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Hepatitis E Diagnosis and Management After Liver, Kidney, or Heart Transplant: A Single-Center Experience

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ABSTRACT

Background. Transplant-related hepatitis E virus (HEV) infection is a rarely recognized phenomenon with significant clinical importance given its potential to result in chronic hepatitis posttransplant.

Methods. We retrospectively evaluated HEV diagnosis and treatment after liver, kidney, and heart transplant in a single center. We identified patients diagnosed with HEV by serologic testing and evaluated their treatment regimens.

Results. Fifteen transplant recipients (12 liver, 2 kidney, and 1 heart) presented with elevated liver enzymes and were positive for HEV IgM antibody. Liver enzymes normalized in 4 patients after being treated with ribavirin. One of the 4 patients had 2 recurrences with positive HEV RNA results following ribavirin treatment but recovered after 12 months of ribavirin therapy. After treatment with reduction in immunosuppression without antiviral treatment, 6 of 8 patients' liver enzymes normalized. One of these patients died of acute pancreatitis 2 months after testing positive for HEV IgM antibody.

Conclusions. The potential for complications related to active HEV infections in transplant recipients necessitates prompt diagnosis and treatment to prevent irreversible damage. Diagnosis with HEV reverse transcriptase−polymerase chain reaction should follow a positive HEV IgM antibody test. This manuscript provides evidence that ribavirin antiviral therapy and reducing immunosuppression are effective treatments for HEV infections in liver, kidney, and heart transplant recipients, which has not been sufficiently investigated in the population of the United States. Larger multicenter studies are needed to confirm the risks and benefits of using ribavirin antiviral therapy as first-line therapy of HEV posttransplant.

THE most common cause of viral hepatitis in the world is hepatitis E virus (HEV) [1−3]. The prevalence of HEV in the United States population is 6%-10% [4]. This increasing prevalence has led to increased recognition of locally-acquired HEV and emphasis on its prevention and detection [5]. HEV is spread via the fecal-oral and zoonotic routes through consumption of undercooked meat [6−9]. Until recently, HEV was thought to cause hepatitis that did not become chronic [3,10]. Nevertheless, HEV can become chronic in immunocompromised patients, such as individuals with human immunodeficiency virus or solid organ transplant recipients [2]. More than 60% of patients who are exposed to HEV and receive a solid organ transplant will go onto develop a chronic infection [1,3]. Chronic HEV has been shown to lead to fibrosis and even severe cirrhosis [3,11]. One factor that has been shown to be associated with developing chronic HEV infection was use of tacrolimus as part of the immunosuppression regimen [12].

Diagnosis of HEV infection is done with serologic antibody analysis because it presents similarly to other hepatitis causing

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Table 1. Demographics and Clinical Characteristics

Variable	Value
Age (y)	
Mean	63
Range	47-78
Sex	
Male	8 (53%)
Female	7 (47%)
Type of organ transplant	
Liver	12 (80%)
Kidney	2 (13%)
Heart	1 (7%)
Treated with ribavirin	4 (27%)
Duration of ribavirin treatment (d)	
Mean	139
Range	56-331
Immunosuppressant reduction	10 (67%)
Positive test for anti-HEV IgM antibodies	15 (100%)
Test done for HEV RNA	11 (73%)
HEV RNA positive test result	1 (7%)
Deceased	2 (13%)
Interval between transplant and positive anti-HEV IgM antibodies (mo)	
Mean	53
Range	3-250

HEV, hepatitis E virus.

organisms [13]. When HEV is suspected, anti-HEV IgM is a useful and common initial test as it is the first antibody produced. However, previous studies have shown that anti-HEV IgM assays are less specific for diagnosis of hepatitis E than anti-HEV IgA [14]. Anti-HEV IgA is not a widely used commercial test, despite its potential to be a more reliable indicator of HEV infection. Other studies have demonstrated that only about 70% of anti-HEV IgM and IgG antibody tests had consistent results, indicating that up to 30% of anti-HEV IgM antibody tests can be inaccurate [13,15]. Compared to antibody tests, HEV reverse transcriptase−polymerase chain reaction (RNA PCR) is a more specific test, but it possesses a narrow time course in which HEV RNA detection is possible because it can only be detected during the initial phase of the infection [13,16].

