Review

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Update on hepatitis E virology: Implications for clinical practice

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Abbreviations: 7mG, 7-methylguanylate; CSF, cerebrospinal fluid; gt, genotype; HCV, hepatitis C virus; HEV, hepatitis E virus; ESCRT, endosomal sorting complexes required for transport; IFN, interferon; IRF3, interferon regulatory factor 3; ISG, interferon-stimulated gene; NF-κB, nuclear factor-κB; ORF, open reading frame; PCP, papain-like cysteine protease; PegIFNα, pegylated interferon-α; PRR, pattern recognition receptor; RdRp, RNA-dependent RNA polymerase; RT-qPCR, reverse transcription quantitative PCR; RIG-I, retinoic acid-inducible gene I; TBK1, TANK-binding kinase 1; Tsg101, tumor susceptibility gene 101.

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Summary

Hepatitis E virus (HEV) is a positive-strand RNA virus transmitted by the fecal-oral route. The 7.2 kb genome encodes three open reading frames (ORF) which are translated into (i) the ORF1 polyprotein, representing the viral replicase, (ii) the ORF2 protein, corresponding to the viral capsid, and (iii) the ORF3 protein, a small protein involved in particle secretion. Although HEV is a non-enveloped virus in bile and feces, it circulates in the bloodstream wrapped in cellular membranes. HEV genotypes 1 and 2 infect only humans and cause mainly waterborne outbreaks. HEV genotypes 3 and 4 are widely represented in the animal kingdom and are transmitted as a zoonosis mainly via contaminated meat. HEV infection is usually self-limited but may persist and cause chronic hepatitis in immunocompromised patients. Reduction of immunosuppressive treatment or antiviral therapy with ribavirin have proven effective in most patients with chronic hepatitis E but therapy failures have been reported. Alternative treatment options are needed, therefore. Infection with HEV may also cause a number of extrahepatic manifestations, especially neurologic complications. Progress in the understanding of the biology of HEV should contribute to improved control and treatment of HEV infection.

Introduction

Hepatitis E virus (HEV) infection is among the most frequent causes of acute hepatitis worldwide, with an estimated 20 million infections and 70,000 deaths attributed to HEV genotypes 1 and 2 every year [1]. However, the majority of infections are thought to remain asymptomatic [2]. The virus has been recognized as a cause of waterborne hepatitis outbreaks in India not related to hepatitis A and B viruses in the early 1980s [3,4]. It was first visualized by immune electron microscopy in a feces sample from a human volunteer infected with stool extracts from presumed cases of epidemic non-A, non-B hepatitis in 1983 [5]. HEV was molecularly cloned in 1990, allowing the rapid development of serological tests and the investigation of its epidemiology [6,7].

HEV has been classified as the sole member of the *Orthohepevirus* genus within the *Hepeviridae* family [8]. The recent development of advanced sequencing technology allowed the identification of novel HEV-related viruses in a variety of animals and led to a revised taxonomic classification of this family (Fig. 1) [9].

Twenty-five years after the identification of the HEV genome, basic and clinical virology research is gaining momentum due to the increased awareness and perceived importance of hepatitis E as a relevant public health issue [10,11]. Indeed, previously unrecognized HEV infections in industrialized countries by genotypes 3 and 4 are now known to be zoonotically transmitted and to cause persistent infection in immunocompromised patients, especially transplant recipients [2,12,13]. Patients with chronic HEV may rapidly develop liver cirrhosis. Moreover, the recent availability of cell culture models (e.g., [14,15]) offers new opportunities for the study of HEV biology and the development of therapeutic and/or prophylactic strategies.

In this review article, we provide an overview on the molecular virology of HEV and its implications for clinical practice. Current understanding of the HEV life cycle, the viral tissue tropism and

