Gastroenterology and Hepatology From Bed to Bench

REVIEW ARTICLE

Enteric hepatitis viruses

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ABSTRACT

Hepatitis viruses are infectious agents that can infect liver and cause inflammation. The infection triggers immune response against infected cells that leads to the destruction of hepatic cells. This destruction has two consequences: leaking ALT and AST liver enzymes which increases during the course of disease and accumulation of bilirubin- a red pigmented compound released from dead red cells- which causes the yellow coloration of eyes and skin. These viruses transmit through diverse routes i.e. blood transfusion, sexual contacts and consuming water or food contaminated by feces. Enteric hepatitis viruses use the latter route for transmission; hence their outbreaks are more common in underdeveloped countries. There are currently two distinguished enteric hepatitis viruses, hepatitis A and hepatitis E. These viruses belong to different family of viruses and their epidemiological characteristics are different. These infections can be diagnosed by an ELISA for IgM antibody. A vaccine has been developed in last decade of twentieth century for hepatitis A virus, which is administered mostly in the developed world i.e. U.S and Japan. Treatment for these infections is mostly supportive; however, in the case of fulminant hepatitis the liver transplantation might be necessary.

Keywords: Hepatitis A virus, Hepatitis E virus, Epidemiology.
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Introduction

Viral hepatitis is a major health concern worldwide, with a higher incidence in developing countries than the developed ones (1). Viral Hepatitis was classified in the first half of twentieth century as either infectious or serum hepatitis according to their epidemiological features (2). Infectious hepatitis turned out to be caused by Hepatitis A virus (HAV) (3) and serum hepatitis by Hepatitis B virus (HBV) (4). However during further investigations, the researchers found out that there are other etiologic viral agents that can cause hepatitis. These were initially calling none A, none B hepatitis (NANBH) (5).

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Hepatitis A also previously known as infectious or epidemic hepatitis virus has been long known to clinicians and epidemics, as a result of contaminated water and food, are well documented (6-8). Hepatitis E virus was discovered more lately, during the late seventies and early eighties (9). The earliest well-documented report of this disease was a large epidemic of water-borne hepatitis in New Delhi, India during 1955 to 1956 (10). Although there are similarities between these two viruses, their epidemiological characteristics distinguish them from each other (11, 12). Hepatitis A is endemic in many populations and most adults and children from endemic areas have serological evidence of previous infection. Hepatitis E is a zoonotic virus (13) and unlike hepatitis A virus, hepatitis E's

prevalence is not so high and most of the children in endemic areas have no antibody against it (14).

The infection of liver with these viruses triggers immune response against infected cells that in turn leads to destruction of hepatocytes (15-17). This destruction has two consequences: leaking ALT and AST liver enzymes which increases during the course of disease and an increase in serum bilirubin- as a consequence of failure to excrete bilirubin into the bile cananiculi and leakage of conjugated bilirubin from hepatocytes.

Morphology, genomic organization and genotypes

Hepatitis A virus (HAV) belongs to Picornaviridae family and *Hepatovirus* genus and has an icosahedral capsid of diameter of 27-32 nanometer with a single stranded RNA as its genome (18). Like other non-enveloped viruses this virus is resistant to harsh environments and is not inactivated by acid (19) or ether (20) or mild heat (21). The genome of this virus is RNA with a length of approximately 7470 nucleotides. The genome is divided into three parts: 5' non-coding region (NCR) of 734 to 740 nucleotides that is attached to a viral protein, a single open reading frame of 2,225 to 2,227 nucleotides and 40 to 80 nucleotides 3' of non-coding region. Isolates from different parts of the world show no significant diversity in their genomes (18). HAV strains recovered from widely separated regions of the world are antigenically similar. In humans, a single serotype of HAV exists (22).

Hepatitis E virus is a non-enveloped virus with a capsid of diameter 30-34 nm (23), which under electron microscopy is distinguishable from Hepatitis A (24). The genome of HEV is a single-stranded, positive-sense, polyadenylated RNA molecule of approximately 7.2 kb in length, excluding the poly (A), which has a cap at 5' end (25-27). Genetic sequencing of HEV strains in different parts of the world shows that virus has three overlapping ORFs (28). HEV has four different genotypes: genotype 1 (Asia, North Africa), genotype 2 (Mexico, Southern Africa), genotype 3 (North and South America, Europe, Asia), and genotype 4 (Asia) (29). All HEV genotypes share at least one major serologically cross-reactive epitope and belong to a single serotype (30).