In 2019, 8897 liver, 24,274 kidney, and 3597 heart transplants were performed in the United States [17]. Even though HEV infections have been reported more frequently in liver transplant recipients, they have also been known to occur in kidney and heart transplant recipients [11,14]. Despite this, not much is known about HEV infections in kidney and heart transplant recipients because it has rarely been investigated in the United States [4,14]. HEV infections have been reported in liver, kidney, and heart transplant recipients, but all solid organ transplant recipients receiving immunosuppressants are susceptible to HEV infections. Currently there are no approved medications for HEV, and therapeutic options for HEV are limited to the off-label use of ribavirin [18]. Ribavirin is an antiviral medication that has been shown to be an effective treatment [19]. Due to its off-label use, there is not an established recommendation for the dosage of ribavirin treatment regimens for HEV. Often regimens vary in dosage, administration, and duration depending on clinician experience and health center policy. However, it is commonly given for at least 3 months. Ribavirin can cause significant hematological side effects. Kamar et al [20] showed that 28% of patients required changes in dosing due to hematological side effects in a cohort of solid organ transplant recipients. Due to the increasing prevalence of HEV and lack of specific therapeutics, we examined HEV diagnosis and management in liver, kidney, and heart transplant recipients to better evaluate successful and systematic diagnostic and therapeutic approaches.

MATERIALS AND METHODS

Study Patients and Data Collection

We retrospectively reviewed the records of 15 patients that received a solid organ transplant (12 liver, 2 kidney, and 1 heart) between June 1998 and December 2018. All patients were from hospitals and clinics in the Henry Ford Health System (HFHS). Medical information including sex, age, date of transplant, liver enzymes, anti-HEV IgM antibodies, HEV RNA PCR, and ribavirin treatment regimens were obtained from a review of patient medical charts. This study was approved by the HFHS Institutional Review Board (protocol no. 14111).

Anti-HEV Antibodies and HEV RNA

In order to detect anti-HEV IgM, enzyme-linked immunosorbent assays were performed at Henry Ford Hospital System. Blood samples were collected and sent to the National Institutes of Health and Associated Regional and University Pathologists laboratories to detect HEV RNA using quantitative RNA PCR.

RESULTS

Seven of the 15 patients were female and 8 were male. The mean age of the patients was 63 years (range, 47-78 years). The mean interval between transplant and positive anti-HEV IgM antibodies was 53 months (range, 3-250 months) (Table 1).

Diagnosis

All 15 patients presented with elevated liver enzymes and demonstrated positive anti-HEV IgM antibodies. Eleven of the 15 patients had HEV RNA PCR tests conducted. Of these 11 patients, 1 patient had a positive HEV RNA PCR while 10 had negative HEV RNA PCRs.

Three patients (2 liver and 1 kidney) were tested multiple times and repeatedly showed positive anti-HEV IgM antibody tests.

Treatment

Due to the lack of standardization of treatment, we were curious to see the variance in how these 15 patients in the HFHS were treated. Four out of the 15 patients were treated with ribavirin. The other 11 patients were not given antiviral treatment and were treated supportively.

Treatment with ribavirin. Four of the 15 transplant recipients were treated with ribavirin for an average of 139 days (range, 56-331 days). These patients usually received either a 600 mg or 800 mg oral dose of ribavirin per day. Patient A received between 400 mg and 1000 mg of ribavirin per day during different periods. Three of these patients received ribavirin treatment for an average of 84 days (range, 56-120 days), 2 of which saw a reduction in their immunosuppression. The fourth patient, however, Patient A, had 2 recurrences of hepatitis E that required longer durations of treatment with the third treatment regimen lasting 12 months (Fig 1). This patient did not have a reduction in immunosuppression. The 4 patients treated with ribavirin did not have significant adverse effects to treatment. All 4 patients' liver enzymes normalized and fully recovered.

Supportive treatment only. Eight of the 15 transplant recipients (6 liver, 1 kidney, and 1 heart) had reductions in their immunosuppressants without antiviral treatment. Eleven of the 15 were treated with tacrolimus as part of their immunosuppressant regimen. One of the liver transplant recipients expired. The other 7 patients fully recovered.

Three of the 15 transplant recipients (2 liver and 1 kidney) had no reduction in immunosuppressants or antiviral treatment. One of the liver transplant recipients expired 6 weeks after a positive anti-HEV IgM antibody test from complications posttransplant, including sepsis. The other 2 patients spontaneously recovered.

