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REVIEW

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Hepatitis E: literature review

Hepatite E: revisão de literatura

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Abstract

Introduction: *Hepatitis E represents a disease with global distribution, being one of the most frequent causes of acute hepatitis worldwide.* ***Objective:*** *Develop a literature review regarding hepatitis E. Method: Qualitative and descriptive review of narrative literature. The databases were PubMed and Scielo, using the term "Hepatitis E" searching for articles published in the last five years, selecting 23 of them.* ***Discussion****: Hepatitis E represents a viral disease with global distribution. The etiological agent belongs to the genus Orthohepevirus of the Hepeviridae family, which includes 8 genotypes and 1 serotype. The prevalence of each genotypes varies by geographic region, with genotypes 1 and 2 being more prevalent in emerging regions and 3 and 4 in developed countries. The clinical picture ranges from asymptomatic patients to those who develop fulminant acute hepatitis. It is known that hepatitis E can become chronic, especially in immunocompromised patients. Manifestations include extrahepatic symptoms, with neurological and renal predilection. Disease transmission occurs through contaminated water sources, direct contact with animals and consumption of contaminated food. Diagnosis can be made by virus antibodies screening or quantification of viral RNA. Treatment is based on supportive measures, and the use of antiviral therapy is recommended only in special situations. The main prophylaxis is vaccination. Furthermore, investment in basic sanitation and improvement in food quality contribute to the reduction of cases.* ***Conclusions:*** *Hepatitis E is a growing cause of acute hepatitis, especially in emerging countries. Therefore, health professionals should consider this diagnosis among other conditions of liver involvement, suggesting studies about this subject.*

Keywords: *Hepatitis E, Hepatic insufficiency, Hepatitis E virus*

Resumo

Introdução: *A hepatite E representa uma doença viral de distribuição global, sendo uma das causas mais frequentes de hepatite aguda em todo o mundo.* ***Objetivo:*** *Desenvolver uma revisão bibliográfica referente à hepatite E.* ***Método:*** *Pesquisa qualitativa, descritiva de revisão da literatura narrativa. Os bancos de dados foram PubMed e Scielo a partir do termo "Hepatite E" em artigos publicados nos últimos cinco anos e selecionados 23 trabalhos.* ***Discussão:*** *O agente etiológico pertence ao gênero Orthohepevirus da família Hepeviridae, a qual inclui 8 genótipos e um sorotipo. A prevalência dos genótipos varia com a região geográfica, sendo os genótipos 1 e 2 mais prevalentes em regiões emergentes e 3 e 4 em países desenvolvidos. O quadro clínico compreende pacientes assintomáticos àqueles que evoluem com hepatite aguda fulminante. Sabe-se que a hepatite E pode cronificar, especialmente em imunocomprometidos. As manifestações incluem sintomas extra-hepáticos, com predileção neurológica e renal. A transmissão da doença ocorre por fontes de água contaminadas, contato direto com animais e consumo de alimentos contaminados. O diagnóstico pode ser realizado pela pesquisa de anticorpos contra o vírus ou quantificação do RNA viral. O tratamento baseia-se em medidas de suporte, sendo preconizado o uso de terapia antiviral somente em situações especiais. A principal forma de prevenção é a vacinação. Ademais disso, investimento em saneamento básico e melhora na qualidade de alimentos contribuem para diminuição de casos.* ***Conclusões:*** *A Hepatite E consiste em uma crescente causa de hepatite aguda, especialmente em países emergentes; logo, profissionais de saúde devem considerar o diagnóstico entre os demais quadros de acometimento hepático, sugerindo estudos acerca do tema.*

Palavras Chave: *Hepatite E, Insuficiência hepática, Vírus da hepatite E*

Introduction

Infection caused by the Hepatitis E (HEV) virus is globally significant, since it is among the most frequent acute hepatitis types[1]. This disease is considered to be of high prevalence in the world population, and to cause a wide spectrum of clinical manifestations[2].

