ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Hepatitis E Virus Infection and Cirrhosis of the Liver

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G&H How common is hepatitis E virus infection?

JMP Throughout the world, there are approximately 20 million hepatitis E virus infections each year. This number includes approximately 3.3 million cases of acute (ie, symptomatic) hepatitis E virus cases, which means that many patients infected with hepatitis E virus are asymptomatic. There are 4 main genotypes: hepatitis E virus genotypes 1 and 2 are mainly found in developing countries, and genotypes 3 and 4 are mainly found in developed countries.

Although hepatitis E virus infection is most commonly found in developing countries, it is important for physicians in developed countries such as the United States to keep in mind that this disease does not occur only in people who have traveled abroad. In fact, most cases of acute hepatitis E virus infection in the United States and Europe are autochthonous. It has been shown that more than 95% of hepatitis E virus cases in Europe are locally acquired, and this number is probably approximately the same or a little less in the United States (where there are fewer data).

G&H What are the risk factors for this disease?

JMP There are different risk factors for hepatitis E virus infection in developing countries (genotypes 1 and 2) as opposed to developed countries such as the United States (genotypes 3 and 4). The main risk factor for hepatitis E virus genotypes 1 and 2 is contamination through drinking water. For example, in the rainy season, feces may contaminate drinking water, which can create a large epidemic of the virus. There can also be sporadic cases of these genotypes.

In contrast, hepatitis E virus genotypes 3 and 4 are contracted by eating contaminated meats. These genotypes are zoonoses, meaning that the virus is present in some animals. These animals are not sick, but they can transmit the virus if their flesh, especially their liver, is eaten. The main species that can transmit hepatitis E virus is swine, but deer and rabbits can transmit the virus as well.

G&H Does hepatitis E virus infection cause cirrhosis?

JMP In hepatitis E virus infection, it is important to differentiate patients who are immunocompetent and those who are immunosuppressed. If an immunocompetent patient, including a patient with cirrhosis, is infected with hepatitis E virus, acute hepatitis E virus infection can develop, but chronic infection will not result. Therefore, hepatitis E virus infection does not cause cirrhosis in immunocompetent patients.

On the other hand, cirrhosis may develop in a patient who is immunosuppressed. Immunosuppressed patients include those who have undergone transplantation, those who are HIV-infected and have low CD4 T-lymphocyte counts, and those on chemotherapy, especially in hematology units. If, for example, a patient who has undergone solid organ transplant is infected with hepatitis E virus, he or she has a 50% risk of developing chronic hepatitis E virus and can acquire liver cirrhosis within several years.

G&H Why do immunosuppressed patients with hepatitis E virus infection develop cirrhosis?

JMP Patients who are immunosuppressed have weak immune systems that cannot eradicate the virus, and thus allow it to stay and replicate in the liver. The patient therefore develops chronic hepatitis and experiences an increase in liver enzymes. For years, the virus continues to replicate, and cirrhosis eventually develops.

In contrast, in immunocompetent patients, the immune system sees the virus replicating in the liver and is able to destroy the liver cells, which creates acute hepatitis. The virus is then cleared, and the patient is cured.

G&H Can the progression to cirrhosis in immunosuppressed patients be reversed or stopped?

JMP The progression to cirrhosis in immunosuppressed patients is fairly rapid. Around 10% of these patients develop cirrhosis within 5 years. Ribavirin is the antiviral agent of choice for patients with chronic hepatitis E virus infection. This direct antiviral agent has been used for years in combination with interferon for the treatment of chronic hepatitis C virus infection. A 3-month regimen of ribavirin monotherapy (600-800 mg/day, according to the weight of the patient) can eradicate the virus and cure approximately 70% to 80% of these patients.

Therefore, it is recommended to treat patients before they develop cirrhosis. Unfortunately, there are usually no specific signs until the patient has overt cirrhosis. Complications of cirrhosis can include jaundice, ascites, encephalopathy, and ruptured varices.

G&H What follow-up care is required in immunosuppressed patients?

