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Case Report: Acute Hepatitis E in a Pediatric Traveler Presenting with Features of Autoimmune Hepatitis: A Diagnostic and Therapeutic Challenge

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Abstract. Hepatitis E virus (HEV) is globally the most common cause of acute viral hepatitis. In industrialized countries, HEV infection can be seen in travelers returning from hyperendemic countries or in individuals at risk for autochthonous infection due to zoonotic exposure. Hepatitis E virus infection is often unrecognized and at times misdiagnosed because of nonspecific findings that can overlap with other causes of hepatitis, including autoimmune hepatitis (AIH). Although most cases of acute HEV infection resolve spontaneously and do not require treatment, life-threatening acute liver failure may occur in some cases. We discuss the case of an 8-year-old boy returning from Bangladesh with progressive acute liver injury and a clinical profile suggestive of AIH, who showed a favorable response to corticosteroid treatment before the diagnosis of an acute HEV infection could be established.

INTRODUCTION

Hepatitis E virus (HEV), the leading cause of acute viral hepatitis worldwide, is a single-stranded RNA virus with four human-pathogenic genotypes. Genotypes 1 and 2 are transmitted fecal-orally via contaminated water supplies in developing countries, whereas zoonotic foodborne transmission of genotypes 3 and 4 account for disease in developed countries.[1] Most infections are asymptomatic or mild, yet severe disease including fulminant hepatitis, can result in death, especially in pregnant women. Extrahepatic manifestations also occur, and chronic HEV infection has been observed among patients on immunosuppressant therapy for solid organ transplants with genotype 3 and 4 infections.[1–4] Travel-associated HEV infection has been described in travelers returning from HEV-hyperendemic countries, mostly in Asia.[5]

The clinical diagnosis of acute HEV infection can be difficult to establish while awaiting the results of the HEV-specific diagnostic assays. Moreover, clinical and liver biopsy findings can be suggestive of autoimmune hepatitis (AIH).[6] Of note, it has been suggested that patients with significant liver injury may benefit from treatment with corticosteroids during this period of diagnostic uncertainty.[7] We present a case of acute hepatitis suggestive of AIH in a returning pediatric traveler who showed a favorable response to treatment with corticosteroids before the etiologic diagnosis of HEV infection was established.

CASE

An 8-year-old boy presented with 6 days of malaise, 2 days of fever, diffuse abdominal pain, and 1 day of generalized jaundice. He was born in the United States but had frequently traveled between his parents' country of origin in Bangladesh and the United States. He had returned from his most recent trip to Bangladesh 1 month before becoming ill. There was no significant past medical history, and the family history was not contributory. On examination, he was febrile to 39.5°C and in mild distress due to abdominal pain. He had diffuse jaundice, and his abdomen was tender in the right upper and lower quadrants. His liver was palpable 2 cm below the costal margin. Findings of the remainder of the physical examination were unremarkable. Laboratory studies at admission were notable for aspartate aminotransferase of 1,033 u/L (< 40), alanine aminotransferase of 1,154 u/L (< 41), gamma glutamyl transferase of 183 u/L (8–61), total bilirubin of 10.1 mg/dL (0.2–1.2), direct bilirubin of 8.3 mg/dL (0.1–0.2), total immunoglobulin G (IgG) level of 1,552 (620–1,474), international normalized ratio of 1.25 (0.88–1.17), and prothrombin time of 14.3 seconds (9.8–13.1 seconds). His antinuclear antibody and anti-smooth muscle antibody (SMA) titers were elevated at 1:160 and 1:80, respectively. The anti-liver kidney microsomal (LKM) antibody 1 titer was negative. Other laboratory studies including serologic tests for hepatitis A, B, C, and human herpes virus 6 infection, a malaria screen, tuberculosis interferon–gamma release assay, ceruloplasmin level, alpha-1-anti-trypsin phenotype, stool cultures, and stool for ova and parasite were all negative. Specific HEV tests (anti-HEV IgG/immunoglobulin M [IgM] and HEV RNA polymerase chain reaction [PCR] assays) were submitted and pending while the patient's liver enzymes continued to rise (Table 1). A hepatobiliary iminodiacetic acid scan showed significant hepatocellular dysfunction, while an abdominal ultrasound examination revealed an enlarged liver but no ascites and a normal portal and hepatic vein flow pattern. A liver biopsy on day 5 of hospitalization revealed active interface hepatitis with predominantly lymphocytes and plasma cells, as well as active lobular hepatitis with scattered collections of predominantly lymphocytes and plasma cells. A probable diagnosis of AIH according to the modified international autoimmune hepatitis group scoring system (IAHGSS) was considered (Table 2).[8,9] Likewise, a simplified scoring system based on the presence of anti-SMA, hypergammaglobulinemia, and compatible liver histology indicated a probable diagnosis of AIH.[10] Treatment for AIH with corticosteroids was initiated on day 6 of hospitalization

