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HEPATITIS E INFECTION - A REVIEW

Gotseva A.,
Kunchev M.
Laboratory of Virology, Military Medical Academy, Sofia, Bulgaria
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Abstract

This review article summarizes the current knowledge about hepatitis E virus (HEV) infection and focuses on its the potential impact on human health. HEV has four major genotypes that cause human disease. Clinical severity of infection varies with HEV genotype, age and immune status of infected individuals. HEV generally causes self-limiting acute hepatitis in young adults. Genotypes HEV-3 and HEV-4 have been responsible to the development of chronic infection in immunocompromised or transplant patients, those with pre-existing liver disease and cancer patients. HEV is associated with progression to fulminant liver failure and high maternal and fetal mortality during pregnancy, particularly in the third trimester. HEV-induced extrahepatic complications can occur in both acute and chronic infection. Standard diagnostic tests for hepatitis E include the serologic and molecular assays.

Keywords: Hepatitis E, HEV genotypes, anti-HEV IgM/IgG, HEV RNA

Introduction

Hepatitis E is an inflammation of the liver caused by infection with the hepatitis E virus (HEV). It is estimated that approximately one-third of the global population has been exposed to HEV. Each year more than approximately 20 million estimated cases of HEV infection occur globally[1]. HEV is an important cause of acute hepatitis, chronic infection and may lead to fulminant hepatic failure (FHF) by risk groups. HEV infection has been associated with a wide spectrum of extrahepatic manifestations. The disease is a major public health concern, in both developing and industrialized countries. There are distinct epidemiological patterns of hepatitis E in different geographic regions. HEV is responsible for multiple epidemics in resource-poor countries and has become increasingly prevalent as a zoonotic viral infection in developed countries as well. HEV seroprevalence is high in the hyperendemic regions, where the source is usually contaminated water. The reported rates of anti-HEV antibodies in adults in these areas are 30 to 80% [2]. In the low endemic regions, which include developed countries (the Americas and Europe) zoonotic transmission plays an important role and hepatitis E occurs as isolated cases and small outbreaks. The prevalence HEV in the Bulgarian population remains underestimated [3]. For the first time, HEV infection in Bulgaria was reported in 1995.

Etiology, Epidemiology

Historically, Hepatitis E virus was first recognized in 1978 during an epidemic in Kashmir Valley in northern India, with 52 000 cases of hepatitis resulting in 17 000 deaths [4]. In 1983, during an unexplained hepatitis outbreak among soldiers the Russian virologist Mikhail Balayan visualized the virus through electron microscopy and confirmed the existence of HEV through self-experimentation by oral administration of pooled stool extracts of 9 patients. This experiment led to the identification of HEV as an enterically transmitted virus [5]. In 1990, Reyes et al. cloned and sequenced hepatitis E virus genome.

HEV is a hepatotropic, single-stranded RNA virus, non-enveloped, of the Hepeviridae family. The viral genome is approximately 7.2 kb in length, comprising a short 5′ noncoding region (NCR), a 3′ NCR, and three open reading frames (ORF1-3). Among these regions, ORF1 encodes nonstructural (functional) proteins (e.g., RNA-dependent RNA polymerase, methyltransferase), ORF2 encodes the viral capsid protein, which is highly immunogenic, and antibodies against this protein have neutralizing and protective features. ORF3 is a small protein, necessary for viral release from infected cells and ORF4 is critical for the replication process [6].

Among the eight different genotypes identified to date, HEV-1, HEV-2, HEV-3, and HEV-4 are the most frequent genotypes causing infections in humans. The genotypes have distinct routes of transmission and geographical distributions. HEV-1 and HEV-2 only infect humans and they spread through fecal-oral route, able to result in large-scale outbreaks originating from contaminated water supplies. Genotypes 3 and 4 are detected mainly in Europe and North America, circulate in animal species such as pigs, wild boars and deer. They are primarily zoonotic and and transmitted to humans through the consumption of raw or undercooked meat, such as pork and deer or shellfish. There are zoonotic reservoirs among swine, wild boars, deer and camels. Swine are the main reservoir and the most commonly implicated source of HEV-3 and HEV-4 [7]. Pig farms are known to have high rates of HEV infections, and the consumption of pork products, especially those containing pig liver is associated with these infections [8]. To summarize, HEV-1 and HEV-2 cause epidemic and endemic diseases in resource poor countries, primarily spreading through contaminated drinking water. HEV-3 and HEV-4 generally cause autochthonous infections and sporadic cases, mainly affecting adults aged older than 40. The