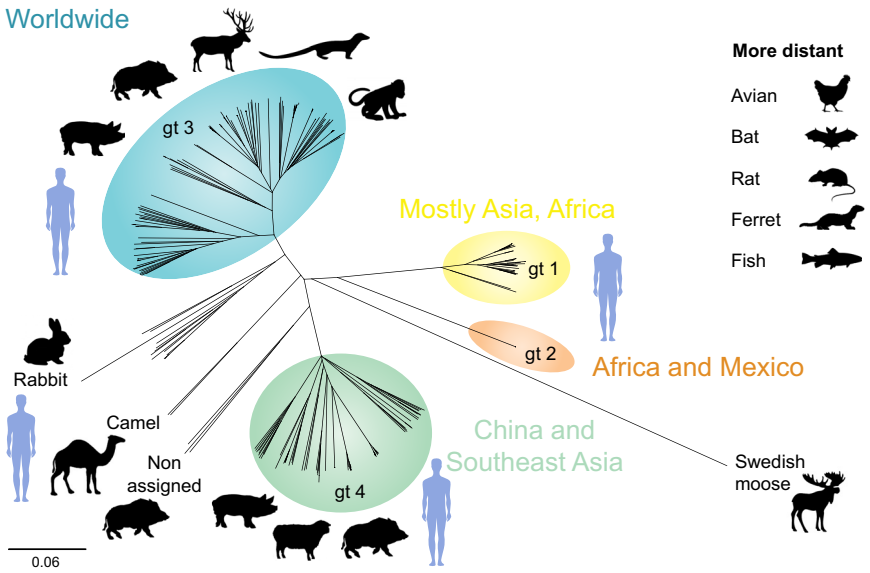

Fig. 1. Phylogenetic relationship of hepeviruses identified in various hosts. Nucleotide sequences of 305 full-length hepatitis E virus (HEV) genomes were retrieved from GenBank and aligned with ClustalW, followed by phylogenetic tree building using the neighbor-joining method (Geneious 7.1 software, Biomatters). While genotypes 1 and 2 (gt 1 and 2) are restricted to humans and to endemic regions such as Asia, Africa and Mexico, genotypes 3 and 4 (gt 3 and 4) are also found in a wide range of animal species. Genotype 3 is present worldwide in various hosts such as swine, wild boar, deer, mongoose and Japanese macaques. Genotype 4 is found mainly in China as well as Southeast Asia and infects swine, wild boar and sheep. Viral strains that have not been assigned to one of these 4 genotypes may also infect humans, as documented recently for camel HEV [129]. Moreover, more distant hepatitis E viruses were identified in birds, bats, rats, ferrets and fish.

host antiviral response as well as potential antivirals shall be discussed.

Clinical course of HEV

Irrespective of the viral genotype, HEV infection leads to a self-limiting illness lasting for few weeks, with a broad range of clinical manifestations ranging from an asymptomatic course to acute liver failure, resulting in fatality rates of 0.2–4%. In general, after a 2–6 week incubation period, liver enzyme elevation occurs and may be accompanied by symptoms such as abdominal pain, nausea and vomiting, anorexia, fever, and jaundice [2,16].

Acute infection

HEV strains infecting humans have been classified into 4 distinct genotypes belonging to a single serotype. Genotypes 1 and 2 are restricted to humans, are spread mainly through contaminated drinking water and represent main causes of waterborne outbreaks of hepatitis in developing regions (Fig. 1). The most severe course of disease is observed in pregnant women infected with HEV genotype 1, with high maternal, fetal and neonatal morbidity and mortality rates as high as 25% [17–19]. Capsid-based recombinant vaccines have proven their efficacy in large studies performed in Nepal and in China [20–23]. However, a vaccine has thus far been licensed only in China.

HEV genotypes 3 and 4 are now recognized as zoonotic agents with their main reservoir in pigs and game (Fig. 1). Autochthonous infection occurs mostly through the consumption of un/under cooked meat [2]. HEV seroprevalence rates in developed regions range between 5 and 20% and peak at 52% in southwestern France [24]. Of note, we and others have found that middle-aged or elderly men are particularly prone to develop symptomatic autochthonous acute hepatitis E [2,25].

Chronic infection

Chronic HEV infections have been reported in immunocompromised patients such as organ transplant recipients and patients with HIV infection or hematological malignancies undergoing chemotherapy [12,13,26–29]. These chronic infections are caused by genotype 3 and possibly also genotype 4 and may rapidly evolve to cirrhosis and loss of a liver graft [12,13].

Molecular organization of HEV

HEV is a non-enveloped, small, icosahedral virus of about 27–34 nm in diameter [5,30]. Infectious

Key point

Hepatitis E virus (HEV) is an important cause of acute hepatitis in developing regions, with a high morbidity and mortality in pregnant women.

Key point

HEV can persist and cause chronic hepatitis in immunocompromised patients.

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