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Hepatitis E virus: A potential threat for patients with liver disease and liver transplantation

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A B S T R A C T

Immunocompromised patients are at risk of acquiring acute hepatitis E virus infection (HEV), leading to chronicity. Chronic HEV infection is associated with persistent viraemia, raised transaminase activity, histological features associated with chronic hepatitis and evidence of rapid development of cirrhosis.

Extrahepatic manifestations have been associated with HEV. Most frequently reported are neurological disorders with predominantly involvement of the peripheral nervous system.

In patients using immunosuppressive drugs antibody production is often delayed and HEV RNA detection is superior to serology to detect infection.

Therapeutic options for chronic HEV includes tapering immunosuppressive and secondly ribavirin, pegylated interferon alpha (PEG-IFN). Present recommendation is to treat chronic HEV patients for 3 months, asses serum HEV RNA and stool HEV RNA and stop therapy if both are undetectable.

Studies are required to determine which other antiviral agents than ribavirin and (PEG-)IFN are of clinical utility in treating HEV in the minority of patients who do not respond to ribavirin.

Introduction

Hepatitis E virus (HEV) is a major cause of viral hepatitis worldwide; it is endemic in both developing as well as developed countries [1]. HEV genotype 1 and 2 are known as a cause of acute hepatitis and fulminant hepatic failure in pregnant women during large waterborne outbreaks in developing countries [2]. While HEV genotype 3 and 4 infection usually will result in a silent infection with HEV IgG seroconversion, it is known that in immunocompetent patients with underlying chronic liver disease HEV infection can result in acute fulminant hepatitis with decompensation [3]. Furthermore, (re)infection with HEV can become chronic in immunocompromised patients with the risk of development of cirrhosis with potential fatal complications. Extrahepatic manifestations of HEV have been described but the spectrum of neurological disease is still incomplete and under investigation.

In this review we will first describe the clinical course of a HEV infection in the immunocompetent and immunocompromised patient, secondly give an overview of the extrahepatic manifestations associated with HEV infection, thirdly summarize the different treatment options of HEV and practice points for physician's in the use of clinical practice.

Taxonomy

HEV is a single-stranded, positive-sense RNA virus. The ~7.2 Kb viral genome is grouped into group IV positive single stranded RNA viruses. The genome consists of a 5′ m^7 G-cap, short 5′ untranslated regions (UTR), 3 partially overlapping open reading frames (ORF) of positive polarity, a short 3′UTR and a 3′ polyA tail [4]. After historic assignments of HEV in the genera Calicivirus (1998) and hepatitis E-like viruses (2008), taxonomic division of the family Hepeviridae was completely changed in 2015 as a result of the discovery of

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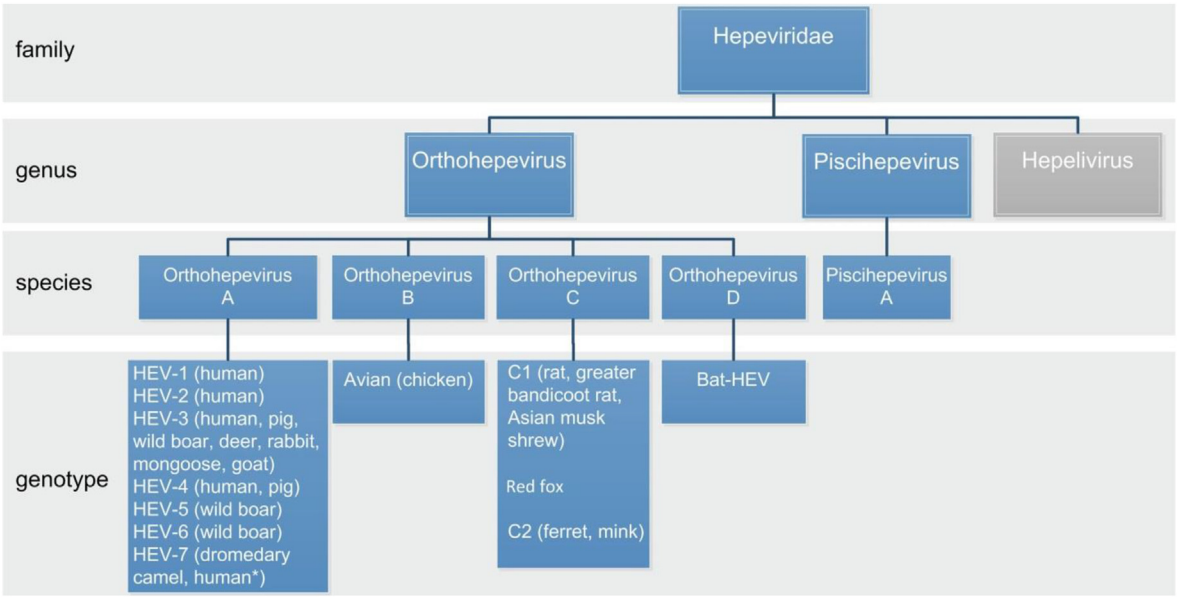