Epidemiological features

In endemic regions, HAV infection occurs mostly during the first decade of children's life and by the age of 18, most of the population have protective antibody against the virus and as the standard of living improves in the region, the peak hepatitis A incidence moves from young children to older ages (31). Food-borne outbreaks are prevalent both in developed countries and developing countries (32, 33). Sea food could also be a major source of infection (34), because the sewage water is mostly disposed untreated into water (35) and oysters for example concentrate these viruses and when people eat these foods raw or under cooked they rosk developing a HAV infection (36). Various monkey species such as chimpanzees, rhesus monkeys, African green monkeys and squirrel monkeys are susceptible to HAV (37). The presence of anti-HAV antibody in the sera of newly captured monkeys shows that infection occurs in the natural habitat of non-human primates (38). This animal reserve will prevent eradication of the disease by mass vaccination.

In disease endemic regions, epidemic of HEV occurs frequently. These outbreaks separated a few years apart and often are followed after heavy rain falls and floods which create conditions that favor mixing of human excreta with sources of drinking water (11). In rural areas, people dispose the human excreta into river and use the water for

drinking and cooking (39); in urban areas the leaky pipes which cross under contaminated soil would carry the infection to people's homes (40). In disease-endemic areas, HEV infection accounts for a large proportion of acute sporadic hepatitis in all age groups. The route of acquisition of infection in most patients with sporadic hepatitis E is unclear. Unlike Hepatitis A, Hepatitis E attack rate is as low as 0.7 to 2.2% and person to person transmission of this virus is uncommon (41). In non-endemic regions, where outbreaks have not been reported, the disease accounts for only a minority of reported cases of acute viral hepatitis. Until a few years ago, most such cases were found to be related to travel to disease-endemic areas, but now the zoonotic transmission of virus accounts for a significant proportion of cases (42) and the presence of HEV virus in meat or liver of animals is a strong indication of this route of transmission (43, 44).

Routes of transmission

HAV is generally acquired by the fecal-oral route, either person-to-person contact or ingestion of contaminated food or water. Hepatitis A is an enteric infection spread by contaminated excreta (45). Transmission by blood transfusion is rare: the donor must be in the viraemic prodromal phase of infection at the time of blood donation (45).

Outbreaks (1992) have occurred among haemophiliacs receiving factor VIII concentrates prepared by a solvent-detergent inactivation process which did not reduce the infectivity of non-enveloped viruses (46). HAV is not transmitted from infected mothers to newborn infants; intrauterine transmission from mother to child does not occur either (47).

HEV transmits via four different routes: a) it transmits through drinking contaminated water, b) it transmits through contaminated food c) it transmits through blood products and d) it transmits from mother to fetus (vertical transmission) (48).

Seroprevalence data

According to the classification of the World Health Organisation (WHO), countries are classified to three endemicity groups. The levels of endemicity correlate with hygienic and sanitary conditions of each geographic area (Figure 1) (49). In developed countries like United States, that belongs to low endemicity area, during 1995-2006, hepatitis A incidence declined 90% to the lowest rate ever recorded (1.2 cases per 100,000 population) (50), which is ascribed mostly to HAV vaccination program in children. In countries with intermediate rate of infection the prevalence of virus is between 30-50 percent. For example in a study in Ukraine 31.9% were seropositive (51) and in other study in Luxemburg the rate reached 42% (52). The seroprevalence rate in endemic countries like China reaches above 70% (53). In Iran the seroprevalence studies has shown that HAV is endemic and the rate in some province reaches over 80 percent (54, 55).

According to the classification of Center for Disease Control (CDC), countries are classified to three endemicity groups (Figure 2) (56). Seroprevalence data regarding HEV can be challenging because the period of time that IgG remains in system of infected people is not clear; in one study, nearly half of those who had been affected during a hepatitis E outbreak 14 years previously had no detectable anti-HEV (57). Anti-HEV antibodies have been found in healthy subjects living in all geographical areas, although the prevalence varies widely. In general, prevalence rates are higher in developing countries where hepatitis E is common than in countries where clinical cases due to hepatitis E are uncommon (54, 55, 58, 59).

