Objectives

1. Discuss the potential clinical impact of Hepatitis D and Hepatitis E infections and how patients are diagnosed.
2. Describe how Hepatitis D and Hepatitis E are transmitted and discuss the effects of these viral infections on pregnancy and the risk of vertical transmission.
3. Discuss the current treatment options for Hepatitis D and Hepatitis E infected individuals, the limitations of treatment, and the potential for future prevention.

Article

Hepatitis D and E

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2. Describe how Hepatitis D and Hepatitis E are transmitted and discuss the effects of these viral infections on pregnancy and the risk of vertical transmission.
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Background and Significance of Hepatitis D

The first virus identified that caused hepatitis, was Hepatitis B, discovered in 1965. This was followed a few years later by the discovery of Hepatitis A in 1973. The Hepatitis D virus (HDV) or delta agent was the third hepatitis virus discovered. The first report on HDV was by Rizzetto and colleagues in Italy in 1977. The virus was identified within the liver cell of a patient who had hepatitis B, but it was distinct from the hepatitis B viral DNA (deoxyribonucleic acid). The viral particle was eventually found to be a defective RNA (ribonucleic acid) virus that was 35 to 37 nanometers in diameter but was encapsulated by the hepatitis B surface antigen protein coating. It is considered to be a defective virus because it requires a co-infection with Hepatitis B in order to support its replication. It is not seen in the presence of anti-HBsAg (the antibody to the surface antigen of hepatitis B) or as an infection by itself.

Three distinct genotypes have been cloned. Genotype I is the most common and has been found worldwide. Genotype II has primarily been found in Japan and other Asian countries, whereas genotype III is primarily found in South America.

An infection with Hepatitis D can develop in 3 separate ways. It can occur as an acute infection simultaneously with an acute hepatitis B infection; or it can present as an acute infection superimposed upon a chronic hepatitis B infection; and lastly it can be a chronic hepatitis D infection superimposed upon a chronic hepatitis B infection. Hepatitis D appears to compete somewhat with Hepatitis B in these co-infections, because the HBV-DNA titer often decreases when an individual becomes infected with HDV.

Even though this virus has been known for nearly 25 years, the significance of its impact on healthcare is still relatively undefined. One of the reasons for this issue is that the virus cannot exist without a co-infection with Hepatitis B. Therefore, the majority of research has focused on Hepatitis B. However, a combined acute Hepatitis B / Hepatitis D infection will often take on a more fulminant course when compared to an acute hepatitis B virus infection alone. In addition, in patients who have a chronic Hepatitis B / Hepatitis D infection, about 75% will ultimately develop cirrhosis and up to 25% of these will eventually die from hepatic failure.
Patients with chronic Hepatitis B infections are at risk for developing hepatocellular carcinoma in the future. Surprisingly, the patients with hepatocellular carcinoma are usually HDV negative. One explanation for this finding is that HDV may somehow inhibit the development of hepatocellular cancer. However, because patients with chronic HBV / HDV infections often progress to cirrhosis quicker than those who are only HBV infected, another explanation may be that the time needed for developing hepatocellular carcinoma is lacking.

**Diagnosis of Hepatitis D**

Originally, the diagnosis of an acute Hepatitis D infection required the detection of the delta antigen in hepatic tissue obtained by liver biopsy. Today, reverse transcription polymerase chain reaction testing or RT-PCR-HDV can be used to detect the presence of the virus. Antibody testing can also be obtained and both IgM anti-HDV and IgG anti-HDV tests are available. For HDV, one of the difficulties is that the IgM antibody can remain positive for years. Therefore, a positive IgM antibody does not always signify a new infection. It must also be stated that the patient has to be HBsAg positive.

