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Review of clinical characteristics, immune responses and regulatory mechanisms of hepatitis-E-associated liver failure

Hepatitis E-associated liver failure

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Abstract

Hepatitis E virus (HEV) is the most common cause of acute liver failure (ALF) and one of the most common factors causing acute injury in acute-on-chronic liver failure (ACLF). When HEV-related LF occurs, a series of changes take place in both the intrahepatic environment and extrahepatic microenvironment. The changed types and distribution of immune cells (infiltrating macrophages and increased lymphocytes) in liver tissue, as well the increased proinflammatory cytokines and chemokines in the blood, indicate that the occurrence and progression of HEV-related LF are closely related to immune imbalance. The clinical features and immune reaction in the body during HEV-related ALF and ACLF are complicated. This review highlights recent progress in elucidating the clinical manifestations of HEV-associated ALF and ACLF, and discusses the corresponding systemic immune changes and possible regulatory mechanisms.

Key Words: Hepatitis E virus, acute liver failure, acute-on-chronic liver failure, immune cells, cytokines, mechanism.

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Core Tip: Hepatitis E virus (HEV) is a common cause of acute liver failure (ALF) and the most common factor causing acute injury in acute-on-chronic liver failure (ACLF). The whole immune environment in the body during HEV-related liver failure (LF) is complicated. This review highlights recent progress in elucidating the clinical manifestations of HEV-associated ALF and ACLF, and discusses the corresponding systemic immune changes and possible regulatory mechanisms.

INTRODUCTION

The threat to public health from hepatitis-virus-associated liver failure (LF) is serious[1, 2]. Global epidemiological surveys have shown that hepatitis E virus (HEV) is the most common cause of acute liver failure (ALF) and one of the most common factors causing acute injury in acute-on-chronic liver failure (ACLF)[1, 3]. HEV infection can develop into severe hepatitis in patients with underlying chronic liver disease, underlying comorbidities, or altered immune responses, such as in pregnant women[4-6].

HEV infection can show symptoms of acute viral hepatitis and abnormal function of extrahepatic organs. According to international standards, coagulopathy, elevated serum transaminase, abnormal bilirubin and altered consciousness level are important indicators to judge LF[3, 7]. When LF occurs, a series of changes take place in both the intrahepatic environment and extrahepatic microenvironment, which is actually a systemic disease response. The aetiology of the systemic response to HEV-associated LF has not been well established, although many studies have shown that dysregulation of immune responses is the key factor driving the occurrence of HEV-associated LF[8-10]. The changed numbers of monocytes-macrophages cells, dendritic cells and the increased several proinflammatory cytokines (IFN-γ, TNF-α, IL-10, IL-18) in blood among HEV patients were along with adverse outcomes. In addition, inflammasome activation in macrophages shows that immune response plays an important role in the development of HEV-associated LF[9, 11, 12], although the exact pathogenesis remains to be clarified.

This review aims to synthesise data on the investigations of HEV-associated LF in an attempt to understand the incidence and clinical characteristics of the disease, and most importantly, to understand the corresponding systemic immune changes and regulatory mechanisms, to facilitate control of the disease.

DISEASE MANIFESTATIONS IN HEV-ASSOCIATED LF

Disease manifestations in HEV-associated ALF.

People infected by HEV manifest from subclinical infection to uncomplicated acute viral hepatitis and even severe fulminant LF[4, 13]. In an individual without underlying chronic liver disease, a syndrome characterised by markers of liver damage (elevated serum transaminases), impaired liver function [jaundice and international normalized ratio (INR) > 1.5] and new hepatic encephalopathy is defined as ALF[14]. The Clinical Practice Guidelines produced by the European Association for the Study of the Liver (EASL) state that hepatic viruses including hepatitis B virus (HBV), hepatitis A virus (HAV) and HEV can cause ALF. The guidelines suggest that HBV-associated ALF has higher mortality than HAV- and HEV-associated ALF. Nonetheless, the incidence of HEV-associated ALF is higher, suggesting the need for serological screening for HEV infection[14]. A systematic review by Patterson *et al*[1] analysed the global epidemiology of virus-induced ALF. The 25 relevant studies published between 2009 and 2019 showed that the prevalence of HEV-induced ALF was 3%–70%. The high rate of ALF among pregnant women reported in previous studies was related to HEV[6, 15], which likewise suggested the necessary to increase attention and extend the use of the hepatitis E vaccine.