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TABLE 1
Liver function test values during hospitalization

Day of hospitalization	AST (u/L)	LT (u/L)	TB (mg/dL)	DB (mg/dL)	Albumin (g/dL)	AP (u/L)	INR
1	1,033	1,154	10.1	8.3	3.4	375	1.25
2	1,115	1,254	12.4	10.3	3.4	393	1.15
3	1,179	930	10.8	8.9	3.1	358	1.34
4	1,587	1,430	12.0	9.6	3.2	367	1.21
5	2,236	1,797	10.8	–	3.2	345	1.14
6*	1,578	1,576	10.2	7.9	3.1	322	1.03
7*	684	1,254	9.8	6.9	3.7	345	–
8*	212	784	6.1	4.0	3.7	313	1.01

Name of laboratory test and respective range of normal values: albumin, 3.3–5.0 g/dL; ALT = alanine aminotransferase, 4–41 u/L; AP = alkalin phosphatase, 150–440 u/L; AST = aspartate aminotransferase, 4–40 u/L; DB = direct bilirubin, 0.1–0.2 mg/dL; INR = international normalized ratio, 0.88–1.17; TB = total bilirubin, 0.2–1.2 mg/dL.
* Treatment with corticosteroids (intravenous methylprednisolone 1.25 mg per kg daily, then transitioned to oral prednisone 60 mg daily) provided on these days.

with subsequent improvement in his clinical status and liver function tests (Table 1). The patient was released on day 8 of hospitalization with a plan to taper corticosteroids gradually in parallel to declining transaminase levels. The use of azathioprine had been considered but then dismissed as the patient's HEV studies (HEV IgM and HEV RNA positive) became available 1 week after hospital discharge. Hepatitis E virus genotype 1 infection was assumed, given the patient's recent travel to Bangladesh, where genotype 1 is the most commonly distributed.[11] The patient has remained asymptomatic with normal laboratory studies for a follow-up period of 6 months.

DISCUSSION

Pediatric travelers returning ill with fever and gastrointestinal symptoms from HEV hyperendemic regions need to be assessed for infections with hepatotropic viruses, including HEV. This case illustrates that clinical, laboratory, and histopathologic features of such patients are not specific for HEV

TABLE 2
Presented case pretreatment modified IAHGSS score[9]

	Modified IAHGSS		Case	
Parameter	Result	Associated score	Result	Score
Gender	Female	+2	Male	0
AP to AST ratio (relative to the upper limit of normal)	< 1.5	+2	0.15	+2
	1.5–3.0	0		
	> 3.0	–2		
Serum IgG (relative to the upper limit of normal)	> 2.0	+3	1.05	+1
	1.5–2.0	+2		
	1.0–1.5	+1		
	< 1.0	0		
ANA, anti-SMA, or anti-LKM antibody titers	> 1:80	+3	Anti-SMA 1:80	+2
	1:80	+2		
	1:40	+1		
	< 1:40	0		
AMA titer	Positive	–4	Not tested	0
Hepatitis viral markers (for hepatitis A, B, and C)*	Positive	–3	Negative (hepatitis E testing was pending at this time)	0
	Negative	+3		
Drug history	Positive	–4	Negative	+1
	Negative	+1		
Average alcohol intake	< 25 g/day	+2	< 25 g/day	+2
	> 60 g/day	–2		
Liver histology	Interface hepatitis	+3	Interface hepatitis with predominantly lymphoplasmacytic infiltrate	+4
	Predominantly lymphoplasmacytic infiltrate	+1		
	Rosetting of liver cells	+1		
	None of the above	–5		
	Biliary changes	–3		
	Other changes	–3		
Other autoimmune diseases (personal or family history)	Yes	+2	No	0
Optional additional parameters:				0
Seropositivity for other defined antibodies	Seropositive	+2	Not seropositive for defined antibodies	
HLA DR3 or DR4	HLA positive	+1	HLA not tested	
Total		15 = definite AIH 10–14 = probable AIH		12 = probable AIH