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Although it presents mild clinical frame in most cases, some infections evolve to acute or chronic liver failure[3].

HEV was identified as different viral agent in 1983, as well as cloned and sequenced in 1991[3]. Initially, there was the belief that HEV would only cause acute infections, and that most of these cases would remain asymptomatic. It was recently shown that HEV can cause chronic infections and quickly evolve to liver failure and cirrhosis, mainly in immunocompromised patients[4].

This disease is considered endemic to many emerging countries; however, a growing number of autochthonous and sporadic infections was recorded in developed countries, in the last few years[5]. According to estimates by the World Health Organization (WHO), HEV accounts for approximately 20 million new infection cases on a yearly basis, as well as for more than 3 million cases of acute hepatitis and more than 55 thousand deaths[6]. Although this disease accounts for significant expenses with public health, it does not get much attention from the medical and scientific community[7].

Method

This qualitative and descriptive research followed the principles of a narrative literature review. Searches were carried out in two bibliographic databases: Pubmed and Scielo. Option was made to use one single descriptor: "Hepatitis E". Only articles published in the last five years (between 2015 and 2020), which were available in English or in Portuguese, were filtered for selection purposes. Duplicated references were excluded after the search in the accessed databases was over.

In total, 60 articles were selected for analysis; collected data were further analyzed and discussed by the authors. This process was subjected to the interference of their subjective perceptions; therefore, only 23 references were chosen to compose the study's references.

Discussion

• Epidemiology

Serum and molecular assessments have shown that HEV is globally distributed. Estimates show that most of the world's population has been exposed to this agent, and it has caused approximately 20 million hepatitis E infection cases, on a yearly basis. Therefore, it became the most common cause of acute viral hepatitis in most regions[8-9].

VHE infection prevalence in a given population can be assessed through serum-prevalence rates recorded for anti-HEV antibodies featuring either current or past infections[10]. Some data are relevant for the prevalence of infected patients, namely: it attacks male and female patients, at 2:1 ratio, in emerging countries, and at ratio higher than 3:1 in developed countries. Besides, serum-prevalence rates are low in children, but this number increases with age. The highest frequency rate of it is observed for patients in the age group 15-40 years[11].

The prevalence of HEV genotypes changes depending on the geographic region – genotype 1 is mostly found in some regions in Southern Asia, Central Asia and Northern Africa; genotype 2 is mainly recorded in Mexico and in Western Africa; genotype 3 is most often observed in the Americas, Europe and Japan; and genotype 4 is mostly distributed in China and in Southeastern Asia[12].

• Emerging Countries

Hyper endemic areas where HEV is caused by genotypes 1 and 2 mainly correspond to developing geographic regions, such as several parts of Asia, Africa, the Middle West and Mexico[10]. HEV in these locations is often transmitted through the fecal-oral route, mainly through water contamination by human feces. The occurrence of large epidemics of it is common, mainly during the rainy seasons and large floods[12-14].

On the other hand, HEV epidemiology in Egypt presents a pattern different from that of other locations. HEV serum prevalence in this country is similar to that of hepatitis A (HAV) virus, because it is more prevalent in children and youngsters, and because it is oftentimes caused by HEV1. Yet, infection in pregnant women is asymptomatic or manifests itself as mild disease. Most of these infections are likely secondary among pregnant women in Egypt; in other words, they emerge after a primary infection in childhood[15].

• Developed countries

HEV is notably a swine-origin zoonosis in developed countries, where genotypes 3 and 4 prevail; these data go against the idea that this infection was limited to travelers from endemic regions. Data published in the last ten years show that HEV infection, either in Europe or in other developed countries, consists in autochthonous cases[8].