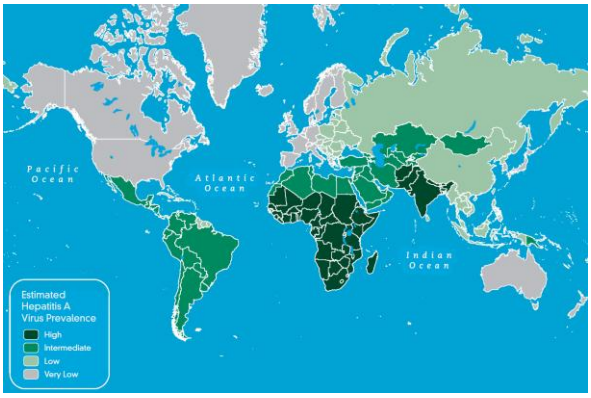

Figure 1. World map of HAV prevalence (http://wwwnc.cdc.gov/travel/yellowbook/2012/ chapter-3-infectious-diseases-related-to-travel/hepatitis-a.htm#362)

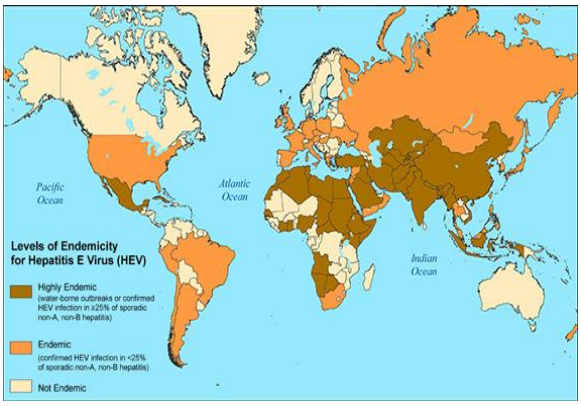

Figure 2. World map of HEV endemic areas. (http://www.cdc.gov/hepatitis/HEV/HEVfaq.htm#section1)

Clinical course

More than 80 percent of adults with hepatitis A are ill for up to eight weeks (60). The preicteric phase lasts five to seven days, with abrupt onset of fever, malaise, anorexia, nausea, vomiting, abdominal pain, and headache. Less common symptoms include chills, myalgias, arthralgias, cough, diarrhea, constipation, pruritus, and urticaria (61). Physical signs include tender hepatomegaly, splenomegaly, bradycardia, and posterior cervical lymphadenopathy (60, 61). The icteric phase, which lasts four to 30 days, begins with conjugated bilirubinuria followed within a few days by pale, clay-colored stools and jaundice (60). Chronic infection does not occur.

HEV infection manifests as subclinical to Fulminant disease in humans. Study of HEV transmission to volunteer shows that the incubation period is ranges from 15 to 60 days with a mean of 40 days (62). Clinical manifestations of HEV infection are similar to those of infection with other hepatitis viruses. The infection may be entirely asymptomatic, or may resemble an acute viral febrile illness without any characteristic features. Icteric hepatitis E occurs with increased severity in pregnant women with almost 20% mortality in the third trimester (63). It has been shown that HEV commonly causes intrauterine infection as well as substantial prenatal morbidity and mortality (48). Death is usually due to encephalopathy, hemorrhagic diathesis or renal failure.

No specific management is necessary for most patients with uncomplicated HAV and HEV infections. Common sense suggests patients should be advised to rest (when necessary) and dietary modification (avoiding foods that may cause digestive discomfort, such as fatty food).

Diagnosis

Initial diagnostic tests include determination of hepatic enzyme and bilirubin levels with follow-up viral serology for viral hepatitis, but there is little correlation between level and disease severity (61).