JMP Treatment is usually given for 3 months. The patient's viral load should be monitored every month during treatment and needs to be negative before the end of treatment at the third month. Also before stopping treatment, the physician should check for the presence of hepatitis E virus in the stool of the patient. If both the patient's blood and stool are negative for the presence of hepatitis E virus, treatment can be stopped after 3 months. The physician needs to check the patient's blood and stools for the virus 1, 3, and 6 months later. If each test is negative, the patient can be considered cured.

G&H Are there any side effects or potential drug-drug interactions associated with hepatitis E treatment in immunosuppressed patients?

JMP The main side effect of ribavirin is hemolytic anemia, so it is important to check the patient's red blood cell counts. It should also be noted that ribavirin is teratogenic.

To my knowledge, there are no significant drug-drug interactions with ribavirin.

G&H Since it is important to treat patients with immunosuppression early, before they develop cirrhosis, how is hepatitis E virus detected?

JMP In immunosuppressed patients, diagnosis relies on genomic testing (ie, polymerase chain reaction testing for viral RNA in the blood or feces). This should be done in any patient who has elevated liver enzymes. Serodiagnostic tests are not very reliable in immunosuppressed patients. This is unlike immunocompetent patients, in whom immunoglobulin (Ig) M levels have a very high sensitivity and specificity when diagnosing acute hepatitis E virus infection.

G&H How does the disease course of immunocompetent, cirrhotic hepatitis E patients compare with that of immunosuppressed hepatitis E patients?

JMP First of all, it should be noted that patients who already have liver cirrhosis are not more likely than non-cirrhotic patients to contract hepatitis E virus infection. If cirrhotic patients who are immunocompetent contract hepatitis E virus infection, they will have more clinical symptoms than other patients. These patients can have ascites, jaundice, encephalopathy, and possibly even ruptured varices, and hepatitis E virus can induce clinical decompensation of their liver cirrhosis. The risk of death is higher in these patients.

G&H What is the mortality rate of hepatitis E virus infection?

JMP The mortality rate is approximately 1% to 2% for acute hepatitis E virus. If the patient develops encephalopathy and has underlying cirrhosis, the mortality rate can be up to 70%.

G&H Should cirrhotic immunocompetent patients with hepatitis E virus receive the same treatment as immunosuppressed patients?

JMP The answer to this question is not completely clear. It is clear that chronic hepatitis E in immunosuppressed patients should be treated. It is not clear whether physicians should treat patients who develop acute hepatitis E virus infection but are not immunosuppressed. Several

studies have shown that it is possible to treat these patients with ribavirin; however, the data thus far on the treatment of acute hepatitis E virus are not strong enough to implement treatment of this disease state, including patients with cirrhosis. It seems like treating these patients would be a good idea, but the data supporting this are weak.

G&H Do you have any advice for clinicians treating patients infected with hepatitis E virus?

JMP It is important to consider the possibility of neurologic symptoms in patients infected with hepatitis E virus. Approximately 5% to 6% of these patients experience neurologic symptoms, which can vary in type from Guillain-Barré syndrome, neuralgic amyotrophy, and mononeuritis to meningitis. Therefore, when a patient with elevated liver enzymes presents with any type of neurologic symptoms, he or she should be checked for hepatitis E virus infection, regardless of whether the patient has been abroad.

G&H What are the next steps in research in this area?

JMP Studies are needed on the treatment of acute hepatitis E virus to definitively determine whether treatment is required in all patients with hepatitis E virus infection. A key question is whether we should treat patients with cirrhosis who develop acute hepatitis E virus because they are at higher risk of dying or having complications of the cirrhosis.

In addition, there are currently several interesting ongoing studies on the neurologic manifestations of hepatitis E virus to determine the prevalence and types of these symptoms. There are also ongoing studies on the replication of hepatitis E virus in neurologic cells as well as on the risk of transmission using blood products. It appears that this risk is approximately 1 in 1200 in most countries in Europe, so it is important to see if this risk is clinically significant.

Finally, studies are also being conducted on the prevalence of hepatitis E IgG antibodies in different countries. Serodiagnostic tests have become more specific, and thus better, so it is now possible to compare the prevalence of these antibodies in different countries. For example, there are studies checking blood donors in Europe, the United States, and developing countries to determine whether there is a difference in the prevalence of IgG antibodies in each specific population.

Dr Péron has no relevant conflicts of interest to disclose.

Suggested Reading

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