Chronic Hepatitis E Resolved by Reduced Immunosuppression in Pediatric Kidney Transplant Patients

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abstract

At present, transient asymptomatic hepatitis E virus (HEV) infection is common among healthy adults in Western Europe, as reported by blood transfusion services. In immune-suppressed patients HEV infection is often without clinical symptoms, but without therapeutic intervention it may become chronic and lead to cirrhosis. This report describes the course of chronic HEV infection after kidney transplantation in 2 children, who cleared the virus after reduction in immunosuppressive therapy. If aminotransferase levels continue to be moderately elevated after transplantation, HEV infection should be excluded.

Hepatitis E virus (HEV) is a nonenveloped RNA virus that belongs to the Hepevirus genus. Phylogenetic studies have identified 4 genotypes, HEV-1 to HEV-4. HEV genotypes 1 and 2 are restricted to humans, whereas genotypes 3 and 4 appear to be zoonotic, infecting pigs, wild boar, and deer as well as humans, probably via consumption of contaminated and undercooked food. HEV-1 hepatitis occurs mainly in Asia and Africa and HEV-2 in Central America. Both are transmitted via the oro-fecal route. HEV-3 infections have been reported in Europe, New Zealand, and North America and HEV-4 has been reported in Japan.\textsuperscript{1–4} Acute HEV-3 infection in immunocompetent individuals is usually self-limiting.\textsuperscript{1,2,5} Symptoms are often absent or nonspecific (malaise, anorexia, nausea, abdominal pain, fever, arthralgia). After an incubation period of 2 to 8 weeks, an immunoglobulin (Ig) M response occurs, followed by IgG antibodies.\textsuperscript{1,4} The prevalence of anti-HEV antibodies, indicating exposure to HEV, was initially reported to be 0.4% to 3% in Western Europe.\textsuperscript{6} More recent studies, using improved antibody assays, showed a much higher seroprevalence, with rates up to 51% in southwestern France.\textsuperscript{2,5} The reported seroprevalence in children aged 2 to 4 years is only \texttt{\~}2%.\textsuperscript{2,7}

In immunocompromised persons, HEV-3 infection can cause chronic hepatitis and can lead to cirrhosis.\textsuperscript{6,8–10} In a large retrospective multicenter study in solid organ transplants, 8 of 56 infected patients developed cirrhosis.\textsuperscript{9} Chronic hepatitis E is defined by the persistence of HEV RNA in plasma for \texttt{\~}6 months. On the basis of combined data from several countries, HEV RNA could be detected in 1.6% of kidney transplant recipients, 65% of whom developed chronic infection.\textsuperscript{6}

Symptoms of chronic hepatitis E in patients receiving immunosuppressive therapy are often unremarkable. Liver function tests, especially alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are only moderately increased. The liver test abnormalities in this situation are often misdiagnosed as drug-induced liver injury.\textsuperscript{11} Recognition of chronic HEV infection in these patients is important. This case report shows that children with chronic hepatitis E can clear the virus after reduction in immunosuppressive therapy.
CASE REPORT A

A 4-year-old boy with end-stage renal disease, caused by pneumococcal hemolytic uremic syndrome, underwent a postmortem-donor kidney transplantation in October 2008. Immunosuppressive medication consisted of prednisolone, mycophenolate mofetil (MMF), and cyclosporine. Cyclosporine was switched to tacrolimus 1 year after transplantation. During the first 1.5 years after transplantation, he developed cytomegalovirus (CMV) reactivation, primary Epstein-Barr virus (EBV) infection, and BK-virus viremia. Almost 3 years after transplantation at a routine check in 2011, ALT (94 U/L) and AST (55 U/L) were found to be elevated (Fig 1). The previous month the patient had a cold and underwent drainage of the middle ear. Kidney function was stable with a glomerular filtration rate of 80 mL/min per 1.73 m² until September 2012, when he was admitted to the hospital because of Klebsiella urosepsis. Liver enzymes remained slightly increased in 2012 and 2013. No clear relation could be found with drugs such as acetaminophen. Repeated testing for EBV and CMV DNA was negative, except for 1 sample that revealed CMV viremia <1000 copies per mL. After temporary normalization, liver enzymes increased again with an ALT of 117 U/L. At that point, HEV RNA polymerase chain reaction (PCR) was performed, and the result was positive. Genotyping of the virus revealed the presence of HEV genotype 3. Retrospectively, archived blood samples were analyzed for the presence of HEV RNA and for anti-HEV IgG and IgM serology. Anti-HEV IgM was positive and IgG negative in the first HEV RNA–positive sample in 2011; later, anti-HEV IgG also became positive. MMF dosage was reduced (800 to 600 mg/m² per day), followed by a reduction in tacrolimus (0.1 to 0.05 mg/kg per day). The prednisolone dosage remained at 5 mg on alternate days (= 2 mg/m² per day). Two months after the first reduction in immunosuppression, HEV RNA became undetectable and serum ALT levels decreased to the normal range, whereas renal function remained stable. Six weeks later, the dosage of tacrolimus and MMF was restored to original levels. During 3.5 months of follow-up, HEV RNA has been repeatedly undetectable, and liver enzymes have been normal.

