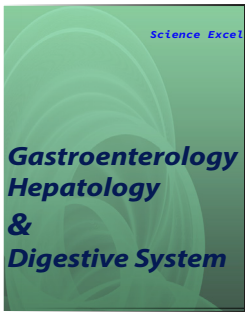
Gastroenterology Hepatology and Digestive System

Short Communication



Current issues in hepatitis E: an overview

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Of the five recognized classical hepatitis viruses, hepatitis E virus (HEV) remains an important etiological agent of acute and chronic hepatitis as well as extrahepatic symptoms [1–5]. HEV infection accounts for a global mortality rate of approximately 2% that includes fulminant liver failure in about 30% of pregnant women [6, 7]. As per the recent consensus classification of the hepatotropic viruses, HEV is categorized as a member of the species *Orthohepevirus* A within the genus *Orthohepevirus* of family Hepeviridae [8]. Further, of the eight identified genotypes of HEV (HEV1-HEV8), HEV1-HEV4 are known to infect humans [8]. While HEV1 transmission is associated with waterborne outbreaks in underdeveloped or developing countries, HEV3 and HEV4 transmission is foodborne, potentially linked to zoonosis in swine and other mammals in industrialized nations [9]. Nonetheless, epidemiology of HEV3 is rather complex because of its hitherto well recognized sources and routes of transmission. Moreover, while HEV1 causes self-limiting acute infection in general population, HEV3 takes a chronic course in clinically immunocompromised patients [3]. Also, as compared to HEV1 associated pregnancy complications in general, there are limited case reports of HEV3 infection in pregnant women [10].

Epidemiology

HEV1 is endemic in Asia and HEV2 is prevalent in African and South American countries, whereas HEV3 and HEV4 are mainly restricted to East Asia, Europe and North America [2, 11]. Further identifying the potential origin and location of source animals and humans and studying the genetic changes and evolutionary patterns would be very important. In addition, generation of epidemiological data regarding prevalence, transmission, and overall burden of the disease as well as mutational characterization during the curse of infection between or within endemic regions would be helpful.

Virology

HEV is a quasi-enveloped particle having a positive single-strand RNA genome (~7.2 kb) defined in to three open reading frames (ORF: ORF1, ORF2 and ORF3), including 5′ and 3′ small untranslated sequences and a 3'poly(A) tail [12, 13]. The largest gene ORF1 codes for the nonstructural polyprotein (pORF1) wherein seven domains (methyltransferase, Y, papain-like cysteine protease, proline-rich hinge/hypervariable region, X/macro, helicase, and RNA-dependent RNA polymerase) have been identified, which play essential roles in viral RNA replication and virion infectivity [1,14]. Although ample of work has been dedicated to expression and characterization of pORF1, it still remains debatable whether it functions as a single polyprotein with multiple activities or undergoes proteolytic-cleavage to produce individual functional proteins [14]. The second largest gene ORF2 encodes the viral capsid, a glycoprotein (pORF2) which is assembled into an icosahedral particle, and encapsidates the viral genome. Though molecular and structural studies on the experimentally produced self-assembled virus-like particles (VLP) have presented a model of HEV capsid [15], they still remain to be verified and authenticated with those isolated from infected individuals. The ORF3 gene partially overlaps ORF1 and ORF2, and encodes the smallest phosphoprotein (pORF3) implicated in the modulation of various host-factors, virion infectivity and egress [16]. Recently, a new coding region ORF4 has been proposed in the HEV1 RNA [17], which is not verified yet from other laboratories. Notably, most of such studies involved in vitro and cell culture models, and lack further in vivo validations. Also, while an RNA packaging signal at the 5' end has been suggested using overexpressed ORF2 in vitro [18], this is not precisely mapped or experimentally validated using heterologous sequences in cell culture model. Therefore, a systematic understanding of critical features of the HEV life cycle from

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cellular entry to genome replication, virion assembly and RNA encapsidation, virion morphogenesis and release is highly required. Further biophysical and biochemical analysis and structural configuration of its capsid and the non-enveloped and enveloped particles are needed.

