Annals of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

VIEWPOINT

July-August, Vol. 17 No. 4, 2018: 544-546

Hepatitis E Virus: Still an Enigma in Mexico

Mauricio Realpe-Quintero,* Oliver Viera-Segura,** Nora A. Fierro**

* Laboratory of Biological Development, Veterinary Hospital of Small Species, University Center of Biological and Agricultural Sciences, University of Guadalajara, Mexico.
** Immunovirology Unit, Molecular Biology Service, Civil Hospital of Guadalajara Fray Antonio Alcalde, Center University of Health Sciences, University of Guadalajara, Mexico.

ABSTRACT

Based on high seroprevalence, null surveillance, and lack of diagnostics, Mexico is a high-risk region for hepatitis E Virus (HEV) infection. However, few local news on infection are available. Clinicians and general population are in need of increasing awareness, and preventive measures should be emphasized.

Key words. Zoonosis. Chronic hepatitis. Risk factors. HEV-genotypes.

INTRODUCTION

Hepatitis E virus (HEV) is a single-stranded RNA virus that is an important cause of acute and self-limitating hepatitis and could lead to fulminant liver failure in the setting of pregnancy. Additionally, in immunosuppressed patients, HEV may cause chronic infection with the development of sequels including fibrosis and cirrhosis. Worldwide, HEV has been also associated with extrahepatic manifestations such as neurological and renal disease. In spite of that, HEV remains poorly characterized and is frequently unidentified or misdiagnosed by clinicians. Although fecal-oral route is the most common via of HEV transmission, HEV can be also vertically transmitted from infected mothers to their fetuses. HEV may spread by zoonotic transmission from infected animals to humans and through person-to-person contact. Moreover, HEV is now recognized as a potentially transfusion-transmitted virus. Currently, it is estimated that there are more than 20 million HEV infections every year worldwide, leading to 3.3 million symptomatic cases and more than 56,000 deaths.[1]

HEV is highly distributed in the globe and has been described with at least 8 genotypes circulating in different species. Genotypes 1 and 2 have exclusively been found in humans, whereas genotype 3 and 4 are zoonotic in nature and are detected in humans and more frequently in animals such as pigs, deers, and boars. Limited sequences of genotypes 5-8 are currently available and are detected in other mammals. It is accepted that manifestation of HEV disease, source of infection, and route of transmission vary by genotype.[2] Thus, accurate identification and diagnosis of HEV has important implications for patient management, disease control, epidemiology, and characterization of transmission mechanisms.

VIRAL HEPATITIS AND LIVER DISEASE IN MEXICO

In the last years, the rates of liver disease have been increasing in Mexico. Alcohol consumption together with hepatitis A, B and C viruses (HAV, HBV and HCV) infections and non-alcoholic liver disease (NAFLD) are the main etiologies described in the country as associated to liver disease.[3]

Despite public efforts, Mexico has the highest rate of deaths in Latin America due to liver cirrhosis, with more than 30,000 deaths per year.[3] Long-term projections of the disease suggest that by the year 2030 the number of cases related to liver deaths in Mexico will increase by 55%.[4] Altogether suggests that the public policies that have been considered in the country still require close revision in

Manuscript received: April 30, 2018. **Manuscript accepted:** April 30, 2018.

DOI: 10.5604/01.3001.0012.0915

order to contend with the main liver pathologies affecting the Mexican population.

According to the local government health agency (Secretaria de Salud, SSA in Spanish), most of the cases of reported liver injury with no aetiological agent have been attributed to NASH. However, the SSA does not report the epidemiological status of HEV associated disease. Hence, HEV could represent a no-sufficiently attended hepatic infection, which could be related with up to 13.4% of viral hepatitis in the country without an aetiological agent detected in 2017, as reported by SSA in Mexico.[4,5]

HEV IN MEXICO

On the basis of an outbreak of acute infection by HEV between 1986-1987 in central Mexico and the first identification of viral genotype 2 in those samples, the country has been considered as an hyperendemic zone.[2] However, thirty-one years since first detection in Mexico, no new reports on genotype 2 have been published or data has been made available from government or public sources. In Mexico, in addition to genotype 2, genotype 3 has also been reported in animals. The first report from 2005 in swine was complemented in 2012 with a report of seroconversion in deers, and more recently confirmed after studies in farming pigs intended to human consumption. Also, a high seroprevalence report of HEV in samples from cirrhotic patients from western Mexico with no other aetiological agent is available, and the highest seroprevalence of HEV in farmed pigs has been found in western Mexico, compared to the rest of country. Based on these findings, the expected seroprevalence and risk of HEV infection in humans in Mexico is rather high,[5] as recently reported in HAV-HEV co-infected pediatric patients exhibiting acute hepatitis.[6] Within Mexico, research studies suggest a variable seroprevalence of HEV in humans depending on the geographical regions analyzed.[5] Furthermore, the frequent detection of HEV-specific antibodies in samples of people with no history of hepatitis suggests underestimation of the local disease burden, and uncertainty on the actual impact that HEV infection could represent in Mexico.

