Frontiers in Liver Transplantation

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

The impact of hepatitis E in the liver transplant setting

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Summary

Hepatitis E virus (HEV) infection has been identified as a cause of graft hepatitis in liver transplant recipients. The true frequency and clinical importance of HEV infections after liver transplantations is a matter of debate. It is proposed that consumption of HEV-contaminated undercooked meat is a main source for HEV infections in developed countries – which might also account for some hepatitis E cases after organ transplantation. However, HEV is also transmitted by transfusion of blood products, likely representing a previously underestimated risk particularly for patients in the transplant setting. HEV infection can take chronic courses in immunocompromised individuals, associated in some cases with rapid progression to cirrhosis within 1–2 years of infection. Diagnosis in transplanted patients is based on HEV RNA testing as antibody assays are not sensitive enough. Selection of immunosuppressive drugs is important as different compounds may influence viral replication and the course of liver disease. Ribavirin has antiviral activity against HEV and should be administered for at least three months in chronically infected individuals; however, treatment failure may occur. HEV infections have also been linked to a variety of extrahepatic manifestations both during and after resolution of infection.

In this review we summarize the emerging data on hepatitis E with a particular focus on the importance of HEV infections for liver transplant recipients.

Introduction

Hepatitis E is caused by infection with the hepatitis E virus (HEV). An infectious agent, leading to acute hepatitis that differed from HAV and HBV, was already suspected in the 1970s. In 1983, Balayan and colleagues showed that oral administration of pooled stool extracts from patients with non-A/non-B hepatitis led to acute hepatitis in a human volunteer in whom virus-like particles were identified in stool samples [1]. Hepatitis E was initially recognized only as an acute self-limited liver disease, which very rarely progressed to acute liver failure. Severe courses were most often observed in pregnant women [2,3] and individuals with chronic liver diseases [4–7]. HEV infections were reported mainly from endemic countries such as the Indian subcontinent, South-East Asia and Sub-Saharan Africa. During the last 3 decades large scale outbreaks of hepatitis E were reported [8–11], even continuing until recently when many hepatitis E cases were reported in refugee camps in South Sudan [12].

For more than 25 years HEV infection was not considered a major clinical problem in developed countries including Europe and the United States. The description of chronic courses of HEV infections in solid organ transplant recipients in France in 2008 [13] increased the awareness for a potentially largely underestimated disease. Since then, persistent HEV infections were described in different cohorts of immunocompromised patients [9,14] but also beyond organ transplantation [15–19]. Subsequently, mechanisms leading to persistent infection were explored in more detail and antiviral therapies were tested in large case series. Importantly, HEV infections seem to take very rapid and aggressive courses in many patients receiving immunosuppressive medications and HEV has been linked with end-stage liver disease and even liver-associated mortality. HEV infections seem to be much more common in Europe than previously thought. Between 10% and 50% of the populations were anti-HEV-positive in various epidemiological studies [20–22]. Thus, millions of – usually clinically silent – infections occur each year in Europe but only a small proportion of infected individuals develop clinical symptoms. HEV infection should also be considered in the differential diagnosis of drug-induced liver disease [23,24], which has also a major importance in the management of liver transplant recipients, receiving various medication before and after transplantation. Of note, HEV has also been linked to extrahepatic manifestations and thus, the clinical implications

Keywords: Hepatitis E; HEV; Liver transplantation; Treatment.
Received 8 July 2014; received in revised form 25 August 2014; accepted 29 August 2014

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Abbreviations: HEV, hepatitis E virus; HVR, hypervariable region; ORF, open-reading frame; GBS, Guillain–Barrè syndrome.

of hepatitis E virus infections are likely to be much broader than previously estimated [25–28].

Key Points

- Hepatitis E virus infection can take chronic courses in immunocompromised individuals. There is limited data suggesting that chronic courses may be more frequent after liver transplantation
- Chronic hepatitis E is often associated with rapid progression to liver cirrhosis
- HEV genotype 3 infection can be a zoonosis and HEV is believed to be transmitted mainly by ingestion of raw uncooked meat. Other sources of transmission are food hygiene and transfusion of HEV positive blood products
- Different immunosuppressive drugs may have distinct effects on HEV replication (either inhibitory or stimulatory) and should therefore be selected accordingly
- Ribavirin can be used to treat HEV infection and should be given for at least 3 months. Treatment failures may occur and require further investigation