Classically, HEV-associated ALF presents as an initial prodromal phase with symptoms of fever, fatigue and nausea. Then, jaundice and dark urine occur subsequently, and alanine transaminase (ALT) and aspartate aminotransferase (AST) increase. Increased bilirubin level, sharply deteriorating coagulation and different degrees of hepatic encephalopathy are the most important features of HEV-associated ALF[14]. In addition, along with symptoms of acute liver deterioration, neurological disorders (Guillain–Barré syndrome and neuropathic muscular atrophy were most reported), abnormal urinary system (particularly glomerulonephritis), and haematological disorders (HEV-associated ALF combined with aplastic anaemia) are increasingly recognized by clinicians[16-19]. We consider that the most important extrahepatic manifestations caused by hepatitis E virus maybe neurological (myelitis, myositis, bilateral peripheral facial paralysis, acute uniphasic brachial plexus disease).

They have a high incidence (5%–30%) and serious clinical impact[16, 20]. Yet, to facilitate the diagnosis and prediction of the HEV-associated LF, many researchers also suggest kidney function as a predictor. Elevated urea nitrogen is closely related to the occurrence and progression of HEV-related LF and plays an important role in clinical prognosis[21, 22]. All the above information indicates that HEV-associated ALF is not a single organ injury, but a systemic condition. Moreover, the involvement and deterioration of the extrahepatic systems accelerate disease progression and increases the mortality rate of HEV-associated ALF. Therefore, to better monitor the changes in the disease, apart from more frequent detection of liver enzyme indicators, bilirubin, coagulation profile and conscious state, there is a need to assess other systemic indicators, such as peripheral hemogram, electrolyte testing, arterial pH, creatinine clearance rate, etc[4, 23].

Disease manifestations in HEV-associated ACLF

ACLF is typically related to a precipitating event among patients with chronic liver diseases (CLDs), such as acute liver damage or acute exacerbation of CLD. Although the definitions of ACLF from the Asia Pacific Association for the Study of the Liver, EASL and American Association for the Study of Liver Diseases have some differences, the same consensus is about deterioration of liver function with high mortality for ACLF[7, 24, 25].

We know that there are significant differences in epidemic areas and disease characteristics among different HEV genotypes. The spectrum of CLDs also varies by region, such as chronic viral hepatitis is endemic in Asia, especially India, while alcoholic liver disease and fatty liver dominate in Europe and America. The above factors result in different clinical manifestations of HEV-related ACLF in different countries and regions. There is significant controversy on the impact of HEV genotypes 3 and 4 in ACLF. In Europe and America, the effect of HEV genotypes 3 and 4 on CLDs was observed to be limited, with low rates of liver decompensation and ACLF[26],

while the occurrence in Asia can be up to 60%[5, 27]. Furthermore, irrespective of the incidence rate of ACLF caused by HEV, the mortality of HEV-related ACLF was lower compared to alcohol-related ACLF and other forms of ACLF[28]. Generally, organ failure is the final progression of ACLF and determines the outcome of patients. Previous studies showed that the rates of renal failure, circulatory failure and respiratory failure in HEV-related ACLF were lower than those of other acute trigger factors, such as alcohol, HBV and cryptogenic elements[28, 29]. Does it means that despite HEV-related ACLF having a higher incidence, it appears to have a better clinical outcome than ACLF triggered by other acute factors? We think that more clinical data are needed to explore this further.

The differences in clinical presentations and outcomes among HEV-related ACLF patients are also due to prior body status. First, the functional status of hepatocytes in patients with different underlying CLDs is not the same. Our previous studies have shown a significantly higher mortality rate in patients with cirrhosis[5, 30, 31]. Second, some underlying comorbidities[5], such as diabetes, nephritis, chronic respiratory diseases and malignancy (particularly, haematological malignancy (data from virology departments across nine NHS health boards in Scotland[32]), are significant predictors of mortality. Although some laboratory tests (higher AST, lactate dehydrogenase and a-fetoprotein and lower triglyceride) can also provide some clues to identify the occurrence and prognosis of HEV-related ACLF and help tailor effective prevention. More attention to the above at-risk groups is essential. We believe that more precise and effective anti-HEV vaccination of at-risk populations is necessary and urgent.