• Epidemiology in South America and in Brazil

The first HEV cases described in South America date back to 1990; initially, in Salvador City, Bahia

State, Brazil; in Mato Grosso State and in the Amazonian region, also in Brazil. Several studies report its circulation through the continent, including its molecular detection in several sources, such as human feces, water and sewage, as well as its identification in serum assessments in subgroups of populations, such as blood donors and HIV positive individuals[16].

Only HEV genotypes 1 and 3 were detected by specific serum and molecular markers in South America (anti-HEV IgM and/or RNA HEV). HEV3 is the most frequent genotype in this continent; it was isolated from human beings, pigs, as well as from environmental samples in Argentine, Brazil, Colombia, Uruguay and Venezuela. This virus presents high heterogeneity, which is evidenced by the large number of subtypes described worldwide, including in the South American continent[16].

Brazil is classified as moderate HEV endemic region, given its high variability in the described serum-prevalence rates, a fact that contributes to the hard time predicting the real load of this disease in the country. Estimates show intermediate HEV serum-prevalence, at rates of 2% and 9% in blood donors, of 12% in injectable-drug users and of 15% in kidney-transplanted patients[17]. Nowadays, none of the routine tests is carried out to detect infection caused by HEV[18].

• Pathophysiology

HEV belongs to genus *Orthohepevirus*, Family *Hepeviridae*. Species *Orthohepevirus* A has eight genotypes; however, only seven of them cause diseases in humans, namely: from VHE1 to VHE7 – only one serum type was identified. HEV genome consists in a single-stranded positive polarity RNA molecule with three open reading frames (ORFs)[10,14].

Infection caused by HEV can be understood based on three sequential phases: incubation, clinical time and convalescence time. Nowadays, knowledge about the infections' pathogenesis is widely based on animal-model data, on cell-culture systems, and on some human-data supplements[10,19].

• Transmission

HEV transmission differs from country to country. Contamination takes place through fecal-oral route in emerging locations. These regions present defective sanitary conditions, and it contributes to food contamination, mainly to drinking water contamination. This is the main HEV1 and HEV2 transmission route, since these strains can only be acquired through interpersonal via[14]. HEV is most often identified in industrialized countries as zoonotic disease, where swine models are their main reservoirs. The infection can be acquired through two different routes: straight contact with infected animals or intake of contaminated food[14,20].

• Clinical Frame

HEV infection can present a wide range of clinical manifestations, from subclinical forms to asymptomatic ones, or even manifest itself as (fulminant) liver failure. Acute hepatitis is its most common manifestation, either in developed or developing countries. However, sporadic cases are often diagnosed as liver failure caused by drugs or autoimmune hepatitis[5]. The likely chronic profile of hepatitis E was recently described; however, the cases were only correlated to infections caused by genotype 3[14].

• Acute cases

HEV infection can be asymptomatic or present mild symptoms, as well as show no symptoms of acute liver injury at all. Hepatitis E's classic form consists in acute jaundice hepatitis, which occurs in individuals at rate ranging from 5% to 30%. These frames last from two to six weeks; they consist of a prodromal phase that lasts one week and is featured by specific symptoms such as malaise, fever, body aches, nausea and vomiting[10].

Pregnant women, mainly in the second and third gestational trimesters, present high risk of developing symptoms after infections caused by HEV1 and HEV2; a large rate of these women evolves to acute liver failure, so that mortality rates recorded for infected pregnant women range from 15% to 25%, not mentioning the risk of increasing adverse outcomes like miscarriage, premature birth, stillbirth and perinatal mortality[10].

• Chronic cases

Chronic HEV infection is defined as viral RNA detection in serum or feces for a time longer than 6 months. Nowadays, it is seen as a well-defined entity given its association with the histological visualization of chronic liver failure[12]. So far, this condition was almost exclusively observed in patients infected with genotype 3, although it may also have occurred with genotype 4[14]. Its evolution to chronic liver disease mostly happens in patients with some sort of immunological system issue, such as transplant, hematologic malignancies and HIV+ carriers, and patients under chemotherapy treatment and attending immunosuppressive therapies[14].