Another interesting finding is that an IgG antibody does not develop in every case. For example, if a person is infected acutely with Hepatitis B and Hepatitis D, they will be positive for HDV by the RT-PCR test and will also have a positive IgM antibody. However, if the infected individual develops immunity to the acute Hepatitis B infection by producing anti-HBsAg and their HBsAg becomes negative, the person's RT-PCR-HDV and IgM for HDV will also become negative (because HDV cannot exist without HBsAg). In some of these cases, an IgG antibody has not formed and therefore, no serologic marker for a prior HDV infection remains. When the IgG antibody does develop, it will usually remain positive in patients who become chronically infected and can persist for years in cases where the patient has become immune.

Diagnosing an acute HDV infection on top of a chronic HBV infection can be difficult, because the IgM antibody can remain positive for years in some patients. However, an acute HDV infection (in a chronic HBV infected individual) is assumed if the patient shows an elevation in their liver function tests in conjunction with a positive RT-PCR-HDV and a positive IgM anti-HDV test. Some researchers suggest obtaining serial titers of anti-HDV antibodies to better differentiate acute from chronic infections. If the patient has a positive RT-PCR-HDV test for more than 6 months, they are assumed to have a chronic HDV infection.

**Transmission of Hepatitis D**

Transmission of Hepatitis D is similar to that of Hepatitis B. In areas of high concentration, such as the Mediterranean and northern parts of South America, it appears that transmission involves both the percutaneous route (illicit IV drug usage and blood products) as well as the permucosal route (through intimate contact, etc). In areas where HDV is not endemic, the primary route of transmission is percutaneous.

Blood and blood products in the United States are not tested for HDV because the virus cannot live without the presence of HBsAg. Blood is always tested for Hepatitis B and if absent, there is essentially no risk of transmitting HDV.

**Vertical Transmission of Hepatitis D**

Vertical transmission of the Hepatitis D virus from a mother to her child has also been documented; however, the complete significance of this is unknown. Very few pregnant women with an ongoing HDV infection have been studied. Therefore, the true incidence of transmission in pregnant women with a dual infection is not known. However, as stated several times before, HDV requires an infection with HBV. Therefore, if the child does not become HBV infected, then perinatal HDV infection cannot occur. Unfortunately, because a dual infection in adults is usually more severe than an HBV infection alone, likewise, a dual infection in a child is usually more severe.

In the cases where vertical transmission has occurred, there is no evidence of in utero passage of the virus. Like Hepatitis B, if perinatal transmission occurs, it probably occurs at the time of delivery. Therefore, appropriate immunization of the newborn in cases where a mother is HBsAg positive will also minimize the potential for HDV transmission.

**Treatment of Hepatitis D**

Unfortunately, for patients with an active HDV infection, no specific treatment has been found that greatly impacts the disease course. Currently, most specialists use interferon alpha therapy. However, as seen with Hepatitis B, relapse is
common when treatment is discontinued. In addition, several researchers have studied the potential benefit of using Lamivudine, a treatment that has been used for Hepatitis B. In these cases, the HBV-DNA titers fell when Lamivudine was administered. Unfortunately, it did not appear to affect the viral load of HDV.

Therefore, the best treatment against HDV is prevention. If children and adults are vaccinated with the Hepatitis B vaccine and become immune, they cannot become infected with Hepatitis D. If a person is acutely exposed to Hepatitis B, the treatment involves the use of hepatitis B immunoglobulin (HBIG) followed by the vaccine series. Therefore, if an individual is susceptible, and is exposed to someone with a dual infection, the acute treatment is still HBIG; no hepatitis D immunoglobulin is available.

**Background and Significance of Hepatitis E**

The first report on this new virus actually occurred in 1957 when approximately 30,000 cases of hepatitis developed in Delhi, India in the winter of 1955-56 following a sewage contamination of the city water. The virus appeared to have an oral-fecal spread and did not have an apparent chronic disease state. The pattern and course of the infection were very similar to Hepatitis A but testing that was performed later revealed that it was something different. The disease was eventually called epidemic enterically transmitted Non-A, Non-B hepatitis.

