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Opinion

Hepatitis E and chronic liver damage in apparently immunocompetent individuals: Now what?

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ABSTRACT

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis worldwide, accounting for 20 million infections per year and 70,000 deaths. In developed regions, sporadic locally acquired infections are most commonly caused by HEV3, and in this setting Hepatitis E is mainly asymptomatic. However, certain group of patients HEV infection may present as a fulminant disease or progressive fibrosis. Chronic HEV infection can occur in immunocompromised individuals, including transplant recipients. A high proportion of solid-organ transplant recipients exposed to HEV are at risk of developing a chronic infection, frequently associated to extrahepatic manifestations. However, clinical phenotype of sporadic cases of HEV infection is still poorly characterized.

A recent work, focused on the retrospective study of HEV as a causative agent of viral hepatitis in adults form Mexico, pose novel challenges to understanding the HEV threat to human health. Main findings are brought into discussion herein, in light of the current knowledge concerning viral pathogenesis and host–pathogen interaction. The role of HEV infection in the development of chronic liver disease is also discussed. Hepatitis E is a cause of mortality and morbidity which negatively impacts the prognosis of patients with chronic liver disease. Recognition of HEV infection must be improved, by increasing awareness and knowledge of the clinical phenotype of the disease.

Hepatitis E virus (HEV) has been recognized as the most common cause of acute viral hepatitis worldwide. About 20 million infections occur per year, resulting in around 70,000 deaths [1]. In developing regions HEV infection and related diseases are of significant health concern, causing both sporadic cases and large outbreaks [1,2]. HEV is classified into 8 genotypes (HEV1–8), of which HEV1-4 are capable to infect human. HEV1 and HEV2 are anthroponotic pathogens and responsible for waterborne outbreaks in developing countries, while HEV3 and HEV4 are zoonotic and infect swine [2].

There is substantial heterogeneity in the clinical presentation of HEV infection between developing and developed countries. In developed regions, sporadic locally acquired infections are most commonly caused by HEV3 [1,3]. In this setting, hepatitis E is mainly asymptomatic but a proportion of patients can course a self-limiting disease with typical symptoms of acute hepatitis, e.g. malaise, nausea and jaundice [1]. In certain group of patients HEV infection may present as a fulminant disease or progressive fibrosis. Pre-existent chronic liver disease is a major risk factor for developing acute-on-chronic liver failure [4]. Chronic HEV infection can occur in immunocompromised individuals, including transplant recipients and patients receiving chemotherapy for hematological malignancies. A high proportion of solid-organ transplant recipients exposed to HEV will develop a chronic infection. In immunocompromised patients infected with HEV3, rapid progression of liver fibrosis to cirrhosis, decompensation and death has been described [1,5]. By contrast, it is generally assumed that if an immunocompetent patient, including a patient with cirrhosis, is infected with HEV, acute hepatitis E virus infection may occur, but chronic infection will not progress.

Despite all these data, clinical phenotype of sporadic and authocthonous cases of HEV infection still remain incompletely characterized, and novel research poses challenges to understanding and appreciating the HEV threat to human health.

Recently, Viera-Segura et al. [6] provided additional evidences that contribute to further complicate things regarding the real burden and impact of HEV infection in less characterized epidemiological contexts, such as Central America, where both sporadic cases and waterborne outbreaks occurs [7]. The work mainly focused on the study of HEV as a likely causative agent of viral hepatitis associated to liver damage in adult population from Mexico. Beyond

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the main purpose of the research, very interesting additional results were observed.

Mexico is generally regarded as hyperendemic for HEV infection, though no outbreaks were reported since the 1980s, when HEV2 had been described for the first time. Even though many crucial epidemiological and molecular information is in general lacking (only specific regions and population groups have been evaluated in Mexico), available data suggest that HEV is indeed widely distributed among humans. Furthermore, domestic pigs are also highly exposed to HEV3 [7]. Additionally, it has been recently showed that HEV is a major cause of acute hepatitis in children, with RNA detection rates as high as 17% [8]. Interestingly, the only genotype detected in those samples belonged to HEV1, previously reported in Central America. Despite this, hepatitis E is still underestimated, and the burden of HEV infection in adult population is completely unknown.

Viera-Segura et al. retrospectively investigated the role of HEV infection in adult patients with non-identified infectious etiological agent (NIIEA). Firstly, results show that about 30% of NIIEA -patients were infected with HEV3 and exhibited viremia. This finding is interesting since clearly it shows that hepatitis E is still a neglected disease and HEV is not oftenly recognized as an important etiological agent of acute and/or chronic hepatitis in Mexico. Furthermore, zoonotic transmission of HEV3 in adults, by contrast to what seems to be occurring in children, likely play a key role as a main cause of hepatitis in this setting. On the other hand, role of HEV2 as a causative genotype of hepatitis E appears to be negligible. Further research is needed to corroborate all these data, specially focused on the disease burden of HEV in selected groups of adults (highly exposed individuals, immunocompromised) but also in child population, where hepatitis E is not generally prevalent worldwide.

Secondly, authors showed that none of the NIIEA-patients that had HEV RNA presented typical symptoms of acute hepatitis, though they had an altered liver function. At first sight this is not surprising given that most HEV infections are asymptomatic. However, many of these viremic patients exhibited advanced liver fibrosis. Whether HEV infection played a role in the development of the chronic liver disease remains to be further investigated in these cases. The natural history of hepatitis E in patients with chronic liver disease is not well understood and a superimposed acute infection may worse the pronostic and increase the mortality, lead by a severe liver decompensation and the occurrence of severe extrahepatic manifestations [9].

Liver damage associated to chronic HEV infection has been almost exclusively seen in immunocompromised individuals. Just isolated cases were observed under an immunocompetent context, but an occult history of immuosupression was often suggested [10]. Interestingly, Viera-Segura et al. observed the all NIIEA-patients infected with HEV that exhibited liver fibrosis and evidences of advance liver damage, were immunocompetent. This finding is remarkable since, even if HEV was not the exclusive etiologic agent of the liver disease, hepatitis E might be probably playing a crucial (unknown) role in the pathogenesis.

But, now what? Altogether, data suggest that the host–HEV interaction and infection dynamics could be much more complex than the initially assumed, and probably certain severe clinical outcomes associated to hepatitis E may occur in an immunocompetent context.

Hepatitis E is still a cause of mortality and morbidity which negatively impacts the survival and prognosis of patients with chronic liver disease. Recognition and diagnosis of HEV must be improved, by increasing awareness and knowledge of basic and clinical aspects of the disease amongst clinicians. Further research efforts should be done aimed to elucidate the clinical phenotype of hepatitis E among risked populations. Prompt recognition of the infection, supported by adequate molecular and serological testing and an early intervention of those groups of patients remains key to achieve effective management.

Conflict of interest

None.

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