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Review

Extrahepatic manifestations of hepatitis E virus: An overview

Fotios S. Fousekis, Ioannis V. Mitselos, and Dimitrios K. Christodoulou

Department of Gastroenterology and Hepatology, University Hospital of Ioannina, School of Health Sciences, University of Ioannina, Ioannina, Greece

Hepatitis E virus (HEV) is a significant health problem with approximately 20 million individuals infected annually. HEV infection has been associated with a wide spectrum of extrahepatic manifestations, including neurological, hematological and renal disorders. Guillain-Barré syndrome and neuralgic amyotrophy are the most frequent neurological manifestations. In addition, HEV infection has been observed with other neurological diseases, such as encephalitis, myelitis and Bell's palsy. Hematologic manifestations include anemia due to glucose-6-phospate dehydrogonase deficiency, autoimmune hemolytic anemia and severe thrombocytopenia. Membranoproliferative glomerulonephritis and relapse IgA nephropathy with or without coexisting cryoglobulinemia appear to be the most common renal injuries related with HEV infection. Also, HEV infection has been associated with acute pancreatitis and other immune-mediated manifestations, such as arthritis and myocarditis. However, the pathophysiologic mechanisms of HEV-related extrahepatic manifestations are still largely unclear. **(Clin Mol Hepatol 2020;26:16-23)**

Keywords: Hepatitis E; Kidney; Neurologic manifestations; Hematologic diseases

INTRODUCTION

Hepatitis E virus (HEV) is a single-stranded RNA virus and was first discovered in 1983,[1] but the viral genome was cloned in 1990.[2] It is estimated that HEV causes 20.1 million infections annually, leading to 3.4 million symptomatic cases with acute hepatitis and 70,000 deaths related to acute liver failure.[3]

HEV has eight genotypes. Genotypes 1 and 2 only infect humans, are detected mainly in Asia and Mexico, respectively and they spread through fecal-oral route. Genotypes 3 and 4 are detected mainly in Europe and North America, circulate in animal species such as pigs, wild boars and deer and occasionally infect humans via consumption of contaminated meat or direct contact.[4] Also, genotype 3 has been detected in shellfishes in Scotland and in southern Italy.[5,6] Genotypes 5 and 6 have been only reported in wild boar and genotypes 7 and 8 have been identified in camels.[7]

The diagnostic tests for HEV infection include detection of antibodies against HEV (IgM anti-HEV and IgG anti-HEV) and detection of HEV RNA. IgM anti-HEV is positive during the first month after HEV infection, while IgG anti-HEV represents current or past infection.[8] Detection of HEV RNA in blood or stool characterizes chronic or acute HEV infection. Chronic hepatitis E is defined as

Abbreviations:

AIHA, autoimmune hemolytic anemia; DAT, direct antiglobulin test; G-6-PD, glucose-6-phospate dehydrogenase; GBS, Guillain-Barré syndrome; HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, hepatitis E virus; MGUS, monoclonal gammopathy of undetermined significance; NA, neuralgic amyotrophy

Corresponding author : Dimitrios K. Christodoulou
Department of Gastroenterology and Hepatology, University of Ioannina, Stavrou Niarchou 1, Ioannina 45100, Greece
Tel: +302651099639, Fax: +302651007838
E-mail: dchristodoulou@gmail.com
https://orcid.org/0000-0001-9694-1160

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HEV RNA being detectable for at least 3 months. In immunosuppresed patients with chronic HEV infection, antibodies are often undetectable.[9] HEV infection is usually self-limiting and causes acute mild illness. However, HEV infection during pregnancy, especially in the third trimester may lead to acute liver failure.[10] Chronic HEV infection is rare and may develop in immunocompromised patients, such as organ transplant recipients.[11]

In addition, HEV has been associated with a range of extrahepatic manifestations, including a spectrum of neurological symptoms and diseases, hematological disorders, renal diseases, acute pancreatitis, myocarditis, arthritis and autoimmune thyroiditis (Table 1).[12] However, the pathophysiologic mechanism of extrahepatic manifestations remains unclear. It seems that viral infections trigger a variety of host-defense mechanisms, which may not be restricted to the primary location of infection and can cause cross-reactions between viral epitopes and self-antigens, leading to multisystemic manifestations. Another possible explanation is that HEV replicates not only in liver, but also in other tissues. HEV has been detected in neuronal cells,[13] human placenta,[14] breast milk,[15] and urine.[16]

