HEPATITIS E VIRUS

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Introduction

Hepatitis E virus (HEV) is the major cause of acute viral hepatitis in adults in the Kathmandu Valley in Nepal, including in the Royal Nepal Army. HEV causes sporadic, year-round cases of acute jaundice as well as recurrent, seasonal outbreaks. The serious negative impact of HEV on the Royal Nepal Army, including its interference with training and readiness for overseas deployment, has been established and previously documented.

Biology

Hepatitis E virus is a single-stranded RNA virus. Analysis of the genome of isolates collected globally has led to classification of three distinct genotypes. Despite this genomic heterogeneity, all known HEV isolates share at least one common, cross-reactive epitope in the viral capsid protein as demonstrated by serologic assays of antibodies to the viral capsid antigen. Therefore, there are several HEV genotypes, but only one known serotype. This situation is very similar to hepatitis A virus (HAV) and suggests that, just like with HAV, a vaccine for HEV should be equally effective against HEV isolates anywhere in the world.

Transmission and Epidemiology

HEV is transmitted to humans by fecally contaminated water or, less commonly, food. Outbreaks typically occur during periods of heavy rains when drinking water is most likely to be contaminated. The key event, however, is cotamination of water supplies and outbreaks may also occur during dry seasons when reduced water flow may lead to contamination and concentration of HEV. Unlike HAV, secondary cases of HEV due to person-to-person transmission are highly unusual. The reason for this difference is unknown but may be because HEV is less stable in the environment than HAV, viral fecal titers of HEV are lower than HAV of because the infectious dose (the number of viral particles required to cause and infection) is higher for HEV compared to HAV.

In some HEV endemic areas, including Nepal, outbreaks of HEV tend to recur regularly. This suggests there might be a reservoir that perpetuates HEV between outbreaks. Humans are the only known reservoir for HAV and this may also be true for HEV. However, it has been recently shown that HEV is quite common in various peri-domestic animals, including pigs, cattle, sheep, rats and other rodents in disease-endemic areas. Furthermore, it has been demonstrated that animal and human isolates within a geographic area tend to be more closely genomically related than human isolates from different geographic areas. Taken together, these data suggest that HEV may be a zoonotic disease.

Clinical Disease

the incubation period for HEV is usually about 6 weeks, with a range from 2 to 10 weeks. Infection may result in several different outcomes. The majority of infections result in no symptoms or clinical illness. Individuals may present with a non-specific febrile illness (anicteric hepatitis) that is likely to go undiagnosed because of the absence of overt jaundice. Acute icteric hepatitis is seen in a small minority of cases. All together, for every 3 or 4 infections, only one cases of jaundice ocurs. When jaundice occurs, it is usually preceded by a non-specific prodromal illness lasting several days and consisting of

fever, "flu-like" symptoms, and abdominal pain. These symptoms resolve rapidly with the onset of jaundice, dark urine, and clay-colored stools. Significant laboratory tests include elevated serum bilirubin (mainly conjugated) and bilirubinuria, and elevation of liver function tests, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). Mild elevation of serum alkaline phosphatase also may be seen. Although HEV is sometimes said to cause "cholestatic hepatitis," this may be misleading. In fact, the clinical and laboratory picture of HEV is indistinguishable from other causes of acute viral hepatitis, including HAV, HBV, and HCV. A cholestatic presentation (persistent jaundice with itching and markedly elevated alkaline phosphatase) occurs in a very small number of cases, similar to what is seen with HAV infections. However, histologic examination of the liver is more likely to reveal a cholestatic type of hepatitis in HEV infections than in other causes of acute viral hepatitis. Most causes of HEV resolve completely after about 2 to 6 weeks. Unlike HBV or HCV infections, HEV does not result in a chronic infection or cirrhosis.