THE IMMUNOLOGICAL MECHANISMS OF HEV-ASSOCIATED LF

It is well known that HEV infections are mostly self-limiting diseases and immune-capable individuals usually can eliminate the virus spontaneously[4, 13]. Otherwise, infected persons with low immunity can develop acute viral hepatitis, leading to chronic infection, extrahepatic symptoms and even LF. Previous studies have shown

that the host immune response, rather than the virus itself, is the driving factor for the occurrence of HEV-associated LF[33]. The gene expression profile of liver biopsy in HEV-infected LF patients shows that there are many upregulated and downregulated genes in liver tissue compared to normal liver tissue, and most of these differentially expressed genes are related to immunity[34]. What interaction is there between virus and host immunity? In particular, what is the specific immune response when HEV-related LF occurs? Past studies may give us several clues.

Involvement of immune cells in HEV-associated LF

The immune response process includes immune cell proliferation, differentiation of antigen recognition activation, and production of immune substances with specific effects. This process is a comprehensive reflection of the functions of various parts of the immune system. During the process, the antigen-presented lymphocytes activate immune molecules to form a series of physiological reactions and immunological effects. The types and distribution of immune cells differ in patients with LF compared to normal subjects[8, 35]. Intrahepatic immune cell count, especially lymphocytes, is many times more than in non-LF populations, which suggests that lymphocytes infiltration is one of the characteristic immune reactions of LF[8, 36]. Wu *et al.*[10] showed that the Th1/Th2 cytokine levels among acute hepatitis E patients, HEV-associated ALF patients and controls were significantly different. Th2 bias (IFN-γ/IL-4) was observed particularly among acute hepatitis E and HEV-associated ALF patients, which infers that hepatocyte damage was aggravated by the persistent imbalance of cellular immunity. The levels of cytotoxic T cells, such as CD3 and CD8 cells, were higher in HEV-infected liver tissues compared to healthy liver tissues. The numbers of natural killer (NK) cells (CD56) and helper T cells (CD4) also differed significantly between the two tissues[35]. NK cells are the main component of liver lymphocytes and play a role in killing hepatotropic viruses. When HEV and other hepatotropic viruses infect the liver, NK cells can be activated by signalling factor, and produce cytokines to exert further immune effects[37]. Importantly, intrahepatic lymphocytes ($CD4^+$ T cells, $CD8^+$ T cells

and NK cells) among ACLF patients have significantly increased counts compared with those in healthy individuals[35, 37]. Although the pathogenesis of ACLF is not fully elucidated, the differences in lymphocyte counts suggest that cellular immunity is involved in progression of the disease. *In vitro* and *in vivo* experiments showed that the number of inflammatory macrophages in a model of drug-induced ALF were significantly increased, which finally resulted in severe liver injury[38, 39]. In conclusion, the difference in lymphocyte distribution in liver tissue is important in LF caused by various agents.

Different types of lymphocytes play different roles in immunoreactions. Immune monitoring mechanisms have advantages and disadvantages. NK cells act as sentinels and "vanguard troops" in the first step of battling against viral infection[37]. NK cells and differentiated NKT cells can be recruited by several cytokines from the peripheral blood and infiltrate the liver, participating in both fighting against HEV and impairing liver cells[40]. Through analysis of the frequency and activation status of NK and NKT cells in peripheral blood mononuclear cells, Srivastava *et al* found that HEV-infected patients had higher numbers of cells in an activated state[37]. The expression of NK group 2A (inhibitory receptor) on peripheral blood NK cells plays a pivotal negative regulatory role in the progression of hepatitis-virus-associated ACLF[41]. *In vivo* and *in vitro* experiments have confirmed that NK group 2D (activating receptor) participates in aggravating liver inflammation (elevated level of IFN-γ and TNF-α) by activating NK cells[42]. The reciprocal action from above inhibitory and activating receptors regulates the function of NK cells, and plays an important role in the progression of hepatitis-virus-related ALF and ACLF.

