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EDITORIAL

The Extrahepatic Manifestations of Hepatitis E Virus: A Peek behind the Liver

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ABSTRACT

Hepatitis E virus (HEV) is inherently a hepatotropic virus that causes acute hepatitis E in general, and chronic liver diseases in some individuals. Notably, pregnancy related complications remain a serious issue in a proportion of HEV infected females. In addition, ample of clinical studies have also reported neuronal, intestinal, renal, cardiac, hematological, and pancreatic disorders in hepatitis E patients. The existing literature on extrahepatic manifestations in hepatitis E patients is, however, mainly based on case reports, small case series or observational studies. The extrahepatic infections or pathogenesis of HEV are suggested to be either directly by viral factors or indirectly by modulation of host-immune systems.

Key words: Hepatitis E virus; HEV genotypes; Chronic hepatitis; Extrahepatic manifestations

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INTRODUCTION

Hepatitis E virus (HEV) is inherently a hepatotropic virus that causes acute hepatitis E and fulminant liver failure as well as chronic infection in some clinically immunocompromised individuals^[1,2]. In addition, ample of studies have also reported extrahepatic manifestations of HEV such as neurological signs and symptoms, renal disorders, acute pancreatitis, cryoglobulinemia and hematological disorders^[3-5]. Globally, hepatitis E accounts for an estimated mortality rate of 2% that includes 20-30% of pregnant women^[6]. HEV has been classified within species *Orthohepevirus A* of genus *Orthohepevirus*, under the family Hepeviridae^[7]. Of the four recognized human genotypes of HEV (HEV1-HEV4), HEV3 and HEV4 are potentially zoonotic to swine, wild boar and other mammals^[7,8]. HEV is a quasi-enveloped RNA virus, which encodes the nonstructural polyprotein (pORF1) necessary for replication, antigenic capsid protein (pORF2), and a small pleiotropic protein (pORF3) required for infection and host-factors modulations^[9]. The existing literature on extrahepatic manifestations in hepatitis E patients is mainly based on case reports, small case series or retrospective/prospective observational studies. However, a recent study based on extensive literature review indicates the commonest form of extrahepatic manifestations associated with neurological (54.94%), cardiovascular and hematological (34.88%), and gastrointestinal/pancreaticobiliary (7.41%) systems, including rare and minor issues with renal, endocrine, respiratory, muscular and immune systems^[10]. The extrahepatic infections or pathogenesis of HEV are suggested to be either directly by viral RNA or proteins or indirectly by modulation of host-immune systems^[5].

GUT MANIFESTATIONS

Abdominal pain, jaundice or nausea is common in acute viral hepatitis. Though gastrointestinal infection or pathogenesis of HEV is rare, it serves as a potential reservoir or source for reinfection in HEV3 infected chronic patients^[11]. This has been very recently supported by detection of HEV RNA and antigen in the deep crypts

of duodenum and ileum of a HEV3 infected organ-transplant patient^[11].

RENAL MANIFESTATIONS

In a proportion of hepatitis E patients, glomerulonephritis, membranous nephropathy, nephroangiosclerosis, cholemic nephrosis, end-stage renal disease, and acute or acute-on-chronic kidney diseases have been reported^[12-16]. HEV RNA and antigen have been detected in the urine of both acute and chronic hepatitis E patients^[17,18]. While renal disorders have been mainly reported in cases with HEV3 infection, few cases are also known to be associated with HEV1 and HEV4 infections^[13-16,19]. Notably, the mechanisms of HEV associated renal disorders are attributed to the deposition of immune complexes in the glomeruli, and infiltration of the immune cells around the deposits^[11,20].

NEUROLOGICAL MANIFESTATIONS

HEV infection of the peripheral or central nervous system is widely reported to be associated with Guillain-Barré syndrome, neuralgic amyotrophy, Miller Fisher syndrome, mononeuritis multiplex, Bell's palsy, polyradiculoneuropathy, paresthesia, neuromyopathy, small fiber neuropathy, vestibular neuritis, oculomotor palsy, meningoencephalitis, transverse myelitis, pyramidal syndrome, pseudotumor cerebri, and meningoradiculitis^[21-26]. Notably, HEV RNA has been detected in the cerebrospinal fluid of HEV3 infected patients with neurological symptoms^[23,26]. Nonetheless, HEV1 and HEV4 associated neuronal manifestations have been also reported^[23,27].