Eeperimental models

The current knowledge on HEV biology, virology and pathogenesis has been largely acquired through developing of various infectious clones and replicons, in vitro expression systems and liver cell culture models [19]. In addition, the clinical aspects of hepatitis E have been studied in experimentally challenged primates [20]. Nonetheless, lack of a robust cell culture system as well as the high-cost and restricted or inaccessible primate facilities remain a bottleneck in HEV research. Owing to the cross-species or cross-tissue tropism of HEV [21, 22], generation of genotype-specific productive infection supporting hepatic as well as extrahepatic cell lines is required to further delineate HEV pathobiology in various hosts. Moreover, identifying and designing controllable animal models to study symptoms, innate immune mechanisms, and associated aspects of immunological protection should be explored.

Diagnosis

Serology (anti-HEV IgM and IgG) and RT-PCR (HEV RNA) are the current diagnostic tests for HEV infection. In acute hepatitis E, both anti-IgM and IgG rise simultaneously in the narrow window of detectable viremia [23]. Several diagnostic assays for anti-HEV IgG and IgM are available; however, the use of anti-HEV IgM assays is still doubtful due to their unreliable specificity and sensitivity. Most of the 'first-generation' anti-HEV IgG assays-based studies had shown very low seroprevalence results. This issue has been considerably resolved by developing more specific and sensitive diagnostics. Nonetheless, in the absence of an approved algorithm, the consistencies of serological tests and viral RNA load quantification in terms of sensitivity and specificity still remain the limiting factors [24]. Moreover, the proper and timely diagnosis of hepatitis E is technically very challenging. The anti-HEV IgM false-positive reactions against other hepatotropic viruses (e.g., EBV and CMV) have been also encountered in clinics [25]. In view of this, developing highly sensitive diagnostic methods are necessary to screen HEV risks groups among blood donors, immunocompromised patients, travelers and pregnant women.

Treatment

Needlessly, there has been no established treatment of acute hepatitis E. However, pegylated interferon- α-2a and ribavirin are the only effective regimen of choice for acute liver failure and chronic hepatitis E [26]. Because HEV exists as a heterogeneous population as quasi-species within infected individuals, ribavirin pressure may result in selection of replication competent variants [27]. In view of this, while ribavirin clears the virus and induces a sustained virologic response (SVR), emergence of HEV polymerase gene mutants leads to drug-resistance or nonresponse in a proportion of patients. Further therapeutic limits of ribavirin include hemolytic anemia, dyspnea, insomnia and irritability, and risk of teratogenicity in pregnant women [28]. Therefore, designing of direct-acting or host-targeting antiviral agents and identifying the alternative treatment modules are highly needed.

Vaccines: There is an effective HEV vaccine (HEV239 or Hecolin) approved in China for mass-vaccination [29, 30], which remains unavailable to other countries. Since HEV3 is associated with chronic hepatitis E, it is still unclear if this vaccine can prevent HEV3 in industrialized nations. Moreover, there is an evident lack of the clinical data on the safety and efficacy of HEV239. In addition, its immunogenicity against other genotypes and variants, effectiveness of less than three doses or long-term protection after completing the immunization remain inconclusive. Importantly, its long-awaited approval by the World Health organization (WHO) and global accessibility need to be resolved as soon as possible.

Conclusively, according to the WHO and European Association for the Study of the Liver (EASL) recommendations, guaranteeing improved sanitation, safe water and pre-screened pork are the first defense towards prevention of hepatitis E, especially in endemic regions. For future perspectives, there remain several unanswered questions regarding its basic and clinical virology, evasion of species-barrier and pathogenic evolution. Therefore, a comprehensive clinical, virological and molecular data are needed to understand and control the viral paradigm shift of disease severity.

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