HEV virology

HEV is a small (27–34 mm) non-enveloped virus which belongs to the family of *Hepeviridae*. It is encoded by a single-stranded RNA (7.2 kb) which consists of three open-reading frames (ORF1–3) [29]. The non-structural proteins are encoded by ORF1 and their translation leads to the synthesis of proteins which are primarily essential for viral replication. In particular, it consists of a methyltransferase, a protease, a macrodomain, a helicase and an RNA-dependent RNA-polymerase [30]. Of note, a hypervariable region (HVR) is localized between the protease and the macrodomain. ORF 2 and ORF 3 on the other hand encode for the structural proteins. The capsid, which is essential for viral attachment and entry into liver cells, is the translational product of ORF2 [31,32]. ORF 3 partly overlaps with ORF2 and leads to the production of a small phosphoprotein, which is involved in the assembly and release of the virus and has been shown to interact with cellular host factors [33].

Similar to other RNA-viruses different genotypes of HEV exist due to a lack of proof-reading activity of the RNA-dependent RNA-polymerase. So far, 5 different HEV genotypes have been identified, which differ in their nucleotide sequences by 19%. Intra-genotypic differentiation into sub-genotypes is made upon a variation of approximately 12% [34]. These distinct genotypes differ markedly in their distribution, clinical presentation and species-specificity.

It is believed, that only genotypes 1, 2, 3 and 4 are able to cause apparent disease in humans, while genotype 5 has been identified only in birds thus far [14]. While genotype 1 and 2 solely infect humans, genotype 3 and 4 are zoonotic pathogens with likely major reservoirs in pigs [35–37], wild boars and deer [38–40]. Some data suggest that genotype 1 may also be able to infect pigs [41], which however needs to be confirmed by additional studies. The worldwide distribution of the different genotypes varies markedly. Genotype 1 and 2 infections have been reported mainly in Asia, India and North-Africa. Genotype 2 HEV has been also identified in Mexico [14,42]. Genotype 3 is present in Western countries as well as in Asia and North America while genotype 4 has been detected in Asian- as well as in European countries [14]. However, genotype 4 might also play a minor role in Europe as supported by recent data, demonstrating evidence for a genotype 4 infection in France [43].

Additionally, several related viral strains have been identified in a variety of species like bats [44], chicken [45], ferrets [46], rabbits [47], rats [48] and trout [49]. However, it is believed that these viruses are not able to infect humans.

Routes of HEV transmission

Distinct HEV genotypes differ in their route of transmission. Contaminated water is the main source for genotypes 1 and 2 infections. Large hepatitis E outbreaks have been described in various African and Asian countries including India, China, Somalia, South Sudan or Uganda [8–10,14]. In contrast, HEV genotype 3 and 4 usually cause sporadic infections, most likely due to consumption of contaminated food. HEV-RNA has been detected in a variety of food products in particular porcine livers and pig sausages in France, the US, the Netherlands and Germany [35,36,50,51]. Consumption of such food increases the likelihood for the development of HEV-infection [43,51–54]. In line with this, people who have close contact to swine and deer – farmers, slaughterhouse-workers, veterinarians – display a significant higher prevalence of HEV-infections compared to the general population [55,56]. Recent publications have delineated that HEV-RNA is even more widely distributed than previously thought, and has been found in various food-products like shellfish [57], mussels [58,59], green vegetables [60] as well as field-grown strawberries [61] (Fig. 1).

HEV transmission by blood products and organ transplantation

Organ transplant recipients frequently receive blood products, either prior to transplantation, during, or after transplantation. In most Western countries, blood products are tested for HCV-RNA and HIV-RNA by mini-pool testing and often even for HBV-DNA. However, blood products are not tested for HEV-RNA, even if transfused to individuals at risk. Several previous case reports suggested that HEV transmission by blood products is possible [14,62], which can obviously also occur after liver transplantation as demonstrated recently by Coilly *et al.* [63]. Clinically healthy European blood donors may carry HEV RNA as reported during the last 2 years for Scotland [64], Sweden [65], England [66], Germany [67,68] and the Netherlands [69] – even though the absolute HEV RNA prevalence is low (0.01–0.04%). Still, the risk for HEV transmission may become substantial if blood products are pooled. In this case, the risk for HEV transmission seems to be substantial as up to 10% of pooled plasma products tested HEV RNA positive in Europe [65]. Indeed, plasma products seem to be a specific cause for HEV infections [62,70]. However, screening of blood products for HEV has not been standardized in any country until now. Currently, there is an ongoing debate concerning this issue.