BIOLOGY OF HEPATITIS C VIRUS: A REVIEW

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ABSTRACT
Background: HCV is a spherical, enveloped, positive-strand ribonucleic acid (RNA) virus that is approximately 55 nm in diameter. It is a member of the family Flaviviridae, yet distinct to be classified as a separate genus, Hepacivirus. Hepatitis C virus (HCV) is a major health burden that affects more than 170 million people around the world
AIM: The aim of this review is to describe the virology, epidemiology, transmission, high risk groups, clinical features, diagnosis, treatment and management of HCV associated with human diseases.
Methodology: Previous studies where reviewed which showed that HCV screening and initial diagnosis are usually determined according to clinical symptoms and elevated liver enzymes (especially alanine aminotransferase [ALT]), and positive enzyme immunoassay (EIA) or chemiluminescence immunoassay (CIA) for anti-HCV antibodies in patients with known risk factors.
Conclusion: The high burden of HCV and its significant health consequences associated with chronic infection make HCV a critical public health priority. . Early diagnosis and suitable treatment of HCV patients are important. Development of new techniques with the ability of rapid diagnosis and quantitative assessment of HCV infection can decline HCV burden in humans.
Keywords: HCV, Flaviviridae, RNA, diagnosis.

INTRODUCTION

Hepatitis C virus (HCV) is a major health burden that affects more than 170 million people around the world (Szabo *et al*., 2003). Unfortunately, most patients who are infected with Hepatitis C infection cannot clear the virus and progress to the chronic infection. This rate is higher in human immunodeficiency virus (HIV) infected patients and lower in women and children (Thomson *et al*., 2011; Hajarizadeh *et al*., 2013). Cirrhosis, portal hypertension, hepatic decompensation, and hepatocellular carcinoma have been reported as results of chronic HCV infection, and it is estimated that more than 300,000 deaths have occurred annually due to HCV infection (Zaltron *et al*., 2012). More than 50% of hepatocellular carcinoma cases in endemic population have happened due to chronic HCV infection and consisted of more than 6% of cirrhosis causes around the world (Bezemer *et al*., 2012). The natural history of HCV infection among patients has been incompletely defined. Many cofounders can have an impact on HCV progression to hepatic fibrosis.

HCV is the most common blood-borne pathogen and a leading cause of morbidity and mortality.

The landscape of treatment has evolved substantially since the introduction of highly active direct-acting antivirals (DAAs) in 2011. The goals of treatment aim at viral eradication, delay fibrosis progression, alleviate symptoms, prevent complications, minimize all-cause mortality, and ultimately maximize the quality-of-life (Mashiba *et al*., 2019; Morales-Arraez *et al*., 2019; Galati *et al*., 2019).

HCV VIROLOGY

HCV is a spherical, enveloped, positive-strand ribonucleic acid (RNA) virus that is approximately 55 nm in diameter. It is a member of the family Flaviviridae, yet distinct to be classified as a separate genus, Hepacivirus. The genome is approximately 9.6 kb in length.

It encodes a polyprotein that then gets processed into at least ten proteins. These include three "structural" proteins, the nucleocapsid protein, core (C), and two envelope proteins (E1 and E2); two proteins that are essential for virion production (p7 and NS2); and five nonstructural proteins that are an essential part of the viral replication complex (NS3, NS4A, NS4B, NS5A, and NS5B). There is a very high level of virion turnover by the NS5B RNA polymerase with an absence of proofreading, resulting in the generation of viral mutants, also known as "quasi species." (Kamimura *et al.,* 2019; Parigi *et al*., 2019; Mukhtar *et al*., 2019).

Hepatitis C is not a DNA virus, thus it cannot enter into the host genome, and it does not proliferate with DNA; its half-life is around 2.5 hours (Bezemer *et al*., 2012). The Hepatitis C virus can penetrate into the hepatocytes via cross-reaction of hepatic cell receptors such as CD8 and RLDL with tight junction protein claudin1 and occludin. Virus genome can escape from host immune system due to heterogeneity and lead to chronic infection (Nguyen and Nguyen, 2013).

