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Research Article

Hepatitis E: New Clinical and Public Health Problem on the Western World? Review

Introduction

Until recently, the occurrence of Hepatitis E in the western hemisphere did not amount to a clinical concern, due to its benign and usually sub-clinical evolution, as opposed to Asia and Africa, where large epidemics with high levels of lethality occur. More sensible diagnostic exams have shown a high prevalence of the infection through genotype 3 in the eastern hemisphere, with reports of hepatic infection, cirrhosis, and extremely severe systemic [1-3] and neurological extra-hepatic manifestations, especially on immunosuppressed patients [4-6]. Hepatitis E: an emerging infection in developed countries [7], suggesting the occurrence of a new and important clinical and public health problem [3,8].

Chronic viral hepatitis E is the most prevalent worldwide. According WHO, HEV causes acute hepatic lesion annually in 3.5 million people, with around 70.000 deaths per year. It presents a single-stranded RNA genome, non-feces enveloped, but present on infected patients blood and in cell cultures. High genomic diversity with at least four major recognized genotypes (HEV1-4), and a few sub-genotypes, that can occur in humans with different epidemiologic and pathogenic characteristics. The molecular mechanisms of HEV replication are not fully understood.

The genotypes HEV 1 and HEV 2 occurs with high endemicity in Asia, Northern Africa, and Mexico. Feces-oral transmission, Anthroponosis (man restricted). Endemic and/or epidemic in Asia (India: 2 million cases per year).

The genotype HEV 3: Predominant in South and North America, Europe, and Southeast Asia. It infects animals (swine, poultry, rats, boar, rabbits and others) and humans. It can be transmitted through contaminated water, by meat consumption (<71 °C), parenteral, blood, from mother to children, (perhaps sexually). Pigs have been reported to act as a reservoir for zoonotic viruses, sometimes emerging ones,

and epidemiological studies have shown direct links between the consumption of uncooked pork offal and cases of hepatitis caused by the hepatitis E virus (HEV) genotype 3 in humans [9,10].

The genotype HEV 4 is predominant in Asia. Transmitted through water and contaminated food. Sporadic cases in both animals and humans.

HEV 5 only occurs in birds.

Family *Hepeviridae*. Gen. *Orthohepevirus* is an anthroponosis (HEV 1, HEV 2 – restricted to humans) and anthrozoonosis (HEV 3, HEV 4 – occurs in humans and animals: swine, poultry, boar, rabbits, rats, cattle, and others). The molecular mechanisms of HEV replication are not fully understood, mostly because there are no efficient cell culture systems.

The incubation period is of 2 to 4 weeks. It can cause both acute and chronic cases. HEV infection may cause a wide range of clinical presentations from subclinical or asymptomatic forms to fulminant liver failure.

The diagnosis is made through serology, ELISA IgM/IgG (98% sensitivity / 75% in immunosuppressed) and molecular tests (RT-qPCR) and by validated exams, since the performance is variable. Due to false negatives, it is needed to research through Western-blot and genome ORF3 detection techniques.

Objective

To discuss, considering recent findings in the subject's literature, the dimension of the problem and research if the Hepatitis E genotype 3, emergent and neglected in the western hemisphere, constitutes of new and important grievance to health.

Methodology

Recent editions of several infectious disease books served as a basic substrate for the research. Then, the authors have investigated all relevant papers published in major 1990

databases to 2016, including:

- PUBMED - National Library of Medicine: <http://www.ncbi.nlm.nih.gov/pubmed>
- Scielo: <http://www.scielo.org>
- LILACS: <http://bibliomed.uol.com.br/LILACS/index.cfm?libcatid=20025>
- MEDLINE: <http://medline.cos.com>
- Google Academic: <http://scholar.google.com.br>
- OPAS / OMS: <http://www.who.int>
- CAPES: <http://www.periodicos.capes.gov.br>
- BIREME: <http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/>

Results

Infection through genotype 3 is very little studied in industrialized Countries [3,7,11-13]. It can become chronic, aggravating immunosuppressed patients' cases [14-22]. Several clinical situations of immunosuppression have been described in which the infection by HEV can produce extra-hepatic diseases and/or chronification and worsening of liver disease, such as: HIV-Aids [23-26], organ or cell receptors [1,5,15,17,27,28], hematologic patients undergoing chemotherapy and immunotherapy [1,5], stem cells receptors, patients with schistosomiasis [29] and other immunologic diseases).

In its chronic form, it can cause extra-hepatic disease: neurological [6,30-34], including cases of S. Guillain-Barrè, neurologic pain amyotrophic, encephalitis, peripheral neuropathy, vestibular neuritis), confirming that HEV in addition to hepatotropic is also neurotropic.

There have been reports of cases with involvement of other organs in the HEV infection, such as: acute pancreatitis [35,36], immune-mediated diseases [37-40], (Hashimoto's thyroiditis, glomerulonephritis, Henoch-Schonlein purpura, myasthenia gravis), hematologic diseases [38,41], (hemolytic anemia, acute myeloid leukemia, severe, thrombocytopenia), mixed cryoglobulinemia [42], inflammatory bowel disease [43]. In pregnant women, infected during the first trimester it generates a 15% to 25% lethality, in the Eastern hemisphere [44,45]. There are also registers of premature deliveries, with a child death rate under 30%. It is little studied in the western hemisphere. However, there are no reports of cases in the Western Region.

Conclusion

- 1) Genotype 3 high seroprevalence in the western regions, the most pathogenic of all genotypes;
- 2) The HEV virus can be transmitted via oral-oral route, parenteral via through blood contaminated, by animal

meat and inter human transmission (including mother to child). Therefore, the risk of transmission through pork meat, and other animal products, implies the need of cook the meat for long periods at high temperatures (viruses can withstand temperatures of 71 °C for 5 minutes) as boil the cow's milk.

- 3) Extrahepatic neurologic manifestations are common in immunocompromised HEV infected patients, especially transplant recipients of solid organs or cells, in chemotherapy / corticoid therapy and AIDS with CD4 <250 cells / mm³. Several other extrahepatic impairments have been described in patients with HEV;
- 4) HEV infection may accelerate the development of liver fibrosis in immunocompromised patients and other viral hepatitis or through other etiologies, causing cirrhosis in about 3 to 5 year;
- 5) Reports suggest that it is a new and important clinical issue on the western hemisphere. Therefore, Hepatitis E is an emergent disease and effectively neglected in all its aspects in occidental regions.
- 6) The exams (serological and molecular) are not available in most eastern countries, despite having many clinical indications. More sensible exams are needed.
- 7) It is always necessary to suspect of HEV in patients with elevated ALT without any apparent cause in the post-transplant; blood and plasma transfusion; and in hepatitis with fulminating or chronic evolution with fast evolution to cirrhosis.
- 8) The need for prophylactic ribavirin usage before immunosuppressive procedures is currently under discussion.
- 9) Its necessary to test the HEV 239 vaccine, human trials allowed in China (87% efficiency with 3 dosages in genotypes 1 and 2) on Eastern hemisphere's risk groups.

Stimulate the pharmaceutical industry and researchers to develop new serological and molecular exams for more sensible and specific diagnosis.

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