CARDIOVASCULAR AND HEMATOLOGICAL MANIFESTATIONS

The cardiovascular manifestations involve case reports on myocarditis and myositis^[28-30], cardiac arrhythmias^[31], long QT syndrome^[32], and Torsade's de pointes^[32]. Blood products such as plasma, apheresis platelets, whole blood pooled platelets, pooled granulocytes and red blood cells are known as potential sources of transfusion-transmitted HEV infection^[33,34]. Hepatitis E associated hematological disorders include severe thrombocytopenia, aplastic anemia, monoclonal gammopathy, hemophagocytic syndrome, red blood aplasia, and hemolytic anemia^[34,35]. Of these, hemolytic anemia is mainly associated with acute HEV1 infection^[33-37]. In addition, HEV infection of hematopoietic stem cells has been also reported in transplant cases^[38,39]. Recently, detection of HEV3 and HEV4 RNA and antigen in acute myeloid leukemia patients' bone marrow has suggested viral replication, which may serve as a potential reservoir in such immunocompromised individuals^[39,40].

PANCREATIC MANIFESTATION

Acute pancreatitis is known to have strong association with fulminant viral hepatitis where burden of mortality primarily lies with severity of hepatitis^[41,42]. The first reported case of non-fulminant HEV associated pancreatitis came into light in 1999^[43]. Acute pancreatitis has been reported in HEV1 infected patients^[44]. It is believed that HEV1 has high tropism for the pancreas^[45]. However, its underlying mechanism still remains unknown. Several other cases of acute pancreatitis are also known^[46,47]. In addition life threatening complications, such as, acute necrotizing pancreatitis, pseudocyst bleeding and multiorgan failure associated with HEV-induced pancreatitis are also known^[45,48,49].

PREGNANCY RELATED COMPLICATIONS

Pregnancy in third trimester can further exacerbate HEV1 infection, affecting both mother and fetus with significant morbidity and mortality rates in up to 30% cases^[6,50]. Compared to developing countries, industrialized nations have very few reported cases of HEV3 infection during pregnancy^[51]. HEV1 infection is associated with the severe outcomes during pregnancy, while HEV3 infection is a mild to moderate, spontaneously self-limited^[51]. These complications are suggested to depend on several factors such as HEV genotypes, viral load, immune status, and hormonal factors^[6]. Elevation in viremia, down regulation of progesterone receptors, and higher interleukins (IL-12/IL-10) ratio are shown to be associated with poor pregnancy outcomes in HEV infected women^[52].

HEV MANIFESTATION IN THE GENITAL SYSTEM

There is no report on HEV infection in the female reproductive tract in the absence of pregnancy. However, HEV4 infection has been linked to impaired sperm quality, reduced sperm count and motility, increased abnormal sperm forms, and decreased testosterone level in Chinese males^[53]. Contrarily, in other study, absence of HEV RNA in the semen has suggested no correlation between HEV3 infection and male infertility^[54]. Also, sexual transmission of HEV has not been observed in homosexual men^[55]. Nonetheless, the pathogenesis of HEV in the genital system is hitherto poorly understood.

CONCLUSIONS

In addition to hepatopathogenesis, pregnancy related complications remain a serious issue in HEV infected females. Moreover, ample of clinical studies have reported extrahepatic infection and pathogenesis of HEV in nervous system, intestine, kidney, cardiovascular system, pancreas and male reproductive system. The existing literature on extrahepatic manifestations in hepatitis E patients is, however, mainly based on case reports, small case series or retrospective/prospective observational studies. The extrahepatic infections or pathogenesis of HEV are suggested to be either directly by viral factors or indirectly by modulation of host-immune systems. Nonetheless, further clinical and molecular studies are required to elucidate the underlying pathophysiological mechanism of such extrahepatic manifestations.

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