CASE REPORT B

An 11-year old girl with chronic renal failure and unknown renal disease underwent a living related donor kidney transplantation in 2013. Immunosuppression consisted of a short course of steroids (discontinued 1 week after transplantation), MMF, and tacrolimus. Pretransplant serum EBV- and CMV-IgG were negative. The donor was seronegative for CMV but positive for EBV. Kidney transplantation was uncomplicated, with a stable kidney function (glomerular filtration rate varied between 92 and 98 mL/min per 1.73 m²). Six months after transplantation, serum aminotransferase levels (ALT: 66 U/L; AST: 47 U/L) were found to be slightly elevated (Fig 2). CMV and EBV PCR were negative. Four weeks later, liver enzymes decreased (ALT: 53 U/L; AST: 42 U/L) to near normal levels. Six weeks thereafter, liver enzymes (ALT: 75 U/L; AST: 58 U/L) were again found to be elevated. At that point, HEV RNA testing was first performed and found to be positive. HEV serology revealed a positive result for HEV IgM and a negative result for HEV IgG. RNA sequencing revealed HEV genotype 3. Retrospectively, archived blood samples were analyzed for the presence of HEV RNA and were found to be positive starting at 3 months after transplantation. At that time, the patient had no complaints except for rhinitis with a mildly elevated blood C-reactive protein of 7.4 mg/L, with normal white blood cell and differential counts. MMF dosage was reduced (935 to 740 mg/m² per day), followed by tacrolimus (in 2 steps: from 0.24 to 0.19 to 0.16 mg/kg per day). Six weeks before HEV infection was discovered, the tacrolimus dosage had been reduced from 0.29 to 0.24 mg/kg per day because of a high trough level of 8.3 μg/L. After 6 weeks of tacrolimus at 0.16 mg/kg per day, the dosage was increased to 0.19 mg/kg per day because of low

![FIGURE 1](image-url)

**FIGURE 1**
Clearance of chronic hepatitis E in an 8-year-old boy after a reduction in immunosuppression as indicated. Step 1 = MMF: 800 to 600 mg/m² per day; step 2 = tacrolimus: 0.1 to 0.05 mg/kg per day. Prednisolone remained unmodified at 2 mg/m² per day. Kidney transplantation was performed in 2008, as indicated by “Tx.” ALT, alanine aminotransferase; creat. creatinine; neg, negative; Tx, transplantation.
trough levels (2.8 µg/L). HEV RNA PCR became negative 2 months after the last reduction in tacrolimus (trough levels varied between 2.8 and 5.0 µg/L) and serum ALT levels decreased to the normal range, whereas renal function remained stable. The current doses of tacrolimus (0.19 mg/kg per day) and MMF (714 mg/m² per day) have yet to be restored to the original levels. During 1.5 months of follow-up, HEV RNA has been repeatedly undetectable and liver enzymes have been normal.

**DISCUSSION**

In 2 pediatric kidney transplant patients with chronic hepatitis E, a careful reduction in immunosuppression induced clearance of the infection. In both cases it took some time before hepatitis E was diagnosed. Because HEV genotype 3 infection is common in parts of the Western world, one should exclude hepatitis E in transplant patients with unexplained elevation of aminotransferase levels, before “drug-induced liver injury” is diagnosed. In immunosuppressed patients, hepatitis E serology often is unreliable, even when modern assays are used: IgM and IgG responses may be late and may wane rapidly. Therefore, in transplant patients, the exclusion or diagnosis of HEV infection must be made on the basis of HEV RNA PCR with a fresh EDTA blood sample.

When unnoticed or left untreated, chronic HEV infection may rapidly lead to cirrhosis. Fortunately, chronic HEV infection can be successfully treated, for example by modest decreases in immunosuppression. Of course, this approach may lead to rejection of the organ transplant. When careful reduction in immunosuppression fails to clear infection, treatment with ribavirin is suggested as a next step. In adult transplant recipients, a limited course of ribavirin causes clearance of HEV in the majority of patients. Ribavirin is typically given for 3 months, with longer courses in patients who experienced relapse when it was discontinued. The most problematic adverse effect of ribavirin treatment is hemolysis, which often leads to significant anemia within the first 3 to 6 weeks of treatment and, in adult renal transplant patients, often necessitates dose reduction, use of erythropoietin, or blood transfusion. Finally, interferon is effective against HEV, but it is even more problematic in renal transplant patients.

HEV genotype 3 is responsible for virtually all reported cases of chronic hepatitis E in developed countries. Chronic hepatitis E has been reported after kidney, liver, and heart transplantation since 2008. In children, few studies have been published. Only 1 study concerned children after kidney transplantation. The transmission of endemic HEV is thought to occur through contaminated or undercooked food or blood transfusions, blood products, and organ transplants. Patient A in this report acquired hepatitis E several years after transplantation and thus his infection was probably food-borne, not from the organ donor or from blood products. Patient B developed hepatitis E 3 months after transplantation. Three archived blood samples, obtained after transplantation and before the onset of hepatitis, tested negative for HEV RNA, making it doubtful that the donor or blood products were the source of infection. The 2 children were viremic for 2 years and 1 year, respectively, before hepatitis E was diagnosed and reduction in immunosuppression was initiated. They cleared the virus 2 and 6 months, respectively, after the initiation of a gradual dose reduction. Apparently, the clearance of HEV was not spontaneous but induced by the reduction in immunosuppression. Their serum aminotransferase levels returned to normal, and there was no evidence of graft dysfunction or rejection.

**CONCLUSIONS**

Two children with well-documented chronic HEV infection after renal transplantation cleared the viral infection and resolved the chronic
hepatitis after a gradual reduction in immunosuppressive therapy. This policy did not result in the rejection of the kidney transplant. A careful reduction in immunosuppression may be the treatment of first choice in favor of an oral course of ribavirin.

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DOI: 10.1542/peds.2014-3790 originally published online March 9, 2015;
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