Table 1. Extrahepatic manifestations associated with hepatitis E virus infection

System	Manifestations
Neurological system	Guillain-Barré syndrome Neuralgic amyotrophy Encephalitis Myelitis Myositis Vestibular neuritis Peripheral neuropathy Bell's palsy Mononeuritis multiplex Seizure Pseudotumor cerebri Oculomotor palsy Polyradiculoneuropathy
Hematological system	Thrombocytopenia Monoclonal gammopathy of uncertain significance (MGUS) Hemolytic anemia Aplastic anemia Hemophagocytic syndrome CD30 (+) cutaneous T cell lymphoproliferative disorder Thrombotic thrombocytopenic purpura
Kidney	Relapse of IgA nephropathy Cryoglobulinemia Membranoproliferative glomerulonephritis
Heart	Myocarditis
Pancreas	Acute pancreatitis
Thyroid	Autoimmune thyroiditis Subacute thyroiditis
Skeletal system	Polyarthritis
Vasculitis	Henoch-Schönlein purpura

NEUROLOGICAL MANIFESTATIONS

Several neurological manifestations have been associated with HEV infection and include Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy), neuralgic amyotrophy, encephalitis, myelitis, myositis, vestibular neuritis, peripheral neuropathy, Bell's palsy and mononeuritis multiplex.[17] In a prospective multicenter study from United Kingdom, France and Netherlands it was found that 2.4% (11/464) of patients with non-traumatic neurologic injury had evidence of HEV infection.[18] Also, a study from France demonstrated the neurologic disorders in patients infected with HEV and found that 16.5% of HEV-infected patients reported neurologic symptoms and neurological manifestations were more frequent in immunocompetent patients compared to immunosuppressed patients (22.6% vs. 3.2%, $P<0.001$).[19] However, a study from China compared the prevalence of acute hepatitis E between 1,117 patients diagnosed with neurological illness and 1,475 healthy controls and found that there was no difference (0.54% vs. 0.68%).[20] A possible explanation is the geographical distribution of HEV. The study from China was conducted in an area endemic for HEV genotype 4, while the European studies reported cases associated with HEV genotype 3. Therefore, HEV genotype 4 seems not to contribute to neurological disorders.[21]

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an acute onset immune-mediated disorder of peripheral nervous system and is characterized by acute inflammatory demyelinating polyradiculoneuropathy, causing rapidly progressing symmetric motor paralysis.[22] HEV infection has been associated with development of GBS. Many studies have reported the high prevalence rate of HEV infection among GBS patients and several case reports have been documented showing the coexistence of acute hepatitis E with GBS. In Netherlands, 201 patients with GBS were compared with 201 healthy controls with a similar distribution in age, sex, and year of sampling and it

was found that the prevalence of acute hepatitis E was higher in patients with GBS compared with healthy controls (5% vs. 0.5%).[23] Additionally, in a similar study in Japan, 4.8% (3/63) of patients with GBS had acute HEV infection preceding the onset illness, while no patients from healthy control group (0/61) suffered from acute hepatitis E. Furthermore, a retrospective cohort study in Belgium found that the prevalence of HEV infection in patients with GBS was 8% (6/73).[24] In all studies, there were no differences regarding course and outcomes of GBS between HEV-related GBS and HEV-unrelated GBS. Also, cases of acute HEV infection have been found in pediatric patients with GBS.[25]

Neuralgic amyotrophy

Neuralgic amyotrophy (NA), also known as Parsonage-Turner syndrome, is an acute and painful unique or multiple mononeuropathy in the upper extremity and is characterized by rapid multifocal motor weakness, amyotrophy and sensory loss.[26] It seems that HEV infection can trigger the development of NA and several studies have been conducted. A cohort study with 64 patients from United Kingdom and Netherlands found that 10% of patients with NA had acute hepatitis E, but HEV was not related to age, sex, severity, disease course or outcome.[27] Also, it seems that patients with NA and HEV have a distinct phenotype. A multicenter European study compared 61 HEV-NA patients with 61 NA patients and found that, HEV-NA appears more often predominately bilateral asymmetrical involvement (80.0% vs. 8.6%, $P<0.001$) and more extensive damage to the brachial plexus. Involvement outside the brachial plexus is more common in HEV-NA (58.5% vs. 10.5%, $P<0.01$).[28]