Another important lymphocyte involved in HEV-associated LF is cytotoxic T cells. Although cytotoxic T cells differentiating from $CD8^+$ T cells (which are promoted by $CD4^+$ T cells) can directly kill HEV, they can also cause liver cell damage[8]. Innate and adaptive immune responses also depend on monocytes and macrophages recognising

pathogens to mediate phagocytosis. When HEV invades the liver, reactive oxygen species and TNF-α were activated and produced by infiltrated macrophages, which can exacerbate local inflammation of the liver and promote the development of LF while fighting the virus[10]. These studies have suggested that the occurrence and progression of HEV-related LF are closely related to the immune response, which acts as a double-edged sword in fighting against HEV infection.

Involvement of cytokines in HEV-associated LF

Cytokines are small molecular proteins with extensive biological activities synthesised and secreted by immune cells (such as monocytes, macrophages, T cells, B cells and NK cells) and some nonimmune cells (such as endothelial cells, epidermal cells and fibroblasts) through stimulation. Cytokines can regulate cell growth and differentiation and promote an immune response by binding corresponding receptors[33, 43]. Markers called inflammasomes act as a hallmark when inflammation occurs[44]. Inflammasomes are like sensors that act as a bridge between pathogens and cytokines and inflammatory factors in the pathogenesis and progression of many inflammatory diseases. A recent study reported the critical role of an important inflammasome (NLRP3) in HEV infection, which can be activated by macrophages and then further regulate host defence. Further research suggests that therapeutic targeting of NLRP3 could benefit treatment of HEV-associated severe liver disease[9].

Several previous studies on cytokines during the pathogenesis of liver injury have shown that many cytokines (including IL-15, IL-18, CXCR3, granzyme B, CXCL8, CXCL9 and CXCL10) promote chemotaxis of immune cells to liver tissue[45], like the migration of NK cells, $CD8^+$ T cells, monocytes and macrophages described above. On the one hand, infiltration of macrophages in liver tissue is one of the main causes of severe liver injury due to excessive production of TNF-α, which can result in liver inflammation and even liver LF. On the other hand, inhibitory cytokines such as IL- 10 and transforming growth factor-β also play an important role in the process of

dysfunction and inactivation of the immune system. Impaired phagocytosis of monocytes and macrophages as well as the release of cytokines can result in inefficient treatment of HEV infection, which may advance liver deterioration toward LF[10].

IFN-γ is an effector molecule produced by various types of cells, and is one of the most important factors in the process of HEV infection. In general, IFN-γ kills infected liver cells and causes liver damage by promoting the differentiation of $CD8^+$ T cells into cytotoxic T cells, as well as helping to clear HEV[45]. In this process, its specific immune function is essentially a double-edged sword. On the one hand, it plays the role of virus removal. On the other hand, it can cause serious liver damage and even LF. Immune-inflammation response is the most important process against virus infection, which is also a balance between proinflammatory and anti-inflammatory immunity. The level of proinflammatory cytokines (IFN-γ and TNF-α) in the liver of HEV-related ACLF patients was significantly higher than that of normal subjects, while the expression of anti-inflammatory cytokines (IL-10) was not different between the two groups[10]. This suggests that the imbalance between the expression of proinflammatory and anti-inflammatory cytokines may be an important immune mechanism during the pathogenesis of HEV-related ACLF.

Last but not least, the liver is an organ with abundant blood flow. Massive perfusion of blood promotes immune cell migration from peripheral blood to the liver[45, 46]. Various cytokines can also travel through the blood vessels of the liver to the rest of the body to affect organ function. Monitoring changes in liver blood flow is also one of the means to evaluate the severity of liver disease. The effective hepatic blood flow is closely related to the severity of hepatitis-virus-related ACLF[47]. Effective blood flow is not only a reflection of liver function, but also a necessary channel for the connection between intrahepatic and extrahepatic environments. Increased migration of proinflammatory factors and chemokines from the liver to the extrahepatic environment plays an

important role in HEV-related LF, and the poor outcome is ultimately the result of multiple organ failure.

CONCLUSION

Here, we have reviewed relevant studies to understand the clinical characteristics of HEV-associated LF and related immunological mechanisms. Overall, HEV is a common cause of ALF and the most common factor causing acute injury in ACLF. The whole immune environment in the body during HEV-related LF is complicated, which involves complex cellular and humoral immunity. We hope this review can develop a better understand of the mechanism of HEV-related LF, and may eventually lead to improved prevention, diagnosis and treatment of the disease.

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