Between 1984 and 1988, several researchers described the detection of virus-like particles by immune electron microscopy in fecal specimens of patients with enterically transmitted Non-A, Non-B hepatitis. In 1989, the detection of a viral antigen in liver tissue using an immunofluorescent method was described. Reyes et al eventually reported the isolation of the virus in 1990. It was found to be a 32 to 34 nanometer, single stranded, non-enveloped RNA virus that was distinct from the other hepatitis viruses and was labeled Hepatitis E (HEV).

The majority of literature on this viral infection in the early 1990’s came from epidemics and sporadic cases seen in Asia, North Africa, and Mexico. In addition, the only cases seen in the United States occurred in individuals who had contracted the virus while traveling in countries where the virus was endemic. However, in the past 5 years, numerous sporadic cases have been reported in Europe, the United Kingdom, South America, and the United States in people who have not traveled and have no explanation for developing the infection. Because of the explosion in viral study and DNA / RNA sequencing, it has now been suggested that several genotypes of HEV may exist due to significant differences between isolates. The first two and most prevalent genotypes are the Asian/Burmese (genotype 1) and the Mexican (genotype 2). The United States genotype is 3 and there may be up to 6 others from China, Argentina, Europe, and North Africa. In addition, recently an HEV-like virus was isolated from swine in Iowa, which could represent a potential for human exposure in and around farm operations.

Hepatitis E has a relatively short incubation of 4 to 10 weeks with a mean of 40 to 45 days. Initially, the knowledge of this virus came from studies involving acute infections and it was assumed that the majority of individuals who contracted the virus had clinical symptoms. However, prevalence studies are now occurring and evidence of past infection in groups of individuals from endemic countries is as high as 50% to 60%, many of which had no symptoms. In addition, seroprevalence rates in non-endemic countries ranges from 1% to 10% (again, most individuals reporting no symptoms). Therefore, many infections are probably sub-clinical, similar to Hepatitis A.

In endemic countries, such as India, Hepatitis E is responsible for nearly half of the acute cases of hepatitis. One has to question why infection with this virus seems to be on the rise or is now playing a major role in cases of acute hepatitis. Some of this is due to the fact that healthcare providers and researchers are now testing for this virus; however, it is also possible that something genetically has changed and the virus has become more pathologic over time.

**Diagnosis of Hepatitis E**

The diagnosis of an HEV infection is by clinical presentation in conjunction with positive serology. Usually, Hepatitis A, B and C are ruled out first. An anti-HEV by fluorescent antibody blocking assay or by enzyme-linked immunosorbent assay (ELISA) can detect IgG and IgM antibodies. A positive IgM antibody is indicative of acute infection and this antibody usually disappears within 3 to 6 months. The IgG antibody will usually stay positive and current research shows that it remains for years.

The virus can also be detected in the blood by polymerase chain reaction (PCR) testing; however, this test is usually only performed in research laboratories. The presence of the virus in blood and stool seems to occur about 1 to 2 weeks before the onset of clinical symptoms, if symptoms develop. Viral shedding in the stool on average only lasts for about 2
to 4 weeks; however, in rare cases, fecal shedding has been reported to last up to 7 weeks. Likewise, viremia is also relatively short and in most cases is no longer detected by the time of biochemical resolution. However, as seen with stool shedding, rare cases of viremia have been reported to last for up to 16 weeks.

**Transmission of Hepatitis E**

When large epidemics of acute HEV occur, the majority of these almost always trace the source to contaminated drinking water (an oral-fecal spread like Hepatitis A). However, unlike Hepatitis A, these studies do not appear to show much person-to-person transmission. Therefore, though not completely tested, transmission from saliva or through intimate contact during acute infections seems uncommon. How transmission occurs in sporadic cases is not completely understood. Because an HEV-like virus has been detected in some swine, it may be shown that some transmissions occur from an animal or insect vector. This possibility, however, has not been proven to date. Finally, because there is no known chronic carrier state, transmission through blood and blood products is minimal. The only potential for this avenue of transmission would be if blood were donated when an individual was viremic.