• Extrahepatic Manifestations

Studies on the involvement of organs other than liver mainly highlight the association between HEV infection and the nervous and renal systems. Furthermore, occasionally, there are reports of cases that correlate this virus to the occurrence of pancreatic, hematological and autoimmune manifestations[12].

Guillain-Barré syndrome, neuralgic amyotrophy, encephalitis and myelitis are the most often recorded neurological manifestations. It was observed that patients with neurological outcomes related to HEV often show normal liver function or mildly abnormal function; mostly anicteric[10]. Kidney function manifestation was observed either in acute infection or in chronic HEV infection. Kidney biopsy samples from HEV1- and HEV 3-infected patients showed evidences of glomerular diseases' patterns, including membranoproliferative glomerulonephritis – with, or without, cryoglobulinemia - and membranous glomerulonephritis[10].

• Diagnoses

HEV is clinically indistinguishable from other vital hepatitis types; thus, it is necessary carrying out laboratory tests to confirm its presence. HEV infection diagnosis in the general population can result from indirect (blood serum) or direct tests (detection of HEV-RNA in blood or feces). Nowadays, the golden standard to diagnose this hepatitis type lies on detecting viral RNA[2].

It is recommended to carry out HEV diagnostic investigation by initially detecting anti-HEV antibodies through enzyme immunoassay (EIA). A confirmation test must be performed in case a positive result for such antibodies is confirmed, because EIA methods do not reach high specificity. This confirmation can take into consideration an alternative anti-HEV IgM, an evidence of increased anti-HEV IgG titers or a detection of HEV-RNA in serum or feces[6].

• Treatment

Acute HEV did not demand anti-viral therapy in most immunocompetent individuals, since HEV infection tends to be self-limiting[5,10,12]. It was not possible determining whether early treatment with ribavirin would be actually capable of accelerating viral depuration or of mitigating the risk of liver failure in these patients[5,10,12].

With respect to patients subjected to immunosuppressive treatment, such as the case of those who have undergone solid organ transplantation, it is possible stating that therapy reduction is considered a top notch option. Therapy with ribavirin must be taken into account in case of failure. Therapy with pegylated interferon alpha (pegylated IFN alpha) is limited to patients who do not respond to ribavirin[10, 21-23].

Finally, the aim of the HEV treatment is to rule out HEV-RNA, and it is expected to be achieved based on a sustained viral response (SVR), which is defined as lack of HEV-RNA through PCR, 12 weeks after treatment conclusion. SVR patients are considered cured, because they do not have viral reservoir; however, they remain under risk of re-infection[6].

• Prevention

Prevention strategies for waterborne genotypes, HEV1 and HEV2, focus on reducing exposure risk by improving the quality of drinking water and sanitation in endemic areas. Improvement in the quality of water, often achieved through water boiling or chlorination, leads to fast decline in disease incidence[10, 12-13].

HEV3 and HEV 4 transmission has been broadly related to food; it is linked to the intake of infected offal, game meat and seafood. Infections can be avoided by the careful preparation of these food types. It is essential to boil them for up to 20 minutes at internal temperature of 70°C in order to inactivate HEV[10].

Nowadays, the main means to prevent hepatitis E is still the commercial availability of a highly-effective three-dose vaccine (higher than 99%). The HEV 239 vaccine (Hecolin, Xiamen Innovax Biotech CO, China) has proven crossed protection against HEV 1 and HEV4; it was developed to induce protective antibodies against all genotypes. Although it was granted with the license for trade and use in China in 2012, it is not yet available for routine or emergency use in endemic areas. Studies on the persistence of antibodies suggest long-term protective immunity (30 years after vaccination)[8,10].

Conclusions

Hepatitis E consists in one of the growing cases of acute hepatitis, mainly in emerging countries; thus, health professionals must take into consideration its diagnosis among the other liver failure manifestations, a fact that suggests the need of broader studies about this topic.

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