AIH = autoimmune hepatitis; AMA = anti-mitochondrial antibody; ANA = anti-nuclear antibody; AP = alkaline phosphatase; AST = aspartate aminotransferase; IAHGSS = International Autoimmune Hepatitis Group Scoring System; IgG = immunoglobulin G; HLA = human leukocyte antigen; LKM = liver kidney microsomal antibody; SMA = smooth muscle antibody. Interpretation of aggregate pretreatment score: 10–15 = probable AIH; 15 = definite AIH.
* Markers of hepatitis A, B, and C viruses include the presence of IgM anti-hepatitis A virus, hepatitis B surface antigen, IgM anti-hepatitis B core, anti-HCV, or HCV-RNA). If a viral etiology is suspected despite seronegativity for these markers, test for other potentially hepatotropic viruses such as cytomegalovirus, Epstein-Barr virus, or hepatitis E may be relevant.

and can mimic AIH, thereby creating a diagnostic dilemma. Special testing for HEV is rarely available on-site in most health centers and relevant assays must be sent out to a commercial laboratory that may run such assays only once or twice per week. This temporary diagnostic uncertainty can further lead to a therapeutic dilemma, when hepatic inflammation advances despite supportive measures. In this case corticosteroid administration was followed by improved hepatic inflammation despite the underlying viral etiology.

Hepatitis E virus infection has been recognized as a travel-associated infectious disease.[12] In a 5-year review of the GeoSentinel surveillance network analyzing data from 53 specialized international travel clinics, only 45 cases were noted among 42,000 ill traveler records reported, suggesting that HEV infection may not be a high-burden infectious disease among travelers.[13] On the contrary, a recent 1-year study of reportable diseases in only one region in Australia noted 24 cases of HEV infection. Moreover, the enhanced surveillance portion of the study revealed a demographic profile of affected patients that is similar to our case: most cases were travel-associated (93%), visiting friends and relatives (VFRs) was the most commonly reported reason for travel (77%), and the majority visited a destination in Asia (77%). Of note, 21% of the travel-associated cases in that study were children.[14] Imported HEV infection has not only been documented in returning travelers, but also in immigrants, refugees, migrant workers, and military personnel.[15–18] As there is no hepatitis E vaccine commercially available outside of China, HEV infection prevention efforts focus on access to a safe water supply and the sole consumption of food that has been thoroughly cooked.[19]

Autoimmune hepatitis is a rare chronic liver disease, clinically characterized by the presence of autoantibodies, hypergammaglobulinemia, and histologically noted for interface hepatitis.[20] Autoimmune hepatitis is a clinical diagnosis based on the presence of a combination of clinical findings, laboratory abnormalities, and liver histopathology. Diagnostic scoring systems such as the IAHGSS (Table 2) have been originally developed for adults and subsequently modified for children as research and not as diagnostic tools.[8–10] The simplified scoring system developed for children was noted not only for its moderate sensitivity but also high specificity.[21] Of note, if the HEV test results had been available in time, the patient would not have fulfilled the criteria for probable AIH.

The pathogenesis of AIH is only incompletely understood, yet exogenous triggers such as acute infections with hepatitis A virus, hepatitis C virus, Epstein–Barr virus, cytomegalovirus, and HEV have been discussed.[22] Hepatitis E virus infection may trigger an immune cascade leading to AIH, and a recent study from Germany found evidence of a significantly higher rate of anti-HEV antibodies in patients with AIH, compared with the general population.[23] Although a subsequent larger Dutch study could not confirm that result, this study also demonstrated that about a third of AIH patients had evidence of a silent HEV infection. It was concluded that all AIH patients require careful diagnostic testing to rule out HEV infection.[24]