Based on clinically apparent infections, the highest attack rate seems to occur in young adults between the ages of 15 and 40. The mortality rate (in the non-pregnant population) is also low ranging from 0.05% to 0.5% overall and is basically only seen in cases that become fulminant.

**Vertical Transmission of Hepatitis E**

Hepatitis viral infections in general are not any more severe in women who are pregnant compared to the non-pregnant state; however, this virus acts differently. In the pregnant population in endemic countries, the attack rate is higher if a woman is pregnant and the mortality rate is increased, reaching as high as 25% in some studies. Whether this increase in severity seen in pregnancy is due to the pregnancy itself or the poor living conditions and malnutrition that is often seen in these populations is uncertain. In the case of pregnancy, the development of fulminant hepatitis needs to be closely observed.

Furthermore, vertical transmission of this virus has been reported though the true incidence is unknown due to small numbers. Khuroo et al described 10 women in India who developed acute HEV in the third trimester. Six of these women developed fulminant hepatic failure and 3 died (two of which were undelivered). In the evaluation of the 8 delivered infants, 5 (63%) showed strong evidence for transplacental infection with positive cord blood for HEV RNA by PCR (all 5), elevated liver enzymes at birth (all 5) and positive IgM antibody (3 of 5). Two of these neonates died and on autopsy, one showed massive hepatic necrosis. All 8 neonates were positive for IgG antibody, as would be expected since IgG antibodies can cross the placenta. The 3 surviving infected neonates remained IgG positive. Two apparently uninfected infants cleared antibody at 3 and 6 months. The final case was still IgG positive at 6 months. Other studies on pregnant women with fulminant Hepatitis E have fetal loss rates reaching 50%. Again, the reason for these high fetal loss rates may be partly due to the living conditions and nutritional status of these pregnant women.

**Treatment of Hepatitis E**

At the present time, no treatment has been described for an acute HEV infection other than supportive care. Standard immune globulin for household contacts is of little or no benefit because significant antibody levels to HEV have not been detected in immune globulin. Future treatment will probably require a separate HEV immune globulin that may need to be developed from plasma obtained in endemic areas where a high concentration of IgG antibody is detected.

The development of a vaccine will also be beneficial to travelers and could also prove useful in immunizing children who live in highly endemic areas. However, an effective vaccine is currently not available.

Some unanswered questions still exist for this virus. During acute infection, is the virus found in other body fluids such as saliva, semen, and vaginal secretions? Can the virus be transmitted between children in daycare settings like Hepatitis A? Can the virus be transmitted sexually during the acute phase of viremia? Is this infection more fulminant for pregnant women and their unborn babies if it develops in industrialized countries such as the United States?

What is becoming apparent is that the detection of this virus is occurring in all continents. In addition, there is some suggestion that there could be an animal or insect vector. Because of this, healthcare professionals should remain cognizant of this virus.
References or Suggested Reading:

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About the Author(s)

Dr. Towers is currently Professor and Vice Chair of the Department of Obstetrics & Gynecology at University of Tennessee Medical Center Knoxville in the Division of Maternal-Fetal Medicine. He is still clinically active managing numerous high-risk pregnancies. He is also actively involved in research with over 90 publications in major medical journals. Though his research has spanned many areas in obstetrics, he has primary interests in drugs in pregnancy, infections in pregnancy, fetal heart monitoring, bleeding in pregnancy, and fetal lung maturity.

He has authored a book for consumers regarding the safety of over-the-counter medications that are used in treating the common cold entitled “I’m Pregnant & I Have a Cold – Are Over-the-Counter Drugs Safe to Use?” published by RBC Press, Inc. He is also one of the new Editors of the reference book for clinical care providers entitled “Drugs in Pregnancy and Lactation,” published by Wolters & Kluwer.