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An overview of Hepatitis C infection

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ABSTRACT

Hepatitis C virus (HCV) infection is recognised as one of the major health issues since the last century with an infection rate beyond 3% of the world total population. Being associated with various hepatic and extrahepatic manifestations, HCV is one of the major causes of liver cirrhosis and hepatocellular carcinoma. For a better understanding of such infection, several issues were covered like HCV prevalence, geographical distribution, Genetic diversity, structure, pathogenesis and complication.

Key words: HCV, Prevalence, diversity, pathogenesis, complication.

Abbreviation: HCV, E1, E2, CD81, HBV.

INTRODUCTION

Hepatitis C is a contagious liver disease that results from infection with HCV. More than 350,000 people die from hepatitis C-related liver disease every year.[1] HCV was initially isolated from the serum of a person with non-A, non-B hepatitis in 1989. It has emerged as a major causative agent of liver disease, resulting in acute and chronic infections that can lead to fibrosis, cirrhosis and HCC.[2, 3, 4] The virus has also been implicated in a number of extra-hepatic "autoimmune" disease manifestations.[4]

Prevalence and geographical distribution

HCV continues to be a major disease burden on the world. WHO estimated a worldwide prevalence about 3% with the virus affecting 170 million people worldwide.[2, 3]

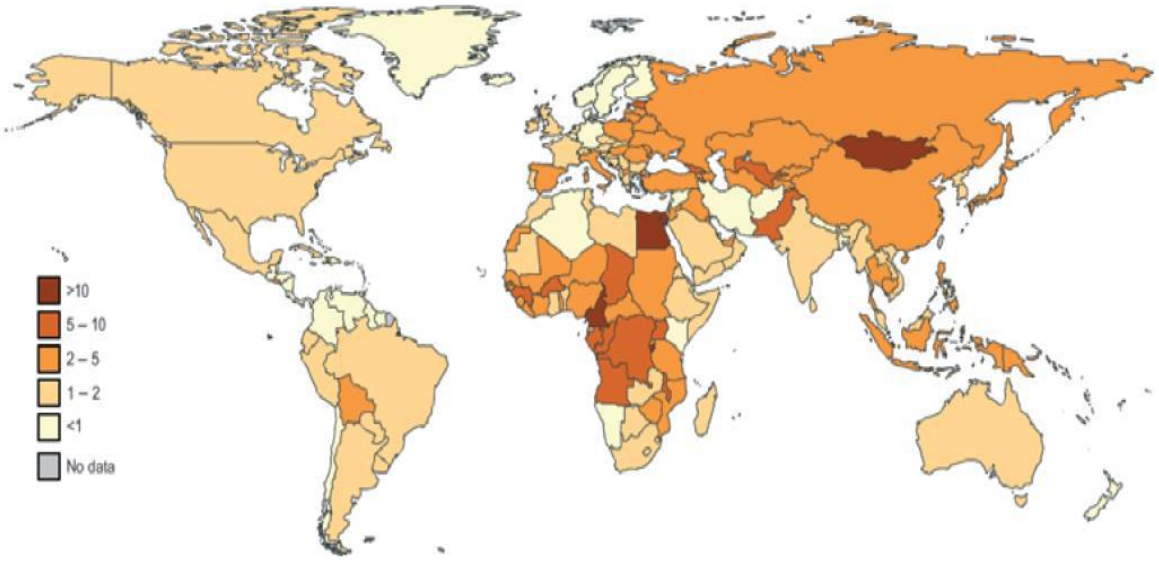

Fig. 1. Global prevalence of hepatitis C.[3]

Genetic diversity

The HCV replication rate is high, approximately 1×10^{12} virions per day. In addition, it has high mutation rate: estimated at 10^3 nucleotide substitutions per year. The reason of the high mutation rate that is an RNA-dependent RNA polymerase encoded by the nonstructural 5B (NS5B) gene is error-prone and lacks proofreading. This is leading to a mixed and changing population of mutants which known as quasispecies that have important implications for viral persistence, pathogenicity and resistance to antiviral agents.[5]

HCV isolates can be classified into genotypes and subtypes. There are seven major genotypes that differ in their nucleotide sequence by 30–35%. Sixty- seven subtypes (designated a, b, c and so on) can be defined that differ in their nucleotide sequence by 20–25%.6 Genotypes 1, 2 and 3 are distributed widely throughout western countries, whereas type 4 was first found predominantly in the Middle East, Egypt and Central Africa and types 5 and 6 are largely confined to South Africa and south East Asia, respectively. The genotype is of great clinical importance in determining potential response to interferon therapy and the required length of such therapy.[7]