Epidemiology

Globally, it is estimated that more than 185 million people are living with HCV. As per the Centers for Disease Control estimates from 2013, approximately 2.7 to 3.9 million people are living with HCV worldwide. In developed nations, the HCV prevalence is typically 1% to 2%. The number of acute cases of HCV reported in the United States increased each year from 2009 to 2013. After adjusting, an estimated 29,718 acute HCV cases occurred in 2013. Of the three types of viral hepatitis (hepatitis A, B, and C), HCV accounted for the greatest number of deaths and the highest mortality rate, 5.0 deaths/100,000 population in 2013. HCV transmission requires that infectious virions contact susceptible cells that allow replication. HCV RNA can be detected in blood (including serum and plasma), saliva, tears, seminal fluid, ascetic fluid, and cerebrospinal fluid. Available data suggest that HCV may get transmitted during sexual intercourse, but this rarely occurs. Perinatal transmission frequency ranges from 0% to 4% in more extensive studies. But for most patients with HCV in the United States and Europe, the infection is acquired via intravenous drug abuse or poor medical practices in resource-limited areas of the world (Soi *et al*., 2019).

TRANSMISSION

The routes of transmission of HCV described in literature are: blood, blood products, tissue and organs; unsafe medical procedure; healthcare exposure e.g. needle stick injury [Xia *et al.*, 2008]; intravenous drug use [Tohme and Holmberg, 2010]; sexual transmission [Jafari *et al*., 2010]; body piercings [Lam *et al*., 2010] and vertical transmission[Owusu-Ofori *et al*., 2005] . In Africa, only 19% of blood is screened for HCV (anti HCV antibodies). The main reason for this low screen rate is the prohibitive cost of the laboratory tests [Jeannel *et al*., 1998]. Also, inconsistent screening procedures for blood donors make blood transfusion a major means of acquisition of HCV infection. This is evidenced by a high HCV prevalence in sickle cell patients (17%) who have received multiple blood transfusions [Touzet*et al*., 2000]. While reported prevalence of HCV in intravenous drug users in the developed world is as high as 80%, little is known about the prevalence of similar risk groups in Africa [Simonsen *et al*., 1999]. However, Madhava *et al*., found drug use to be an uncommon means of HCV transmission in Africa [WHO, 1999]. While there is significant variation between countries, WHO estimates that in sub Saharan Africa, approximately 18% of injections are given with reused syringes or unsterilized needles thus increasing risk of transmission through unsafe injection practices [Gibb *et al*., 2000]. Vertical transmission is low but significant in the setting of co-infection with HIV, a condition that is of pandemic proportions in Africa [Alter, 2007].

According to the World Health Organization, thousands of new cases of the HCV infection (as a result of an occupational exposure via skin injury), are registered annually [Prüss-Ustün *et al*., 2005]. Most of these cases occurred during surgery in emergency departments, and routine medical procedures [Makary *et al*., 2007]. Seroconversion rates in infected individuals are ranging from 0% to 10.3% (+/- 0.75 %) [Kubitschke *et al*., 2007; Wilkins *et al*., 2010]. For instance, after accidental needle stick, seroconversion rate was reported as 1.8%[CDC, 2012]. During a 5-year period (2008-2012), a total of 16 HCV outbreaks resulting in 160 outbreak-associated cases and more than 90000 at-risk persons notified for screening were reported by the Centers for Disease Control (CDC) and Prevention[CDC, 2012]. Among dentists[Younai *et al*., 2001] and surgeons[Marasco and Woods, 1998], an eye protection should be reinforced because of possible HCV transmission by splashes of blood and other body fluids[Marasco and Woods, 1998]. Cosmetic procedures and/or acupuncture, as well as circumcision are extensively associated with HCV transmission, but the risk seems to be small [Mele *et al*., 1995; Sun *et al*., 1996]. Lacking of sterile techniques and/or nonprofessionally performed tattoos or piercings, especially before the mid-1980s, raised the HCV transmission rate significantly[Hwang *et al*. 2006; Hurley *et al*. 1997; Briggs *et al*., 2001; Balasekaran *et al.,* 1999; Karmochkine *et al*., 2006; Ernst *et al*., 2003; Davies *et al*., 1991].