The overall mortality rate of HEV is less than one percent. However, pregnancy is associated with a more severe liver disease and a high mortality rate (15-30%), especially when infection is acquired during the third trimester. Spontaneous abortions, stillbirths, and maternal death are also more common when HEV infection complicates pregnancy. The liver injury caused by HEV infection is most likely due to the resultant cellular immune response, including cytotoxic lymphocytes, rather than any direct cytoxicity of the virus itself. However, the reason for the more severe liver disease in pregnancy is not currently understood.

Diagnosis

Infection with HEV can be diagnosed by detection of serum antibodies to HEV or by identification of virus RNA by the reverse transcriptase polymerase chain reaction assay (RT-PCR). HEV RNA can be found in almost all patients in either the serum or feces at the time of onset of jaundice and RT-PCR usually remains positive for about 2 weeks. In unusual cases, HEV RNA may persist in serum or feces for as long as 2 to 4 months before RT-PCR becomes negative. Relapse of viremia or fecal shedding, which is seen with HAV infections, has not been reported with HEV infections.

Serologic assays are also helpful in diagnosing infection with HEV. At the time of presentation with jaundice, both IgM and IgG anti-HEV antibodies are usually present in the serum. The presence of IgM antibodies is diagnostic of acute HEV infection. Serum IgG anti-HEV antibodies may persist for months to years and, therefore, amy indicates either recent or distant infection. However, recent infection can be established by a rise in IgG anti-HEV antibodies in serial serum specimens collected during the acute and early convalescent phases of illness.

Prevention

As is the case with other entrically transmitted diseases, prevention of HEV is best achieved by access to clean drinking water. If clean water is not availalbe, boiling water is likely to be effective. It is not clear if administration of immune serum globulin collected from donors in a disease-endemic area could effectively prevent HE disease; studies to date have yielded conflicting results. However, it has been demonstrated that protection of monkeys experimentally challenged with HEV can be achieved when anti-HEV antibodies are given in sufficiently high amounts. Therefore, lack of protection in some human studies may be because the ISG contained insufficient levels of anti-HEV antibodies.

Unfortunately, standard hygience control measures have not been effective in eliminating this disease. Therefore, effective vaccines are needed to assist in the prevention and control of HEV. No commercial vaccine is currently available, but experimental vaccines are being developed. Because HEV cannot be

effectively grown in tissue culture, current vaccine efforts have focused on developing recombinant HEV proteins. The capsid protein is the main target of these efforts because viral capsid antigens have been found to induce protective immune responses for a variety of other viruses. This is the same approach used to manufacture the hihly effective and safe vaccine against HBV. Recombinant proteins for vaccines are most often produced in yeast, Escherichia coli, or baculovirus expression systems. Recombinant HEV (rHEV) capsid protein expressed by the baculovirus system has been demonstrated to protect monkeys from experimental challenge with HEV. Researchers at the Walter Reed Army Institute of Research (WRAIR) conducted the first clinical trial of a rHEV vaccine in volunteers in the U.S. WRAIR and Nepalese scientists subsequently collaborated to extend the safety and immunogenicity record of the vaccine in volunteers in Nepal. The Royal Nepal Army and WRAIR are currently conducting an efficacy trial of the rHEV vaccine in a randomized, double-blinded study in 2,000 volunteers. The results of this trial should be available in late 2002. No other HEV vaccine has reached the stage of human safety and immunogenicity tests. This trial offers the best hope of identifying a safe and effective vaccine against HEV.

Conclusion:

Hepatitis E virus is a serious medical threat to the Royal Nepal. Army. Not only is it costly to provide the required medical care, infected soldiers are unable to train for weeks until they return to their regular health and are unavailalbe for deployment to overseas peacekeeping missions. Standard hygiene and sanitation control measures have not yet eradicated this disease, either in the RNA or in the civilian sector in the Kathmandu Valley. Therefore, a vaccine will also be very useful in the efforts to control HEV. The ongoing rHEV vaccine trial may identify the world's first vaccine to prevent HEV disease. This will be a great benefit to the RNA in its continuing efforts to maintain the good health of its service members.

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Suggested Reading:

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