hepatitis E illness is uncommon in locations with improved water supply and sanitation. The poor hygiene and sanitation remain significant contributors to hepatitis E transmission in developing countries

The global distribution of HEV has distinct epidemiological patterns based on socioeconomic and ecological factors. Hepatitis E is found worldwide, but it is most common in sub-Saharan Africa and east and south Asia. Major hepatitis E outbreaks have been reported in Asia, the Middle East, Africa, and Central America [9]. Many hepatitis E cases were reported in refugee camps in South Sudan [10].

People are infectious during the detection of HEV in the stools. HEV can be transmitted via the fecal-oral route, zoonotic route, blood transfusion and vertical transmission (maternal-fetal). Infected blood or blood products from a viremic patient should be considered as a possible transmission route for HEV [11]. In recent years, the transmission of HEV-3 and HEV-4 through blood transfusions has been increasingly reported in Europe [12].

Clinical presentation

Hepatitis E can present with a wide range of clinical manifestations. The majority of HEV infections are asymptomatic. Symptomatic cases present as acute icteric hepatitis, which occurs in 5%-30% of infected people and resolves within 2–6 weeks [13]. Patients with acute infection may have prolonged cholestasis with protractrd jaundice. An altered immune status, hormonal levels, and viral factors may be related to the severity of the disease [14]. HEV usually causes acute, self-limited hepatitis in immunocompetent individuals. The major risk groups for HEV infection are pregnant women, immunocompromised individuals and patients with underlying chronic liver diseases. Chronic infection, almost exclusively with HEV-3, occurs in immunocompromised individuals [15]. Approximately 20% of solid-organ transplant patients develop persistent HEV infection, often asymptomatic or with minor liver enzyme increases. Immunosuppressive therapy has been proposed to be a key factor for developing chronic hepatitis E in solid-organ transplant recipients. Pregnant women, recipients of solid organ transplants, those with pre-existing liver disease and immunocompromised patients, may develop fulminant hepatic failure. HEV is an important contributor to maternal morbidity and mortality. The pregnant women infected with HEV-1 are the risk group for a severe HEV course [16].

HEV infection in pregnancy is associated with high risk of preterm labor and vertical transmission, and can be life-threatening with mortality rate up to 30% due to the development of HEV-induced fulminant hepatitis [17]. The mechanism of liver injury is not yet clear. During pregnancy, levels of progesterone, estrogen, and human chorionic gonadotropin increase as pregnancy advances. These hormones play a considerable role in altering immune regulation and increasing viral replication. During an outbreak in Sudan in 2010 to 2011, among 39 pregnant women with HEV infection there were 14 intrauterine deaths and 9 premature deliveries [18]. During the HEV outbreak Niger in 2017, 44.7% of recorded deaths, were in pregnant women [19]. Some studies have reported the prevalence of HEV among pregnant women in China from 0.2–4.11% (anti-HEV IgM) and 11.1–20.27% (anti-HEV IgG), respectively [20,21].

HEV-induced liver cirrhosis is a complication only seen in immunocompromised patients. HEV infection increases the rate of liver disease progression in patients with chronic HBV infection.