Chronic HEV Infection (Patient A)

Chronic HEV infection is defined as viral persistence in peripheral blood for more than 3 months [21]. One of the liver transplant recipients initially presented with an HEV infection and had an HEV viral load of 360,000 IU/mL and a peak alanine aminotransferase (ALT) of 156 IU/L (Normal = 52) and aspartate aminotransferase (AST) of 104 IU/L (Normal = 35). This patient was treated with 1000 mg of ribavirin per day for about 7 months from postoperative day (POD) 1468-1673 (Fig 1). After this treatment, the patient's liver enzymes were elevated a second time with a peak ALT of 65 IU/L and AST of 53 IU/L and a positive HEV RNA viral load <50 IU/mL (this RNA viral load was detectable, but not quantifiable). After this second elevation in liver enzymes, ribavirin was restarted at a dose of 400 mg per day for the second time for 5 months (POD 1777-1991). About 3 weeks after initiating the second round of treatment, liver enzymes stabilized. Four months after completing the second round of treatment, liver enzymes rose again with a peak ALT of 91 IU/L and AST of 86 IU/L and an HEV RNA viral load of 108,000 IU/mL. After liver enzymes were elevated for a third time, ribavirin was restarted at a dose of 600 mg for a duration of 20 months (POD 2225-2842). Liver enzymes have been normal since continuation of the third round of ribavirin therapy (Fig 1). Patient A had mild anemia after each initiation of ribavirin but did not require dose adjustment. This chronic HEV patient is on long-term ribavirin therapy.

DISCUSSION

In the present study, we evaluated the diagnosis and outcomes of the management of HEV infections in solid organ transplant recipients. There were a number of patients that had positive anti-HEV IgM antibody tests but had undetectable HEV RNA. A prompt HEV RNA PCR is an important step in following up a positive anti-HEV IgM antibody result. HEV RNA PCR is the gold standard diagnostic test, but an HEV infection can easily be missed with an HEV RNA PCR and it can be negative in the early phase of infection [22,23]. HEV RNA is detectable about 1-2 weeks before symptoms present and continues for only about 1 week in the serum. While several of the patients in this study had undetectable levels of HEV RNA, this cannot exclude a diagnosis of hepatitis E because of the test's narrow diagnostic window [13]. Anti-HEV IgA antibody tests should follow anti-HEV IgM antibody tests because the anti-HEV IgM antibody test has a lower specificity [14]. Despite this information, only 1 patient out of 15 in this study received the IgA confirmatory test. This study brings to light the importance of the IgA confirmatory test and the need for ordering this test in all HEV patients. HEV can be detected in the stool about one week before symptomatic presentation and it can continue until about 2 weeks after presentation [24]. The sensitivity of HEV RNA stool and serum assays have not been completely investigated, but some reports have shown that the stool assay is more sensitive [25]. An HEV RNA stool test is a valuable complementary assay that should follow a positive anti-HEV IgM antibody test in order to not miss the diagnosis.

HEV infections can become chronic and have significant consequences. Patient A in this study is an example of how an HEV infection can become chronic. Therefore, it is important to acquire all tests in order to get an accurate diagnosis and begin treatment. Additionally when considering immunosuppressive medication, tacrolimus use has been shown to be linked to development of chronic hepatitis E, so alternatives should be used, such as cyclosporin A [12].

The results presented here support previous research in demonstrating that ribavirin and immunosuppression reduction are effective treatments for HEV infections in solid organ transplant recipients [26]. There is a vaccine for HEV in China, but there are currently no targeted treatments for HEV infections. Because ribavirin is used as an off-label treatment for HEV infections, it is important to establish sufficient evidence must be established to demonstrate its effectiveness. Patient A had mild anemia after initiation of ribavirin but did not require dose adjustment. Patient A is of particular interest because this patient had spikes in liver enzymes and HEV RNA positivity immediately after cessation of the first 2 rounds of ribavirin treatment. This patient is on long-term ribavirin therapy without elevated liver enzymes. One of the other patients developed anemia after completing the ribavirin regimen with full recovery and resolution. The other 2 patients treated with ribavirin did not develop anemia and did not require dose adjustment. While some patients had reduction in immunosuppressants following HEV infection, their primary immunosuppressant agents were not changed because the patients tolerated their medications without side effects.

There is limited research on HEV infections in liver transplant recipients, especially in kidney and heart transplant recipients. This study provides further evidence of the effectiveness of ribavirin and immunosuppression reduction in HEV infections in liver, kidney, and heart transplant recipients. There is