Differentiating HEV from AIH clinically may be challenging. There are known phenomena of patients with AIH testing positive for HEV-specific immunoglobulin and patients with HEV temporarily showing immunologic signs suggestive of AIH, as did our patient.[25,26] Furthermore, the serologic diagnosis of HEV infection can be problematic as assays vary in performance. The only specific testing which can definitively distinguish HEV from AIH is isolation of HEV viral RNA by PCR, which can only be isolated during a narrow window of viremia.[1]

This patient's clinical team was faced with the practical question of how to treat an acutely ill patient whose clinical presentation was suggestive of AIH, who was clinically not improving despite supportive care, and for whom HEV testing results were not immediately available. Although AIH treatment recommendations include timely initiation of corticosteroids with subsequent transition to long-term immunosuppression, immunosuppressive treatment may seem counterproductive for acute HEV.[27] In fact, long-term immunosuppression is a known risk factor for developing chronic HEV infection with genotypes 3 and 4.[1] However, as the principal mechanism of liver damage in HEV is thought to be immune-mediated rather than due to a HEV-specific cytopathic effect, short-term immunosuppressive treatment may limit immune-mediated liver and extrahepatic damage in HEV.[28] In fact, corticosteroids have been successfully used to treat presumed immune-mediated extrahepatic manifestations of HEV such as thrombocytopenia and glomerulonephritis.[3] Moreover, there have been three previously published case reports of patients with acute HEV infection, who had been treated with corticosteroids, all of whom had a good clinical outcome (Table 3). Although these case reports, including our case, suggest that the administration of corticosteroids in acute HEV infection may be beneficial, it is possible that the observed improvements might have reflected the natural course of the patients' HEV infection.[30] Moreover, publication bias and lack of

TABLE 3
Published cases of acute hepatitis E infection treated with corticosteroids

Case	Presumed diagnosis	Age, gender, location of case	AIH-related laboratory findings	HEV-specific tests	Treatment received	Outcome
#1[7]	Drug-induced liver injury	63, male, Germany	ANA (+) Anti-SMA (–) Anti-LKM (–) Total IgG (+)	IgM (–) IgG (+) RNA (+)	P	Details lacking on duration of hospitalization and follow-up, but outcome described as good with resolution of the HEV infection.
#2[25]	AIH type 1	58, female, Portugal	ANA (+) Anti-SMA (+) Anti-LKM (–) Total IgG (+)	IgM (+) IgG (–) RNA (+)	P and A	Hospitalized for 2 weeks Treated with corticosteroids for 2 months Clinically well with normal laboratory values off treatment for 4 months
#3[29]	AIH	25, female Japan	ANA (+) Anti-SMA (+) Total IgG (+)	IgM (–) IgG (+) RNA (–) IgA (+)	M and P	Hospitalized for 15 weeks Treated with corticosteroids for 8 months Clinically well with normal laboratory values off treatment for 1.5 years

A = azathioprine; AIH = autoimmune hepatitis; ANA = anti-nuclear antibody; HEV = hepatitis E virus; IgA = immunoglobulin A; IgG = immunoglobulin G; LKM = liver kidney microsomal antibody 1; M = methylprednisone; P = prednisolone; SMA = smooth muscle antibody; (+) = positive and/or elevated; (–) = negative and/or within normal limits.

analytical studies represent important limitations to the observed beneficial effect of corticosteroid on patients with acute HEV infection. Future investigations need to address the question whether corticosteroids can improve outcome of patients with acute HEV infection associated liver failure, which may carry a significant risk for mortality, and more specifically whether the pediatric end-stage liver disease score would be useful to justify the need for short-term corticosteroid therapy in children with acute HEV infection.[31]

In summary, acute HEV infection is an important diagnosis to consider in pediatric travelers returning ill with fever and a gastrointestinal symptom complex from HEV-hyperendemic regions, especially if they are VFR travelers. Clinical, laboratory, and histopathologic features are not specific for HEV infection and overlap with those of AIH. Consequently, there can be a diagnostic and therapeutic dilemma if HEV diagnostic assays are not readily available and liver function continues to deteriorate. More timely access to HEV-specific assays would be helpful, especially at institutions that frequently serve mobile communities with close ties to HEV-hyperendemic regions. The case reported here and other limited observational reports have shown a potentially positive effect of short-term corticosteroid treatment in patients with acute hepatitis E with progressive hepatic inflammation, and additional research is needed to further assess its impact and safety.

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