In addition to hepatic manifestations, extrahepatic complications (pancreatitis, renal impairment, neurological symptoms, hematological disorders, and mixed cryoglobulinemia) can occur in both acute and chronic HEV infection, [22]. The extrahepatic manifestations induced by different genotypes of HEV vary. Involvement of both the peripheral nervous system and CNS can occur together or in isolation. HEV infection has been associated with development of Guillain-Barré syndrome (GBS). Many studies have reported the high prevalence rate of HEV infection among GBS patients and several case reports have been documented showing the coexistence of acute hepatitis E with GBS. Also, cases of acute HEV infection have been found in pediatric patients with GBS [23]. GBS and neuralgic amyotrophy are the most frequent neurological manifestations. In the Netherlands and the UK, neuralgic amyotrophy has been reported in up to 10% of cases. It is characterized by painful upper extremity mononeuropathy and motor weakness, frequently affecting the brachial plexus [24]. Hematologic manifestations include anemia due to glucose-6-phospate dehydrogonase deficiency, autoimmune hemolytic anemia and severe thrombocytopenia. Membranoproliferative glomerulonephritis and relapse IgA nephropathy with or without coexisting cryoglobulinemia appear to be the most common renal injuries related with HEV infection. Also, HEV infection has been associated with acute pancreatitis [25]. Membranoproliferative glomerulonephritis and relapse IgA nephropathy with or without coexisting cryoglobulinemia appear to be the most common renal injuries related with HEV infection. Renal biopsies in affected patients show histological patterns of membranoproliferative and membranous glomerulonephritis. Most typically, HEV genotypes 1 and 3 may be associated with glomerulonephritis. All extrahepatic signs are caused by either direct HEV replication in these tissues, or indirectly by various immune mediated mechanisms.

Diagnosis

Laboratory diagnosis of hepatitis E infection is usually based on the detection of HEV- specific antibodies (anti-HEV IgM/IgG) and detection of HEV RNA. Anti-HEV IgM antibodies have a positivity for a short period of time (approximately 3-4 months), but sometimes it persists for a year [26]. Anti-HEV IgG antibody is relatively long-lasting, but do not provide lifelong immunity and their levels in the serum decreases over time. IgG anti-HEV represents current or past infection [27].

Serologic tests are not reliable enough tools in immunosuppressed patients. Because of the possibility of undetectable antibody levels, molecular testing is preferable over antibody testing in these individuals.

Detection of HEV RNA in blood or stool characterizes chronic or acute HEV infection. Chronic HEV infection is defined as an HEV viremia for more than 3 months. The detection of HEV RNA facilitates the diagnosis of HEV infection in immunocompromised patients without an adequate antibody response. The molecular diagnosis of HEV infection by polymerase chain reaction (PCR) exhibits high sensitivity and specificity. PCR assays are important for the detection of acute HEV infection as well for monitoring chronic cases of hepatitis E. Detection of HEV-RNA by molecular genetic methods has been considered the "gold standard" [28]. HEV RNA can be detected in the blood after 3 week of exposure, and viral shedding lasts approximately 4-6 week in the stool. In immunocompromised individuals, HEV can take up a more chronic course with prolonged viremia [29]. Immunosuppressive therapy has been proposed to be a key factor for developing chronic hepatitis E in organ transplant recipients. European Association for the Study of the Liver (EASL) suggests testing for hepatitis E in patients with unexplained flares of chronic liver disease.

Tretmant, Prophylaxis

Ribavirin has antiviral activity against HEV. Within the past years, ribavirin has been successfully used to treat chronic HEV infections. The associated sustained virological response is approximately 80%.

The recombinant hepatitis E vaccine, the first prophylactic vaccine against HEV infection, was approved in China in December 2011 [30]. The vaccine is given in a three-dose schedule (0, 1, and 6 months). To reduce the risk of contracting HEV while traveling to endemic areas, it is important to maintain hygienic practices.

Conclusion

HEV has increasing prevalence worldwide. The HEV infection it was traditionally thought to occur in individuals travelling to areas where the disease is endemic, however, cases of sporadic hepatitis E have been reported in individuals with no history of recent travel. In the European countries, in most cases HEV infection is an autochthonous. Although HEV mainly results in acute self-limiting hepatitis in the immunocompetent individuals. Immunocompromised patients, infected with genotype 3 or 4 may develop chronic infection, which then may lead to cirrhosis. Certain populations, such as pregnant women are at particularly high risk of severe HEV infection. Progression to fulminant liver failure is rare.

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