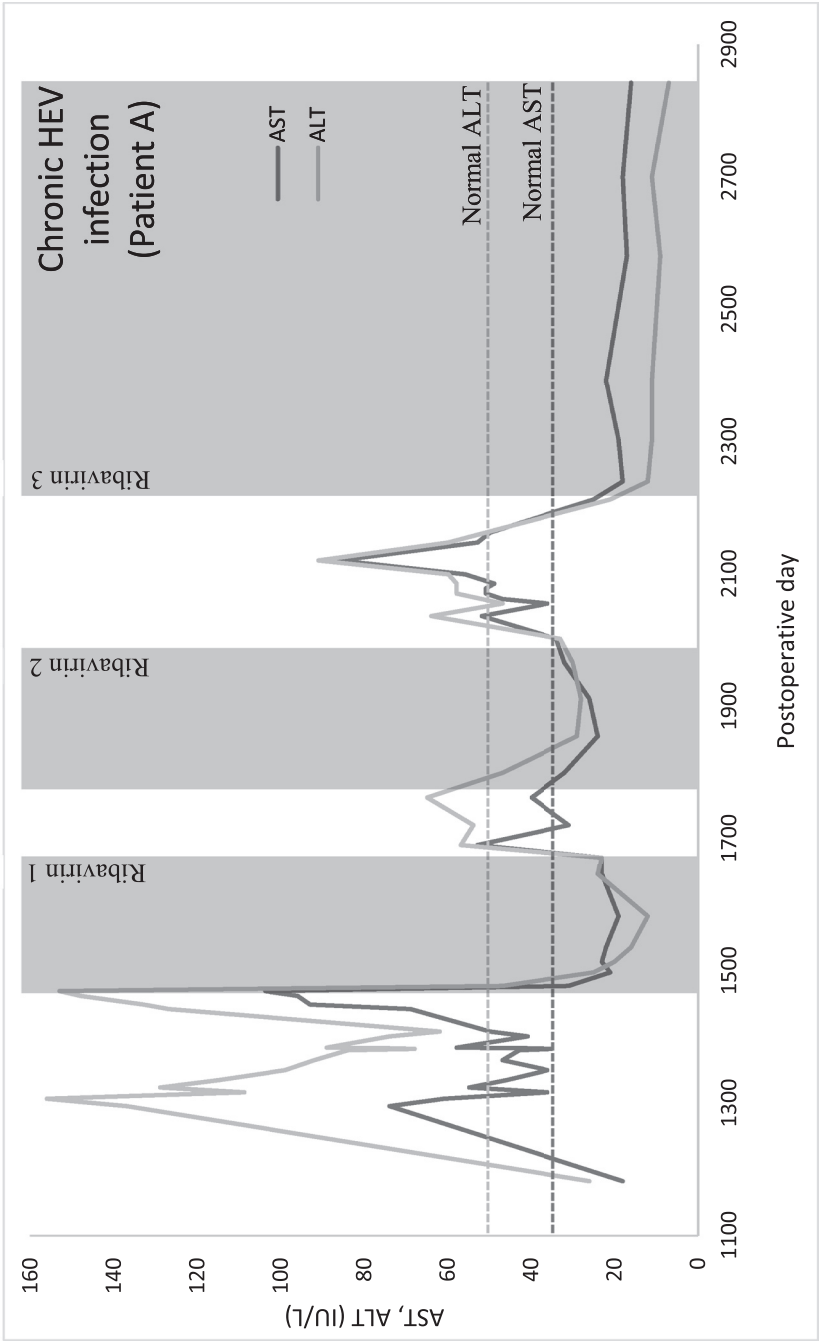

Fig 1. Clinical timeline of the chronic hepatitis E virus infection case. Ribavirin treatment in gray boxes from POD 1468-1582, 1777-1915, and 2225-2556. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HEV, hepatitis E virus; POD, postoperative day.

insufficient data on the treatment of HEV infections in the United States population. Because distinct populations from unique demographics respond differently to treatments it is important to understand how transplant recipients with HEV infections in the United States respond to immunosuppressant reduction and ribavirin treatment. This article contributes important evidence to the understanding of the effectiveness of ribavirin and immunosuppressant reduction in transplant recipients with HEV infections in the United States. Additionally, the prevalence of HEV infections is likely higher than the reported numbers. There are not regular screenings for transplant recipients posttransplant. Due to the consequences that can result from chronic HEV infections and the limitations in current testing techniques, this research demonstrates the importance of having a higher index of suspicion for a diagnosis of HEV in transplant recipients. This is a retrospective study, so we were limited by evaluating what had already been done, and we were unable to acquire further test results on these patients.

CONCLUSIONS

HEV infection after solid organ transplant is rare. The number of HEV infections in liver transplant recipients is growing as there are an increasing number of liver transplants in the world [20]. In this study, all patients treated with ribavirin therapy achieved normalization in liver enzymes and fully recovered. We conclude that immunosuppression reduction is an effective way to prevent HEV infections from becoming chronic, but combination with ribavirin was the best. In our experience, it is important to initiate ribavirin treatment promptly and complete at least a 3-month regimen of ribavirin to avoid recurrence. Without completing a full course of ribavirin treatment, it is possible for HEV infections to become chronic. Nevertheless, large multicenter studies are required in order to evaluate optimal dosing and duration of ribavirin for HEV infections in solid organ transplant recipients.

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