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Editorial

Candidate New Hepatitis Viruses: Juggling with Alphabets

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Abstract

Hepatitis viruses (HAV, HBV, HCV, HDV and HEV) are attributed to a wide spectrum of acute and chronic liver diseases, including carcinomas. Worldwide, >250 million become chronically infected by HBV and ~150 million by HCV every year. Though, new hepatotropic viruses, such as HGV, GBV, TTV and SENV are identified in chronic liver diseases, thousands still suffer of unknown etiology. Despite a protective vaccine against HBV and effective antiviral drugs against HBV, HCV and HEV, millions are dying every year. Nevertheless, viral hepatitis can be prevented by providing safe food and water, effective drugs, vaccines, and screening of donated blood samples etc. The future challenges to combat new hepato viruses include a need for constant surveillance, efficient diagnosis, and developing new drugs and vaccines.

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INTRODUCTION

Viral hepatitis is the leading cause of a wide spectrum of chronic liver diseases, including cirrhosis and hepatocellular carcinoma (HCC) [1]. Hepatitis is actually a disease of antiquity, mentioned by Hippocrates (460-375 B.C.) when he wrote of *Infectious Iceterus* [2]. Historically, in the 18th century, many epidemics were reported during military campaigns, notably at the Siege of Saint-Jean-d'Acre (1799) and Paris (1870). The American Civil War (1861-1865) was reportedly plagued by >50000 cases of hepatitis [3]. While in world war-I (WW-I), both the Western forces were heavily plagued by hepatitis, the estimated death toll of hepatitis was 16 million cases in WW-II, unknown that time as a result of viral infection [3]. After the discovery of hepatitis B virus (HBV) in 1960s, followed by hepatitis A, C, D and E viruses (HAV, HDV, HCV and HEV), we have an enormous amount of information on its biology, mode of transmission, and mechanisms of pathogenesis. Inherently, hepatitis viruses are hepatotropic, and genetically DNA (HBV) and RNA (HAV, HDV, HCV and HEV) pathogens. Worldwide, approximately 1.4 million people are infected by HAV, >250 million become chronic for HBV, and about 150 million have chronic HCV infection every year, around the world [4]. Of these, chronic hepatitis B and C are attributed to up to 80% of HCC cases, globally [5]. Despite a protective vaccine against HBV and effective antiviral drugs against HBV and HCV, millions are dying of severe hepatitis every year. While there is now a vaccine available for HEV, we still do not have this for HCV. Though, new hepatotropic viruses are identified in chronic liver diseases, thousands still suffer of unknown etiology. Moreover, the unpredictable nature of emerging novel hepato viruses, the rare occasions of outbreaks, the small number of confirmed cases as well their further occurrences in remote areas, present another challenge in the management of chronic liver diseases.

CANDIDATE NEW HEPATITIS VIRUSES

Hepatitis F Virus (HFV)

In 1994, evidence for the transmission of the enteric agent responsible for sporadic non-A, non-E hepatitis to rhesus monkeys was reported [6]. Spherical virus particles, measuring 27-37 nm with a large 20 kb genomic DNA was provisionally named as hepatitis French (for origin) virus or HFV. Unfortunately, there have been no reports to confirm the finding of HFV since then, and its status as a true human hepatitis virus remains doubtful.

GB viruses (GBV)

The first link in the chain of events that led to the discovery of the GB viruses was when successful transmission of viral hepatitis to marmosets was published [7]. A sample from a Chicago surgeon (GB, initials of name), who had developed acute hepatitis caused by an unknown source in 1996, produced biochemical hepatitis when inoculated into tamarins. Later studies showed that there was no serological reactivity to HBV, HCV or HEV [8]. It was evident from these results that the marmoset sera containing the passaged GB agent was a potential source of an uncharacterized hepatitis virus. Subsequently, two new members of the family *Flaviviridae*, named GBV-A and GBV-B, were identified in tamarins that developed hepatitis following inoculation. Fortunately, neither virus infects humans, and a number of GBV-A variants were identified in wild New World monkeys. However, a related GBV identified as GBV-C and

named hepatitis G virus (HGV), is discussed below. Further, a more distantly related GBV, named GBV-D was discovered in bats. Only GBV-B, a second species within the genus *Hepacivirus* (as for HCV), has been shown to cause hepatitis; it causes acute hepatitis in experimentally infected tamarins. Based on phylogenetic relationships, genome organization and pathogenic features of the GBVs, a new classification has been proposed to renaming 'GB' viruses within the tentative genus *Pegivirus* to reflect their host origin [9].

Hepatitis G Virus (HGV)

GBV-C or HGV was discovered by two independent groups of investigators in the study of cases of hepatitis non-A, non-B, non-E [10,11]. HGV, like GBV-A, GBV-B, and HCV, belongs to the *Flaviviridae* family. Comparison of the genomes of GBV-C, GBV-A, GBV-B, and HGV has demonstrated that their RNA does not bear a more than 32% similarity, thereby supporting the hypothesis that these viruses are independent. The HGV genome is similar to HCV RNA in its organization, i.e. the structural genes are located at the genomic 5' and non-structural genes are at the 3' end [12]. Even though there is only limited amino acid sequence homology (25%), there is no close relationship between the two viruses.

TT Virus (TTV)

Further, Nishizawa et al. isolated a novel DNA virus, named transfusion-transmitted virus (TTV), from the serum of a Japanese patient who developed post-transfusion hepatitis of unknown etiology [13]. Partial characterization of the virus showed that it contained a single-stranded, circular DNA genome (3.8 kb) and lacked an outer envelope [14].The virus particle has not been convincingly detected by electron microscopy, but results from filtration studies allow the size of the virion to be estimated at 30-50 nm. The data suggested that TTV is most clearly related to the virus family *Circoviridae*. However, because of significant difference in physicochemical properties and lack of sequence similarities to members of that family, it has been tentatively classified as the only member of a new family, *Circinoviridae* [15]. Since the discovery of TTV, reports on describing the prevalence of TTV infection in people with acute or chronic hepatitis as well as in blood donors and drug users and also in healthy persons has been published [16,17].

SEN virus (SENV)

Subsequently, scientists working at the DiaSorin Bio-molecular Research Institute in Italy claimed to have discovered another new virus that may be the primary cause of most cases of non-A-E hepatitis. The virus has been provisionally named SEN virus (SENV) after the source patient, and preliminary information suggests that the original isolate is a representative of a virus cluster containing at least eight other members (SENV-A through H) [18,19]. Partial molecular characterization has revealed that SENV also lacks an envelope and contains a 3.2 kb single stranded linear DNA genome. The characteristics revealed so far for SENV show a remarkable parallel with those of TT virus and might share a common ancestor.

CONCLUSION

Though we know that newly identified hepatotropic viruses, such as HGV, GBV, TTV and SENV are responsible for human etiology**,** there are still large numbers of evolving viruses, to that human are yet to be exposed and adapted. Nevertheless, despite road blocks in the control modalities, viral hepatitis can be prevented by providing safe food and water, effective antiviral drugs and vaccines, and screening of donated blood samples etc. The future challenges include a need for constant surveillance and prompt, efficient diagnosis; a necessity to develop and deploy new drugs and vaccines to combat new hepatoviruses.

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