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Viral hepatitis: A to E and beyond

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Abstract

Hepatitis is inflammation of the liver that can be caused by chemical or biological-infectious agents. Infectious hepatitis caused by hepatotropic viruses is called viral hepatitis. Globally, five major hepatitis viruses (HAV, HBV, HCV, HDV and HEV) are known to cause acute or/and chronic liver diseases, leading to over 1.5 million deaths each year. Notably modern viral hepatitis research began in 1963 with the discovery of HBV 'Australia antigen'. Nonetheless, despite availability of protective vaccines for HAV and HBV, and effective antiviral drugs against HBV, HCV, HDV and HEV, viral hepatitis remains an important public health issue. In addition, new hepatotropic viruses (HFV, HGV, GBV, TTV and SENV) have been also identified in liver disease patients, of which some have unknown etiology. Notably, the most recently emerged SARS-CoV-2 has been linked to hepatitis and other hepatic dysfunctions in pneumonia patients. Though we have enormous information on virus biology, epidemiology, transmission modes, immunopathology and treatments, future challenges to combat novel pathogenic viruses would need constant surveillances, developing sensitive diagnosis and discovering effective intervention strategies.

Keywords: viral hepatitis; hepatotropic viruses; hepatopathogenesis; chronic liver disease; antivirals.

Introduction

Infectious hepatitis caused by hepatotropic viruses is called viral hepatitis [1,2]. Viral hepatitis with symptoms of jaundice and nausea may be mild or self-limiting, which generally gets resolved in a week. Hepatitis of less than six months duration is called 'acute hepatitis', which may cause fulminant liver failure. Hepatitis persisting beyond six months is called 'chronic hepatitis', which can lead to permanent liver damage, including cirrhosis, hepatocellular carcinoma (HCC), and even death [1,2]. Viral hepatitis is actually a disease of antiquity when epidemics of jaundice were documented in Babylonia and China over thousands of years ago as well as mentioned by Hippocrates (460-375 B.C.) in *Infectious Iceterus* [3,4]. In the Medieval ages, outbreaks of 'campaign or epidemic jaundice' were frequently associated with wars, famines, floods or earthquakes, ranking only behind cholera and plague [5].

In 1885, 'serum hepatitis' was first observed without any clue of viral infection, which was further recognized in 1908 as a viral infection [6]. Subsequently, identifications of a novel antigen (Australia antigen) and spherical virus-like particles (Dane particles) in the serum of hepatitis patients led to the discovery of the hepatitis B virus (HBV) [7,8]. In 1960s, marmosets (dwarf monkeys) were demonstrated susceptible to transmission of waterborne hepatitis, and the agent was later called hepatitis A virus (HAV) [9,10]. A new form of transfusion-associated 'non-A, non-B' hepatitis was then recognized as hepatitis C in 1970s, and the agent was named as hepatitis C virus (HCV) in 1989 [11,12]. In the meantime, a new antigen (delta antigen) in hepatitis B patients was reported, leading to the discovery of hepatitis D virus (HDV) in 1977 [13]. Further, a serologically distinct but hepatitis A-like acute and self-limiting hepatitis pathogen was observed in 1980s and designated as hepatitis E virus (HEV), which could transmit by the fecal-oral route [14,15]. In

addition to these well recognized hepatitis viruses, several new candidate hepatotropic viruses have been implicated in chronic liver diseases [16,17]. Though we have now advanced knowledge of their biology, epidemiology, diagnosis, pathogenesis, natural history, treatment, and prevention, the unpredictable nature of emerging new hepatotropic viruses, their rare outbreaks, and small number of confirmed cases remain important challenge.

Classical hepatitis viruses

Five major biologically-unrelated hepatitis viruses (HAV-HEV) are the leading cause of about 1.5 million deaths each year worldwide, predominantly attributed to HBV (>887,000 deaths) and HCV (>399,000 deaths), followed by HEV (>44,000 deaths) and HAV (>11,000 deaths) [2,18,19]. Notably, of these hepatitis viruses, HBV is the only DNA virus while others are RNA viruses. And interestingly, modern viral hepatitis research began in 1963 with the discovery of HBV 'Australia antigen' by Blumberg and Harvey [8].

Hepatitis A virus

Following the discovery of 'Australia antigen', similar methodologies were applied to find the waterborne HAV with focusing from serum to feces. HAV is a non-enveloped single-strand RNA virus (~7.5 kb) of family *Picornaviridae* [20,21]. HEV causes acute and self-limiting hepatitis, mainly in children at an early age who remain asymptomatic and subsequently acquire lifelong immunity whereas both children and adults in low endemic regions can become symptomatic [22]. Nonetheless, acute hepatitis A is more severe with higher mortality in adults than children. The incubation period of HAV is ~4 weeks, and symptoms include malaise, anorexia, nausea, vomiting, and jaundice. Only <1% of HAV cases result in fulminant hepatic failure, and the infection does not progress to chronicity [23]. There is an effective vaccine, included in infant immunization program, globally, and no specific medication is recommended.

