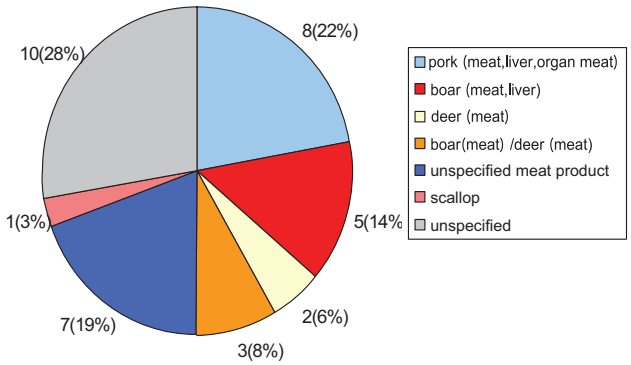

Fig. 3. Food source of infection of domestic hepatitis E cases, Japan, 2009 ($n = 36$).

latter 60s for females. Imported cases are mainly in their 20s to early 30s. This observation is quite similar to that of other developed countries (IDSC, 2005).

HEV is a food-borne infectious disease in Japan. Outbreaks or sporadic cases of food-borne HEV infection has been reported from different part of Japan (Tei et al., 2003; Li et al., 2005; Nakano et al., 2006; Inoue et al., 2009), particularly in northern island, Hokkaido (Ohnishi et al., 2003; Yazaki et al., 2003; Mizuo et al., 2005; Ishida et al., 2006; Kang et al., 2010). As shown in Fig. 2, in 2006–2008, many cases were from Hokkaido and their main food source was uncooked- or undercooked-pork.

HEV transmission through blood transfusion was reported in Hokkaido (Matsubayashi et al., 2004, 2008; Ikeda et al., 2009). Furthermore, Mitsui et al. (2004) in their meticulous retrospective study among haemodialysis patients, showed a case of transfusion-associated HEV transmission as early as in 1979. The potential risk of post-transfusion hepatitis E cannot be negligible.

Hokkaido is thus considered as HEV "endemic" in Japan. Two extensive studies are going on; (i) Hokkaido Red Cross Blood Center initiated general blood screening by PCR from 2005. Until now (June, 2010), altogether 1,512, 246 donated blood was tested. HEV RNA positive blood was 179 (0.1%) (reported in the Steering Committee of the Blood Advisory Council, Ministry of Health, Labor and Welfare of Japan, August 11, 2010, Tokyo). Among HEV RNA positive donors, genotype 3 was dominant. Male vs. female ratio was 2.8 vs. 1. The follow-up studies of positive donors revealed that most of them remained asymptomatic (Ikeda et al., 2009). (ii) The active network in Hokkaido was organized in 2007 and clinico-genetic prospective HEV infection surveillance has started. Recently, they found a cluster of sporadic cases in Sapporo, Hokkaido with HEV genotype 4. Further genomic analysis indicated that these isolates were similar to the strains that previously caused severe cases reported in Kitami district (2004) and Abashiri district (2006), which are different part of Hokkaido (Kang et al., 2010).

4. Risk factors of hepatitis E in developed countries

HEV is transmitted primarily by the faecal–oral route. In developing countries, epidemics of hepatitis E are principally due to drinking faecally contaminated water. In contrast, in developed countries, sporadic hepatitis E is zoonotic and food-borne. It is associated with eating uncooked or undercooked meat or viscera of deer, boars, and pigs. In 2009, among 39 domestic hepatitis E cases in Japan, food source were identified in 26 cases (72%), with leading cause of uncooked or undercooked pork (Fig. 3). Song et al. (2010) suggested a potential risk factor of contaminated oysters in Korea.

HEV viremia was first described in clinical observation in Nepal (Clayson et al., 1995a). The report of a hospital outbreak of HEV infection raised the potential risk of in-hospital spread of HEV from an acutely infected patient (Robson et al., 1992). Blood transfusion is definitely one of the risk factors of HEV transmission as first proved in Japan (Matsubayashi et al., 2004, 2008) and later in other industrialized countries (Pischke et al., 2010). Accordingly, haemodyalysis patients in endemic as well as non-endemic countries are at higher risk (Ayoola et al., 2002; Lee et al., 2005; Taremi et al., 2004; Hosseini-Moghaddam et al., 2010).

5. Persistent, chronic infection

In developed countries, as in endemic countries, HEV infection is basically self-limiting and never becomes chronic (Emerson and Purcell, 2003). However, some unique cases, acute HEV infection induced chronic cholestatic jaundice (Mechnik et al., 2001; Suzuki et al., 2003). Recently, a persistent HEV infection with chronic hepatitis and cirrhosis was reported in patients with reduced immune surveillance as induced by chemotherapy or post-transplant immunosupression (Haagsma et al., 2008; Gerolami et al., 2008; Kamar et al., 2008, 2010; Mansuy et al., 2009; Ollier et al., 2009; Legrand-Abravanel et al., 2010; Pischke and Wedemeyer, 2010) or immunocompromised patients from various reasons, for example, lymphoma or HIV co-infection (Peron et al., 2006b; Tamura et al., 2007; Dalton et al., 2009). These patients should avoid possible HEV contaminated uncooked meat.

6. Environmental detection of HEV

Environmental survey was done recently in the endemic Gokulpuri area in Delhi, India. 4.3% of sewage and 1.5% of drinking water respectively were positive for HEV RNA. They were all genotype 1 (Hazam et al., 2010). In developed countries, Li et al. (2007) surveyed bivalves yamato-shijimi for the presence of HEV RNA from river waters from different part of Japan. Genotype 3 HEV RNA was detected. Since HEV cannot grow in bivalves, the detection indicates that HEV contaminates river water in Japan. However, since Japanese do not eat such bivalves raw, their role in the transmission to humans may not be significant. This work should be considered as an environmental study.

7. Infection control

Hepatitis E is a typical "think globally and act locally" infectious disease. For the global level understanding of hepatitis E, it is urgently necessary to have a reliable, internationally standardized anti-HEV assay system (FitzSimons et al., 2010; Teshale et al., 2010). Information sharing of different genotypes isolated from different parts of the world is particularly important (Lu et al., 2005). Recently, possible new "genotype 5" was isolated from a wild boar in Japan (Takahashi K. et al., 2010).

Preventive vaccine is the key. Vaccines should be used for mass vaccination of individuals in endemic countries. HEV vaccines used in these countries should provide long-lasting immunity and be low in cost, effective, and readily available. For developed countries, they would be used for high risk people; for example, travelers, soldiers and other long term visitors to endemic countries. Combined vaccines, in particular hepatitis A virus, would be extremely useful.

8. Concluding remarks

Hepatitis E virus infection was initially considered to be endemic mainly in underdeveloped or developing countries. However, it is a serious form of viral hepatitis in all parts of the world. Its zoonotic nature, together with recently found possible chronicity, make the control of this virus difficult. HEV reservoir and routes of transmission are not fully understood yet. Development of prompt

and accurate diagnostic system, effective anti-virals and preventive vaccines are needed.

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