Fig. 1. Taxonomy of HEV. Blue boxes indicate accepted taxonomic positioning, grey box is currently unconfirmed. The species *Piscihepevirus A* was previously called cut throat trout virus. Although ICTV does not specify classification on the level of genotype, it is illustrated in this figure for historical reference.

multiple HEVs in different hosts and the contradictory taxonomical can cause significant positioning proposed by researchers. The family *Hepeviridae* now comprises the genera, *Orthohepevirus* and *Piscihepevirus* and an additional, unconfirmed genus *Hepelivirus*, of which the genus taxonomic positioning is based on partial RdRp sequences only [5] (Fig. 1).

The recent reclassification of HEV genotypes was defined on basis of ORF1 motifs (methyltransferase, helicase and RdRP) and concatenated ORF1/ORF2 sequences. Within the species Orthohepevirus A, there are five genotypes, HEV gt 1–4 and 7, known to infect humans, which can be divided into three groups (genotype 1–2 and 3–4, and 7) on basis of host, epidemiology and geographical distribution [6]. Among genotypes 1–4 the nucleic acid identity ranges between 73 and 77%, with >83% within a genotype [7]. The utility of HEV subtypes within HEV gt 3 is a subject of debate. Inconsistencies of the previously suggested 24 subtypes [8] have been observed [9,10], probably due to the small part of ORF2 not being representative for the complete genome sequence variation. Therefore the ICTV recommends not to use subgenotyping, but rather assignments as 'clades'. HEV gt 1–7 belong to one serotype [11,12].

Epidemiology and transmission of hepatitis E

While contaminated drinking water is the main source of HEV-transmission in developing countries with reduced sanitary conditions, zoonotic transmission, predominantly by infected swine meat, has been assumed to be the major source of HEV genotype 3 and 4 transmission in industrialized countries. Prevalence of genotype 3 HEV RNA in pooled grab samples collected at Dutch pig farms was estimated to be about 55%, and 6.5% of commercially available porcine livers tested positive for HEV RNA, while the viruses could also be detected in surface waters [13,14]. Furthermore, HEV infected blood products are a possible source of infection. Asymptomatic infection is common and accounts for the large numbers of blood donors who are viraemic at the time of donation [15]. Antibodies directed against HEV and HEV RNA have been found in donated blood in a number of countries. Table 1 shows a literature overview of studies in Europe, China and the USA (mainly HEV gt 3 endemic countries) where seroprevalence and HEV viremia in blood donors were assessed. Due to the use of relatively insensitive serological assays, seroprevalence has been underestimated in the past. In some studies the same dataset was assessed with different assays showing up to seven times underestimation of the actual seroprevalence when measured with insensitive ELISAs [16]. Multiple well-designed studies in the Dutch, American, British and Danish blood donors showed a high correlation between age and HEV antibody seroprevalence [15,17–19]. It has been demonstrated that when evaluating seroprevalence levels, indeed we face an age cohort-effect. This means that not only as people get older they encountered more HEV infections during their lifetime, but also that the prevalence of HEV infection in the population was higher in previous decades. This resulted in a relatively high seroprevalence today due to the detection of those long-life HEV antibodies in the elderly [17].

Clinical course of hepatitis E virus infection

Natural history

Acute HEV gt 3 and HEV gt 4 infections in immunocompetent persons are usually (>95% of cases) self-limiting illnesses that last 4–6 weeks, requiring no treatment. If clinical symptoms occur, the incubation period of 2–6 weeks is followed by symptoms of hepatitis, fever and nausea, abdominal pain, vomiting and jaundice in approximately 60% of patients. Asymptomatic infection is very common, in an outbreak of HEV gt 3 on a cruise ship, 67% of the infected individuals had no symptoms [20]. However in sporadic cases, mostly older men or patients with underlying liver disease, an acute HEV infection can develop into a fulminant hepatitis, that may even require liver transplantation. Pregnant women do not to seem to suffer from severe HEV gt 3 and 4 infections.

HEV infection in patients with underlying liver disease

In immunocompetent patients, HEV-3 rarely causes a symptomatic hepatitis, but it can result in acute fulminant hepatitis with decompensation and even death in patients with underlying chronic liver disease.