Hepatitis B virus

HBV is the smallest known enveloped DNA virus that belongs to the *Hepadnaviridae* family. HBV causes acute and chronic hepatitis B in about one-third of world's population, of which approximately 360 million are at risk for developing cirrhosis or HCC [24]. In acute hepatitis B, a majority of patients experience mild illness and <1% develop fulminant liver failure. Patients in the acute phase infection present with symptoms of anorexia, malaise, fatigue and jaundice [25]. Acute hepatitis B is preceded by an incubation period ranging from 45-120 days. In symptomatic patients, clinical symptoms include fever, malaise, anorexia, fatigability, nausea and jaundice. Currently, three modes of transmission have been recognized: perinatal, sexual and parenteral/percutaneous transmission [26]. Perinatal or vertical transmission from infected mothers to neonates is a major route of infection in endemic areas.

HBV genomic DNA (~3.2 kb) has four partially-overlapping open reading frames (ORFs): pre-S/S, pre-C/C), pol, and X which code for its envelope (HBs), core (HBc) and e-antigen (HBe), polymerase (HBpol)and X (HBx) proteins, respectively [27]. Of these, HBsAg, HBcAg and HBeAg are the serological diagnostic markers of HBV infection. HBV has been defined into seven major genotypes (A through G) [26,27]. Genotype A is common to North America, Western Europe and Sub-Saharan Africa, while genotypes B and C are confined to Eastern Asia. Genotype D is widely distributed and is predominant in the Mediterranean region, the Middle East, East Africa and the Indian subcontinent. Genotype F appears to be restricted to Central and South America, whereas genotype G is found in the United States and Europe [27].

There is an effective vaccine for HBV included in universal immunization program, which has very significantly controlled the infection. Nucleoside analogs (NA) which are viral polymerase/reverse-transcriptase inhibitors (e.g., Lamivudine, Adefovir, Tenofovir, Emtricitabine, Entecavir, Telbivudine, Famciclovir and Ganciclovir) are the most effective drugs in treating chronic hepatitis B [28]. Though these drugs are generally safe and well tolerated, prolonged treatment with Lamivudine, Adepovir, Famciclovir or Entecavir often leads to drug-resistance due to emergence of viral polymerase mutants [27]. In addition, chemokines like interferon alpha (pegIFN-α-2a) is also active but are no longer commonly used because of non-response or side-effects in some chronic patients. Also, there are several herbal formulations popular as traditional Chines medicine (TCM), such as, Zexie, Bo He, Gan Cao, Ji Guo Cao, Chai Hu, Bai Fang and Zhen Chu Cao used for treating chronic hepatitis B [30].

Hepatitis C virus

HCV is an enveloped RNA virus from the *Flaviviridae* family. HCV infects over 180 million people worldwide, of which about 70 million chronic cases remain at high risk of developing liver cirrhosis and HCC [31]. Most cases of acute hepatitis C remain asymptomatic, of which ~55-85% of patients become chronic, including 30% progressing to cirrhosis or HCC. During acute phase, hepatitis C patients present symptoms similar to those of hepatitis B. However, ~80% of patients remain asymptomatic and do not develop jaundice [32]. Transmission roots are mainly sexual, blood-transfusion and vertical.

HCV single-strand RNA (~9.6 kb) codes for a single large polyprotein, which undergoes proteolytic processing to produce three structural (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) [33]. The HCV-core antigen is the serological marker of infection. Seven genotypes (1 through 7) and 67 subtypes (a, b, c etc.) of HCV have been characterized by a distinct geographic distribution and clinical manifestations [34]. Notably of these, genotype 1 is prevalent in Americas, Japan and Europe, and genotype 1b is frequent among patients who received blood transfusions [35].

There is no vaccine available for HCV so far. The most effective anti-HCV NA drug Ribavirin is generally given in combination with and pegIFN-α-2a. In addition, the HCV reverse-transcriptase inhibitors (e.g., Daclatasvir, Elbasvir, Lepidasvir, Ombitasvir, Velpatsvir, Sofosbuvir, Dasabuvir and Pibrentasvir) and protease inhibitors (e.g., Boceprevir, Telaprevir, Simeprevir, Paritaprevir, Grazoprevir and Glecaprevir) are currently available [28]. Combinations of two or more of these drugs (Harvoni, Technive, Viekira Pak, Zepatier, Epclusa and Mavyret) with enhanced activity are also marketed. Nonetheless, non-response or failure of some drugs is also observed due to emergence of HCV mutants in a proportion of chronic patients [36]. Further, TCM like Silymarin and Glycyrrhizin are commonly used by chronic hepatitis C patients [37].

