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Opinions

The story of hepatitis E virus infection and chronic kidney disease without liver damage

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In the late 1980s, viral stool particles recovered from an outbreak of hepatitis in Mexico served as a basis for the molecular characterization of a new virus, hepatitis E virus (HEV) [1]. This event placed the country as an epicenter in the study of viral hepatitis and explains our fascination with this intriguing pathogen.

HEV is an RNA virus belonging to the *Hepeviridae* family and the *Paslahepevirus* genus. It exists in two conformations: as a naked particle present in the stool or as a quasi-enveloped virus present in the blood [1]. Both forms are infectious and allow virus dissemination. Importantly, the quasienvelope allows evasion of the host immune response, and this conformation might be related to the distribution of the virus in different tissues [2]. Indeed, although HEV exhibits hepatocyte tropism and infection impairs liver function with the potential to cause fibrosis and cirrhosis [3], accumulating reports suggest that HEV leads to systemic disease, as evidenced by numerous extrahepatic manifestations (neurological, renal, hematological, and gastrointestinal) associated with the infection, with kidney disease being commonly reported [4]. The variability in hepatitis E pathogenesis is related to specific genotypes (gt), as well as to the host immune response. Progression to the chronic state defined in the setting of liver disease is related to gt3, gt4, and gt7, with gt3 being the best studied. Similarly, gt3 is the genotype most strongly associated with the development of extrahepatic manifestations [2].

Initially, considered a poverty predictor responsible for waterborne endemic outbreaks due to gt1 and gt2 in low-income countries in Africa, Asia, and America, the study of HEV underscored its wide circulation in high-income regions, where zoonotic gt3 and gt4 are present. In addition, the virus can be transmitted vertically during pregnancy, via blood derivatives, via transplants and through direct person–person contact [5,6]. The WHO indicates that one-third of the world's population is at risk for HEV infection, which is recognized as the main etiology causing viral hepatitis worldwide. However, there is still no specific treatment for the virus, and the only licensed vaccine is exclusively available in China and has been recently employed in outbreaks in Africa. Estimates indicate that approximately 939 million individuals have experienced HEV infection at one time and that between 15 and 110 million have experienced a recent or ongoing infection [7]. Considering that this information essentially comes from virus studies in the context of liver disease, we are still far from aware of the real picture of the infection.

Chronic kidney disease (CKD) is a multifactorial condition that results in alterations in the structure and proper functioning of the organ. It is estimated that approximately 10 % of the total adult population suffers from CKD at some stage; this condition is responsible for 1–2 million deaths annually worldwide and carries a significant economic global burden [8,9]. The development of CKD is closely associated with some of the most prevalent pathologies worldwide, such as diabetes, glomerulonephritis, and hypertension. In most cases, end-stage renal disease can lead to the total loss of kidney function, requiring dialysis [8]. Recently, we reported that 14.5 % of patients who underwent renal replacement therapy with hemodialysis in a Mexican cohort were seropositive for HEV. Notably, acute infections denoted by viral RNA corresponding to gt3 were identified in the absence of seroconversion [10]. Moreover, the follow-up of cases allowed us to identify the progression to chronic hepatitis E in a case of CKD in the absence of liver damage, the first case with these characteristics reported in the world [11], which coincides with increasing evidence of neurological manifestations without direct involvement of the liver [2] and emphasizes the necessity of studying, in detail, the direct effect of infection on the kidney.

Abbreviations: CKD, Chronic kidney disease; gt, Genotypes; HEV, Hepatitis E virus

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HEV chronicity may result in liver fibrosis and cirrhosis in immunosuppressed individuals. Since immunosuppression is required to avoid transplant rejection, hepatitis E has been studied in this cohort, specifically in kidney transplant recipients. In this group, the minimum concentration of tacrolimus needed to prevent graft rejection is a determining factor in the development of chronic HEV infection. Therefore, reducing the doses of immunosuppressive drugs is the first-line treatment for chronic HEV infection in posttransplant patients; however, in situations where this management is not feasible, the use of low doses of ribavirin represents an alternative to achieve viral elimination and avoid the consequences of the disease [12]. Unfortunately, the implementation of these strategies is limited, and the infection is still neglected in endemic regions, where the implementation of specific guidelines constitutes a priority.

Notably, although HEV-associated renal injury has been reported mainly in immunocompromised patients, a large proportion of non-immunocompromised acute hepatitis E patients (25 %) with proteinuria have recently been reported [13]. In that sense, the absence of seroconversion in hemodialyzed patients we found [10,11] is in line with the fact that detection of HEV RNA in plasma and stool remains the gold standard irreplaceable for diagnosis in immunosuppressed individuals and, according to our data, in specific conditions even in apparent immunocompetence.

The pivotal role of the kidney in the pathogenesis of hepatitis E is supported by evidence that patients with chronic HEV infection are at risk of developing glomerulonephritis. The mechanisms responsible for renal disease during hepatitis E are still not clear. However, a recent report pointed toward the deposition of immune complexes of the HEV ORF 2 protein in the kidney as the cause rather than the viral replication in this tissue [14]. In addition, in line with the relationship between hepatitis E and the kidney, the presence of a cleaved form of approximately 20 kDa corresponding to the virus capsid (ORF2) has been identified as a reliable marker of HEV infection, as the antigen is eliminated in the urine [15].

Undoubtedly, hepatitis E oversimplifies the pathogenesis associated with HEV, which demands fluid and continuous communication between specialties, including hepatology and nephrology. This communication is crucial given that HEV is not included in the differential diagnosis of kidney diseases and is particularly relevant in scenarios where infection is endemic but still neglected.

Declaration of competing interest

None.

CRediT authorship contribution statement

Addi P. Figueroa-Miranda: Writing – original draft. **Edgar D. Copado-Villagrana:** Writing – original draft. **Nora A. Fierro:** Conceptualization, Funding acquisition, Supervision, Writing – original draft.

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