Hepatitis E Virus and the Liver

Clinical Settings and Liver Pathology

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KEYWORDS

• Liver • Hepatitis • Hepatitis E virus (HEV) • Histology

KEY POINTS

- Hepatitis E virus (HEV), a fecally-orally transmitted RNA virus, occurring endemically as well as sporadically, is a leading cause of acute hepatitis worldwide.
- Of the 4 major genotypes infecting humans, genotypes 1 and 2 are restricted to humans, whereas genotypes 3 and 4 also are zoonosis.
- Hepatitis E is generally self-limited, presenting similar to other forms of acute hepatitis, but rarely leads to fulminant liver failure, or takes a chronic course in immunocompromised individuals.
- Hepatitis E displays a spectrum of histological changes which, besides the typical acute (cholestatic) hepatitis pattern, also comprises fulminant cases with (sub)-total necrosis and chronic hepatitis prone to fibrosis development.
- Awareness of HEV, familiarity with its clinical and histopathologic spectrum, and knowledge of diagnostic tools will enable clinicians and pathologists to reliably and promptly diagnose HEV.

INTRODUCTION

Hepatitis E virus (HEV) infection, although already described in a large outbreak that took place in Delhi, India, more than 60 years ago,[1] and long known as a leading cause of acute hepatitis worldwide, only in recent years has experienced increased awareness, and is now globally recognized as a significant health problem.[2,3] If nothing else, the increased interest in HEV is due to the fact that HEV is also known to be highly prevalent in industrialized countries[4,5] with seroprevalence rates of up to more than 30% in France.[6] In developed countries, the virus is generally transmitted zoonotically, and may take a chronic course in immunocompromised patients.[7,8] Accordingly,

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clinicians as well as pathologists are increasingly challenged with the differential diagnosis of HEV infection in their daily practice, requiring knowledge of clinical presentation and histopathologic changes to reliably come to this diagnosis in due time. Herein, we aim to provide an overview on the basic, clinical, and pathologic aspects of HEV with a focus on histopathology, by reviewing the current literature, illustrated with cases observed in our own practice.

HEPATITIS E VIRUS

Virology and Genotypes

The HEV is a small, nonenveloped, positive-strand RNA virus of the family *Hepeviridae*, genus *Orthohepevirus*.[9] Its 7.2-kb genome comprises 3 open reading frames (ORF): ORF1 coding for a nonstructural protein responsible for viral replication, ORF2 coding for a capsid protein, and ORF3 coding for a small phosphoprotein required for viral particle secretion. ORF2 and ORF3 are extensively overlapping, and this overlapping sequence is highly conserved intragenotypically and intergenotypically. Besides the 7.2-kb full-length RNA from which the ORF1 protein (~190 kDa) is transcribed, a 2.2-kb subgenomic RNA is generated during HEV genome replication, allowing the expression of ORF3 protein (13 kDa) and ORF2 protein (72 kDa).[10]

HEV strains infecting humans belong to a single serotype, and have been classified into 4 major genotypes (**Table 1**).[10,11] Whereas HEV genotypes (GT) 1 and 2 (GT1 and GT2) are restricted to humans, genotypes 3 and 4 (GT3 and GT4) are also zoonosis, which have been detected in a wide range of species including their main reservoir in domestic pigs, deer, wild boars, and other game animals, but also oysters and bivalves. In line, HEV genotypes circulating in humans and animals of the same geographic areas have been demonstrated to be closely related phylogenetically[12] (**Box 1**).

Global Distribution

The global distribution of HEV varies considerably.[13,14] Whereas HEV GT1 and GT2 are mainly restricted to endemic regions such as Asia, Africa, and Central

Table 1
Hepatitis E virus genotypes

	Genotype 1 (GT1)	Genotype 2 (GT2)	Genotype 3 (GT3)	Genotype 4 (GT4)
Geographic distribution	Endemic regions, for example, Asia, Africa, Central America	Endemic regions, mainly Africa and Central America	Worldwide	Southeast Asia, China
Spread	Contaminated drinking water	Contaminated food or drinking water	Consumption of uncooked or undercooked contaminated meat	Consumption of uncooked or undercooked contaminated meat
Transmission	Fecally-orally	Fecally-orally	(Fecally)-orally, blood products	(Fecally)-orally
Host	Restricted to humans	Restricted to humans	Humans and zoonotical transmission	Humans and zoonotical transmission
Reservoir	Humans	Humans	Animals	Animals