The anti-hepatitis A virus IgM test is the preferred confirmatory test for acute hepatitis A because it has high sensitivity and specificity when used on specimens from persons with typical symptoms (64). Serum anti-hepatitis A virus IgM usually can be detected five to 10 days before symptom onset, and the level remains elevated for four to six months. The anti-hepatitis A virus IgG level begins to rise soon after the IgM level, and anti-hepatitis A virus IgG is present throughout the person's lifetime, conferring immunity.

HEV can be detected via several tests. The first most routine test performed for those suspected of HEV infection is ELISA for IgM and/or IgG antibodies. These are also inexpensive and suitable assays for routine diagnosis and serology based epidemiological surveys. A positive result for anti-HEV IgM indicates acute HEV infection. The presence of high or increasing titer of anti-HEV IgG may additionally support the diagnosis of acute HEV infection and in such cases acute hepatitis E can be presumed even in the absence of IgM anti- HEV.

RT-PCR could be used to detect HAV and HEV RNAs in acute phase patients both in sera and in stool samples (65-68). Viruses could also be detected in sewage and untreated water using this technique, too (69, 70).

Prevention

Almost all HAV infections are spread by the fecal - oral route, good personal hygiene, high quality standards for public water supplies and proper disposal of sanitary waste have resulted in a low prevalence of HAV infections in many well developed societies (31). Within households, good personal hygiene, including frequent and proper hand washing after bowel movement and before food preparation, are important measures to reduce the risk of transmission from infected individuals before and after their clinical disease becomes apparent.

For pre-exposure protection, the use of hepatitis A vaccines instead of IG is now highly recommended. Immunization should be a priority for persons at increased risk of acquiring hepatitis A. For post-exposure prophylaxis of non-vaccinated people, the passive administration of IG can modify the symptoms of infection, provided it is given within 2 weeks of exposure. No special precautions are demanded for vaccinated persons (71).

There is an inactivated vaccine for HAV that is administered in two doses to children above 2 years old in United States and some other developed countries. The vaccine is also should be administered to those risk groups like homosexual men, intravenous drug addicts and health care workers who are in professional hazards of infection (72). Universal immunization would successfully control hepatitis A, although at present, high costs and limited availability of vaccines preclude such a recommendation (73).

As fecal–oral transmission is the predominant mode of transmission of HEV infection, measures aimed at proper treatment and safe disposal of human excreta, provision of safe drinking water supply and improvement in personal hygiene form the keystones for its prevention. In addition, it may be important to place emphasis on implementing sanitary food-handling practices, and avoiding consumption of undercooked or uncooked meat and vegetables. The virus has been shown to be heat labile (74).

During an epidemic setting, measures to improve the quality of water, even one as simple as boiling, have been shown to lead to rapid abatement in the number of new cases. Chlorination of water supplies may be useful in neutralizing the virus. In an outbreak in India, a failure of chlorination was associated with an increase in the number of cases (75).

In non-endemic areas where occasional cases of HEV infection appear to have been acquired by a zoonotic route, preventive measures directed against such spread (particularly cooking porcine and deer meat) may be useful. Prophylactic efficacy of pre- and post-exposure immunoglobulin has been evaluated for controlling HEV infection. The administration of immune serum globulin from endemic areas did not decrease infection rates during epidemics (76).

At present, no commercial vaccine is available against HEV. However in experimental animals, passive immunization with high-titer convalescent

phase sera from a cynomolgus monkey, previously infected with HEV, appeared to provide protection against clinical disease (icterus), but could not prevent virus replication and shedding in stool (77). In another study, a recombinant vaccine was tested on military personnel in Nepal that showed good protection (78), but this study did not prove that virus inhibits virus replication, thus transmission and the titer of antibodies dropped in high percentage of volunteers at the end of study.

Conclusion

The first line of defense against these infections is improvement of sanitary and hygienic practices to eliminate fecal contamination of food and water. HAV vaccination has been effective in reducing the incidence of infection in different communities (79, 80). Even though there is no commercially available HEV vaccine, improving the sanitation conditions and administering careful procedure in preparing food and chlorination or even boiling the water has been shown to decrease the HEV infection rate in epidemics, until the time when an efficient and cheap vaccine would be available in near future for public use. However unfortunately, these two infections cannot be eradicated, since both of the viruses responsible for these infections have animal reservoirs.

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