Hepatitis D virus

HDV is a single-strand RNA (~1.7 kb) virus, classified within the *Deltavirus* genus. HDV is a satellite virus of HBV, which occurs as a coinfection in about 13% of chronic hepatitis B patients, worldwide [38]. It is the most severe form of chronic hepatitis with the highest risk of developing liver cirrhosis and HCC. Symptoms are similar to acute hepatitis B, but HDV co-infected chronic patients tend to progress more rapidly to fulminant liver failure, cirrhosis than those with chronic hepatitis B alone [39].

HDV genomic RNA (~1.7 kb) encodes a single ORF responsible for the expression of the delta antigen (HDAg), in two isoforms, the small (S-HDAg) and large HDAg (L-HDAg), which is the serological diagnostic marker of infection [40]. HDV genotype I mostly endemic to Europe and North America, and genotype II prevalent in East Asia are associated with a milder course. Genotype III is endemic in South America, and is associated with very aggressive forms of chronic liver disease [41]. To date, only pegIFN-α-2a is recommended for HDV infection where poor-response rates or intolerance in many patients remains a big challenge [28,42].

Hepatitis E virus

HEV is a quasi-enveloped RNA virus, classified within the *Hepevirideae* family. About 20 million people are estimated to be infected with the HEV globally, and there have been approximately 44000 deaths due to hepatitis E virus infection [43]. HEV generally cause self-limited acute hepatitis similar to hepatitis A, which is milder than acute hepatitis B. However, HEV infected females in the third trimester of pregnancy have 20-30% mortality due to fulminant hepatic failure [44]. In recent decade, HEV is evolved to cause chronic infection in immune-compromised patients who have received solid-organ or bone marrow transplants [45]. Moreover, HEV has shown wide spectrum of extrahepatic manifestations, notably neurological signs and symptoms [46,47]. Of the four recognized pathogenic HEV genotypes (genotype 1 through 4), genotype 1 and 2 infect only humans while genotypes 3 and 4 are potentially zoonotic, mainly to swine and boar [48]. Genotype 1 is endemic in Asia and genotype 2 is prevalent in African and Latin South American countries, whereas genotypes 3 and 4 are mainly limited to Japan, Europe and North America [45]. Notably, HEV genotype 1 associated with waterborne infections in pregnant women whereas genotype 3 is attributed to foodborne autochthonous chronic infection in industrialized nations [45].

The HEV genome is a single-stranded, positive sense RNA (~7.2 kb) that contains three partially overlapping genes: ORF1, ORF2 and ORF3, which code for viral replicase polyprotein (pORF1), capsid (pORF2) and a small pleotropic protein (pORF3), respectively [49]. HEV capsid antigen is the serological marker of infection, where assay insensitivity or cross-reactivity is a diagnostic challenge [50]. There is an effective vaccine for HEV, recently developed in China, which is however not accessible to other countries [51]. Needlessly so far, there has been no treatment for self-limiting acute hepatitis E. However, with the emergence of chronic infections, Ribavirin and pegIFN-α-2a are the only anti-HEV regimens [28,52]. Though Ribavirin effectively inhibits HEV replication, drug-resistance associated mutations in HEV RNA polymerase lead to non-response or therapeutic failure in some [53].

Other hepatotropic viruses

In addition to the classical hepatitis viruses (HAV-HEV), several non-A– non-E hepatotropic viruses have been identified in chronic liver disease patients. These include hepatitis F virus (HFV) [54], GB virus (GBV) [55,56], hepatitis G virus (GBV) [56], transfusion-transmitted virus (TTV) [57] and SEN virus (SENV) [58]. There are other hepatotropic viruses which directly or indirectly infect liver, and occasionally cause liver diseases. Of these, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are commonly associated with self-limited icteric and acute hepatitis, chronic hepatitis and Budd-Chiari syndrome [59]. Moreover, the human immunodeficiency virus (HIV-1) has also evolved as a hepatotropic retrovirus [60], and implicated in disease severity, especially in cases of HBV or HCV co-infection [61]. Notably, the most recently emerged severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been also linked to liver dysfunction and hepatitis in a proportion of pneumonia patients [62].

Concluding remarks

Since the discovery of HBV, we have comprehensive information on hepatitis viruses and their epidemiology, modes of transmission and immunopathology. Despite availability of protective vaccines for HAV and HBV, and effective antiviral drugs against HBV, HCV, HDV and HEV, viral hepatitis remains an important public health issue. In addition, candidate new hepatotropic viruses, such as HGV, GBV, TTV, SENV along with EBV and CMV are implicated in chronic liver disease. Notably, while HIV is also evolved as a hepatotropic virus, the most recently emerged SARS-CoV-2 has been linked to hepatopathogenesis. Nevertheless, viral hepatitis can be prevented by providing safe food and water, effective antiviral drugs and vaccines, and screening of donated blood samples. Though we have enormous information on virus biology, epidemiology, transmission modes, immunopathology and treatments, there are still unknown evolving viruses, humans are yet to be exposed or adapted. Therefore, future challenges to combat such novel pathogenic viruses would require constant epidemiological surveillances and prompt development of sensitive diagnostics as well as identification of effective treatment and preventive modalities.

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