HCV structure

HCV is a positive sense single stranded RNA (ss RNA) virus and the only member of the genus hepacivirus within the Flaviviridae family. Although exciting progress has been made towards determining virion structures of some of the related alpha viruses and flaviviruses, HCV has not definitively been visualized; HCV particles are 40–70 nm in diameter. The members of the Flaviviridae family share a number of basic structural and virological characteristics. They are enveloped in a lipid bilayer in which two or more envelope proteins are anchored. The envelope surrounds the nucleocapsid, which is composed of multiple copies of a small basic protein and contains the RNA genome.[7, 8]

HCV pathogenesis

The putative steps in the HCV life cycle including attachment, entry, uncoating, translation and polyprotein processing or maturation, replication, assembly, egress and release.[9]

Pathogenic mechanisms that lead to degeneration and necrosis of hepatocytes in patients with HCV infection are not fully understood. HCV entry into hepatocytes is a multistep process. At first, the circulating HCV particles are accompanied by low-density and very low-density lipoproteins. HCV envelope proteins (E1 and E2) recognize and bond

with the Cluster of Differentiation 81 (CD81) receptors present on the surface of hepatocytes and lymphocytes. CD 81 may not be sufficient for viral entry and it has been postulated that additional roles are played by low density lipoproteins receptor and the scavenger receptor class B type 1. Claudin 1 was recently identified as co- receptor required at late stage of HCV entry.[9, 10]

Following by HCV enter the cell through endocytosis, the nucleocapsid is released into the cytosol and the genomic RNA is then released and serves as an mRNA template for polyprotein translation and subsequently as a template for RNA replication. After co- and post-translational modification, mature viral proteins can then form replication complexes and assemble into new virions. The new viral 'RNA's are packaged and transported to the surface of the host cell so that they can disseminate and complete a new cycle. HCV replicates in T-lymphocytes and suppresses T-cell proliferation and cytokine production. The production of Th1-type cytokines (i.e., IL-2 and IFN-γ) is dramatically been suppressed in peripheral T-cells of chronic HCV patients. Finally, persistent infection appears to rely on rapid production of virus and continuous cell-to-cell spread with a lack of vigorous T-cell immune response to HCV antigens.[9, 11, 12]

The liver is the principal site of HCV replication and the infection outcome is heterogeneous. Acute phase (first 6 months after infection), only small percentage of patients (20%) spontaneously clear the virus during this phase. The majority of patients are unable to clear the virus, leading to chronic infection that can progress to liver cirrhosis and HCC. Most of these patients have asymptomatic disease or nonspecific symptoms.[2, 3]

Acute hepatitis C

Clinical acute hepatitis is a minority of HCV cases. The majority of cases are asymptomatic and about 20% of adults with acute HCV, infection may develop clinical symptoms. The symptomatic onset ranges from 3 to 12 weeks after exposure. Symptoms may include malaise, weakness, anorexia and jaundice. Serum alanine aminotransferase (ALT) levels indicating hepatocytes necrosis which begin raising 2 to 8 weeks after exposure and often reach levels of greater than 10 times the upper limits of normal. HCV RNA can be detected in the serum within 1 to 2 weeks after exposure. It is commonly diagnosed among patients presenting with jaundice.[12] The 80% of cases of acute hepatitis C progress to chronic infection; 10–20% of these will develop complications of chronic liver disease, such as liver cirrhosis and 1–5% will develop liver cancer making HCV a health problem of global importance.[2, 13]

Chronic hepatitis C

As mentioned earlier, the majority of persons with HCV infection progress to chronic infection, which is characterized by inflammatory lesions in the liver, often accompanied by intrahepatic lipid accumulation (steatosis), progressive fibrosis of variable degrees and long term progression to cirrhosis, liver failure and HCC. Most of the patients experience no symptoms and the remaining show mild and non-specific symptoms such as fatigue, arthralgia, myalgia, anorexia, weight loss and depression. Once a patient develops cirrhosis, symptoms and signs like fluid retention and abdominal swelling are commonly seen. Physical findings of cirrhosis may include enlarged liver, enlarged spleen, jaundice, muscle wasting, excoriations, ascites and ankle swelling. Chronic HCV is characterized by the persistence of elevated aminotransferase; most HCV-infected patients develop high-titer of antibodies. Paradoxically, these antibodies were not able to control HCV.[2, 3, 14]

Complication of HCV

HCV infection leads to steatosis, fibrosis, cirrhosis and oxidative DNA damage. In addition, several HCV proteins have been shown to have direct oncogenic effects and to up regulate mitogenesis[2, 9, 14]

Host environmental and viral factors appear to play an important role in determining progression of chronic HCV to liver cirrhosis and HCC. HCV infection with overt or occult hepatitis B virus (HBV), HCV infection and alcohol or HCV infection and liver steatosis increases the relative risk of HCC development. In HCV-related cirrhosis patients, HCC is the most common complication with a 20-fold increased HCC risk compared with persons without HCV infection.[14, 15]

CONCLUSION

HCV is a global health problem has serious complications. Therefore, more studies urgently to overcome this global problem and its serious complications.

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