Other neurological manifestations

Other neurological cases associated with HEV infection include vestibular neuritis,[29] Bell's palsy,[30] acute ataxic neuropathy,[31] transverse myelitis,[32] acute encephalic Parkinsonism,[33] oculomotor palsy,[34] myositis,[35] seizure,[36] pseudotumor cerebri,[37] bilateral pyramidal syndrome,[38] polyradiculoneuropathy,[39] and mononeuritis multiplex.[40] In addition, central nervous system infections, such as encephalitis and meningitis, with HEV have been reported and HEV RNA has been demonstrated in serum and cerebrospinal fluid at the time of acute illness. Also, many patients with CNS infection were immunosuppresed as a result of solid organ transplantation.[41]

Pathogenic mechanism

The pathogenic mechanism between HEV and neurological disorders has been not clarified, but it seems that HEV is also neurotropic. Shedding of HEV RNA into the cerebrospinal fluid and intrathecal production of IgM anti-HEV has been detected in a patient with NA and acute HEV infection.[42] Additionally, a study demonstrated that human neuronal-derived cell lines such as neuroepithelioma, desmoplastic cerebellar medulloblastoma, glioblastoma multiforme, glioblastoma astrocytoma and oligodendrocytic cells can support HEV RNA replication.[43]

It is recommended that clinicians consider the possibility of HEV infection in patients with neurological disorders and concurrent liver enzyme alteration, especially those with peripheral nerve involvement.[44]

RENAL MANIFESTATIONS

Renal disorders have been reported during HEV infection, including membranoproliferative glomerulonephritis and cryoglobulinemia. A retrospective study assessed kidney function and histology in 51 cases of solid-organ transplant patients during genotype 3 HEV infection and they observed statistically but not clinically significant decrease in estimated glomerular filtration rate (-5 mL/min, $P=0.04$) during HEV infection. In renal biopsies, glomerular diseases were identified. They included relapse of IgA nephropathy and membranoproliferative glomerulonephritis. The majority of these patients had cryoglobulinemia. After HEV clearance, cryoglobulinemia resolved and proteinuria and renal function improved.[45] Additional cases of HEV-related membranoproliferative glomerulonephritis and membranous nephropathy have been reported.[46,47] In one case, HEV infection triggered monoclonal gammopathy of renal significance.[48]

The association between cryoglobulinemia and HEV infection has not been fully investigated. In a study with solid organ recipients, who suffered from HEV infection, the prevalence of cryoglobulinemia was increased during chronic phase of infection (52.9%) compared to acute phase of infection (36.4%) and HEV-negative solid organ recipients (23.6%) ($P<0.01$). Also, HEV infection was identified as an independent predictive factor for cryoglobulinemia (odds ratio, 2.3).[49] Another retrospective study from Germany compared the prevalence of IgG anti-HEV between patients with cryoglobulinemia and healthy controls. They found that the anti-HEV seroprevalence rate was significantly higher in

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patients with essential cryoglobulinemia than in non-essential cryoglobulinemia patients (P=0.043), suggesting that previous HEV contact might play a role in some cases of cryoglobulinemia that are currently classified as essential.[50]

HEMATOLOGIC MANIFESTATIONS

Anemia

Different patterns of anemia have been reported during HEV infection, including hemolytic anemia due to glucose-6-phospate dehydrogonase (G-6-PD) deficiency, autoimmune hemolytic anemia (AIHA) and aplastic anemia. Hemolytic anemia may be a complication of acute viral hepatitis and the frequency rate of hemolysis has been reported in up to 23% of patients. The prevalence of hemolytic anemia may rise up to 70% in patients who have G-6-PD deficiency.[51] Patients with G-6-PD deficiency have low levels of glutathione in red blood cells, leading to accumulation of oxidants during viral hepatitis and resulting in hemolysis. Several cases of hemolysis in patients with G-6-PD deficiency and acute HEV infection have been reported.[52-54] In some cases of hemolysis in patients with acute HEV infection and G-6-PD deficiency, there was development of renal failure, as a result of possible obstruction of renal tubules due to hemoglobulin and bilirubin.[55,56]