TREATMENT

Limited information is known regarding specific treatments against HEV infection. This information is already available for endemic regions such as India and, no guidelines have been proposed for Mexico. So far, no specific drug has been approved for the treatment of infection based on World Health Organization (WHO) recommendations. Lowering the dose of immunosuppressive drugs and administration of ribavirin has been suggested to treat immunocompromised individuals.[2] However, taking into account that only 50% of HEV infections in immunosuppressed transplant recipients lead to chronic HEV infection, this choice has to be revised. Studies in specific populations should be conducted in order to identify pharmacological approaches of benefit for patients.

Since 2012, an effective vaccine is available in China; however, there is still no data on the efficacy of this vaccine in other endemic regions of the world.

RECOMMENDATIONS

Considering the recommendations given by the WHO to eradicate infectious hepatitis by 2030, joined efforts are required in order to assess and better know the disease burden due to HEV, particularly in those geographical regions where infection is considered endemic such as Mexico.

With the mission of improving diagnosis and general management of HEV infections, having virus eradication as the ultimate goal, the following recommendations could be followed:

- To implement the use of NAT-based assays for HEV RNA detection in Mexico with the aim of harmonizing detection methods to globally available standards.
- To study the genomic variability of the virus in general population, high risk populations, including pregnant women, immunosuppressed patients, children, patients with NASH, patients with chronic infection with HBV and HCV, and patients with high alcohol consumption. This is in order to identify specific risk population in Mexico.
- To analyze the origin and transmission of HEV infections in Mexico in order to identify chains of transmission. The systematic study to identify the risk represented by water, particularly in areas considered to have poor health conditions and deficient sanitary treatment of the water, is required. Moreover, the risk of blood banking as a source of HEV infection requires to be tested in Mexico, as already done in other regions.
- Finally, it is imperative to increase awareness for HEV associated disease amongst health care practitioners, as well as including HEV information as part of health teaching programs for the general population. Increasing flow of information related to risk factors for HEV infection for educational purposes to general public, and to health-care professionals, is an urgent necessity in order to cope with the particular epidemiological situation in Mexico.

Altogether, these recommendations might be extended to other endemic regions[7] and could be translated in

strategies intended to improve general disease management, and to implement locally preventive and controlling programs to contend and limit the spreading of this enigmatic virus.

ACKNOWLEDGEMENTS

The authors thank to Diana Jennifer Carrillo-Casillas and Jose David Ramos-Solano for editing the manuscript.

REFERENCES

1. Murrison LB, Sherman KE. The enigma of hepatitis E virus. *Gastroenterol Hepatol* 2017; 13: 484-91.
2. Kamar N, Izopet J, Pavio N, Aggarwal R, Labrique A, Wedemeyer H, Dalton HR. Hepatitis E virus infection. Nat Rev Dis Primers 2017; 3: 17086.
3. Torres-Valadez R, Roman S, Jose-Abrego A, Sepulveda-Villegas M, Ojeda-Granados C, Rivera-Iñiguez I, Panduro A. Early detection of liver damage in mexican patients with chronic liver disease. *J Transl Int Med* 2017; 5: 49-57.
4. Secretaria de Salud. Boletin epidemiológico sistema nacional de vigilancia epidemiológica sistema único de información [Internet]. Mexico: gob.mx; 2018 [update 2018 april 23; cited 2018 april 27]. Available from: http://www.gob.mx/salud/acciones-y-programas/direccion-general-de-epidemiologia-boletin-epidemiologico.
5. Fierro NA, Realpe M, Meraz-Medina T, Roman S, Panduro A. Hepatitis E virus: an ancient hidden enemy in Latin America. *World J Gastroenterol* 2016; 22: 2271-83.
6. Realpe-Quintero M, Copado-Villagrana ED, Trujillo-Ochoa JL, Alvarez AH, Panduro A, Fierro NA. Cytokines signatures discriminates highly frequent acute hepatitis A virus and hepatitis E virus coinfections from monoinfections in Mexican pediatric patients. *Pediatr Infect Dis J* 2017; 36: 689-92.
7. Realpe-Quintero M, Montalvo MC, Mirazo S, Panduro A, Roman S, Johne R, Fierro NA. Challenges in research and management of hepatitis E virus infection in Cuba, Mexico, and Uruguay. *Rev Panam Salud Publica* 2018; 42: e41.

Correspondence and reprint request:
Nora A. Fierro, Ph.D.
Unidad de Inmunovirología. Servicio de Biología Molecular en Medicina. Hospital Civil de Guadalajara Fray Antonio Alcalde. Hospital No. 278 Col. El Retiro. Guadalajara, Jalisco, 44280. México. Tel./Fax + 52 33-3614-7743.
E-mail: noraalma@gmail.com