HIGH RISK GROUPS

High risk populations include: Intravenous drug users; HIV-infected; patients on hemodialysis; patients with history of blood transfusions or organ transplantation; health care workers after needle stick injuries; children born to HCV infected mothers. Also, sexually active adults with multiple partners have higher prevalence rates. Available data on HCV reveal high prevalence in patients with hepatocellular carcinoma or chronic liver disease: (Burundi; 55%, Rwanda; 45.7 %) and sexually transmitted diseases (Ethiopia; 38.2%). Countries with low HCV prevalence in high-risk groups include Zimbabwe (1.3 %) and Kenya (1.7 %) [WHO, 1999].

CLINICAL FEATURES

Most patients with chronic HCV are asymptomatic or may present with nonspecific symptoms such as fatigue or malaise. Some of them may have arthralgia and myalgia. Patients with decompensated disease may display peripheral manifestations of cirrhosis, such as palmar erythema, spider nevi, Dupuytren's contracture, gynaecomastia, parotid enlargement, temporal muscle wasting, ascites, hepatosplenomegaly or testicular atrophy (Kleiner, 2005).

DIAGNOSIS

HCV screening and initial diagnosis are usually determined according to clinical symptoms and elevated liver enzymes (especially alanine aminotransferase [ALT]), and positive enzyme immunoassay (EIA) or chemiluminescence immunoassay (CIA) for anti-HCV antibodies in patients with known risk factors (Figure 2). First- (EIA-1), second- (EIA-2), and third- (EIA-3) generation enzyme immunoassays detect antibodies against a variety of HCV core, NS3, NS4, and NS5 antigens. Currently, second- and third-generation EIAs are the principal laboratory tests used to detect HCV exposure. Seropositivity by these tests occurs as early as 8 to 10 weeks after exposure to the virus and the tests remain positive for 6 months to a lifetime after infection (Figure 2). The specificity of EIA-2 and EIA-3 is 99% or greater (Alter *et al.,* 2003). The sensitivities of EIA-2 and EIA-3 are 95% and 97%, respectively, in high-prevalence populations (Gretch, 1997).

TREATMENT/MANAGEMENT

Treatment can permanently eradicate HCV infection such that HCV RNA is no longer detectable in blood or liver with a decline in antibody titers and improved liver pathology.

Before the development of the all-oral DAAs, the mainstay of therapy was injectable pegylated interferon and ribavirin. In addition to only having a cure rate of 40% to 60%, this form of treatment led to numerous adverse effects, including flu-like illness, hematological effects like neutropenia, thrombocytopenia, and severe anemia; and neurocognitive effects. With the advent of DAAs, immense progress has been seen toward shortening the duration of treatment from 48 weeks to 12 weeks, improving the adverse effects, increasing cure rates to 90% to 97%, and eliminating the need for injectable agents. Currently, three classes of DAAs include (1) second-generation protease inhibitors that inhibit the NS3/4 serine proteases, (2) the NS5A inhibitors which interferes with the structural protein NS5A, a crucial element in the formation of the replication complex and (3) the NS5B polymerase inhibitor which inhibits the enzyme responsible for transcription of a negative-strand intermediate for future viral progeny. These three classes are used in different combinations to make a robust treatment regimen against the various genotypes of hepatitis C [Mukhtar *et al*., 2019; Cunningham *et al*., 2019].

CONCLUSION

The high burden of HCV and its significant health consequences associated with chronic infection make HCV a critical public health priority. . Early diagnosis and suitable treatment of HCV patients are important. Development of new techniques with the ability of rapid diagnosis and quantitative assessment of HCV infection can decline HCV burden.

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