Autoimmune hemolytic anemia has been described in association with a variety of hepatotropic viruses, such as cytomegalovirus, hepatitis A virus (HAV) and hepatitis B virus (HBV).[57] AIHA is diagnosed based on clinical presentation, spherocytosis, laboratory findings and positive direct antiglobulin test (DAT). However, DAT was negative up to 15% of AIHA cases. In four published cases of AIHA-related with hepatitis E, the treatment was supportive and their outcomes were favorable.[58-61]

Hepatitis-associated aplastic anemia is an uncommon but distinct variant of aplastic in which pancytopenia appears 2 or 3 months after an acute attack of viral hepatitis. Several viruses, such as parvovirus B19, cytomegalovirus, Epstein-Barr virus, HAV and HBV, have been associated with aplastic anemia.[62] Three cases of HEV-related aplastic anemia have been reported. In one case there was no response to treatment with cyclosporine and in the second case, the patient expired due to sepsis and in the third case, the patient was treated with thymoglobulin, cyclosporine, corticosteroids, filgastrim and transfusions.[63-65]

Thrombocytopenia

Thrombocytopenia is a well-recognized complication of infections, including those from hepatotropic viruses. A variety of possible mechanisms of thrombocytopenia have been reported and includes hypersplenism, reduced hepatic production of thrombopoietin, bone marrow suppression by hepatotropic virus or treatment and development of anti-platelet autoantibodies and platelet-associated immune complexes.[66] Several cases of HEV-associated thrombocytopenia have been documented. In most cases, thrombocytopenia was self-limited, while in other cases, the patients needed to receive platelet transfusion, intravenous globulin and/ or corticosteroid. It is worth mentioning that, anti-platelet antibodies were detected in some cases of HEV-related thrombocytopenia.[44,61,67,68]

Other hematological diseases

HEV infection has been related with other less common hematological disorders. Few cases of HEV-related hemophagocytic syndrome have been documented.[69-71] Also, HEV infection has been detected in patients with CD30 (+) cutaneous T cell lymphoproliferative disorder[72] and monoclonal gammopathy of undetermined significance (MGUS). However, the relation between MGUS and HEV remains uncertain.[73] Additionally in one case, thrombotic thrombocytopenic purpura relapse induced by acute hepatitis E transmitted by cryosupernatant plasma. HEV infection treated with ribavirin and thrombotic thrombocytopenic purpura remitted with remission of HEV infection.[74]

ACUTE PANCREATITIS

A wide variety of infectious agents has been associated with acute pancreatitis and these include viruses, bacteria and parasites. The association between acute pancreatitis and viral hepatitis is well known and HAV, HBV, and hepatitis C virus have been implicated most often.[75,76] A proposed pathogenetic mechanism is the development of edema of the ambulla of Vater, causing obstruction of pancreatic fluid flow.[77] Several cases of HEV-induced acute pancreatitis have been reported.[78,79] In a single-center study from France, 2.1% (16/790) of patients with acute pancreatitis had serological evidence of recent HEV infection with no other discernible cause of pancreatitis.[80] The typical profile of a patient is a young male from an endemic area or having recently travelled

to that area, who develops mild to moderate acute pancreatitis.[81] However, life-threatening complications, such as, acute necrotizing pancreatitis, pseudocyst bleeding and multiorgan failure, have been reported.[82-84]

OTHER MANIFESTATIONS

Development of many other diseases has been reported during HEV infection, but further studies are needed to establish the association. In previous literatures, three cases of HEV-associated myocarditis have been reported.[85] Furthermore, HEV infection has been correlated with thyroid diseases. These include autoimmune thyroiditis, subacute thyroiditis and Grave's thyrotoxicosis.[86-88] In addition, a case of Henoch-Schönlein purpura triggered by acute HEV infection[89] and another case of HEV-induced myasthenia Gravis have been described.[90] Lastly, HEV infection may cause acute polyarthritis.[91,92]

CONCLUSION

Several extrahepatic manifestations and diseases have been documented during acute and chronic HEV infection. Neurologic diseases are demonstrated to be the most common extrahepatic manifestations of HEV infection, followed by hematological disorders and kidney injury. However, the pathophysiology of these manifestations and the causal relation with HEV infection remain ambiguous. Therefore, further studies are needed to estimate the epidemiological characteristics of HEV-related extrahepatic manifestations and to elucidate their underlying pathogenetic mechanisms.

Author's contribution

FSF: Data selection, writing, study design, IVM: writing, DKC: Supervision, study design, writing

Conflicts of Interest

The authors have no conflicts to disclose.

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