

Viral Hepatitis: An Insight in to Chronic Liver Disease Caused by Hepatitis C Virus (HCV)

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Introduction

Hepatitis is the infection of hepatocytes, the liver cells. Hepatitis may be seen in infections caused by various microorganisms including bacteria (*Leptospira icterohemorrhagiae*), fungi (Systemic fungal infections caused by *Histoplasma capsulatum*, *Cryptococcus* spp), parasites (*Fasciola hepatica*-Liver fluke, *Entamoeba histolytica*-Amoebiasis) and viruses (enterovirus group, yellow fever, Cytomegalo Virus (CMV), Epstein Barr Virus (EBV), rubella and others) [1,2]. Viral hepatitis is a systemic disease primarily involving liver. Hepatitis A, B, C and E are the common viruses responsible for viral hepatitis. Acute inflammation of liver results in fever, jaundice and Gastrointestinal (GIT) symptoms including nausea, vomiting, diarrhea and/or constipation. Among the viruses causing hepatitis, Hepatitis A and E (HAV and HEV) viruses are transmitted by consumption of contaminated food and water. Hepatitis B virus (HBV) was considered to be transmitted through blood transfusion. Many patients who developed post transfusion viral hepatitis which was due to virus other than Hepatitis B virus, commonly termed as Non-A, non-B hepatitis later was identified as Hepatitis C virus (HCV) [3]. An estimated 200 million (~3% of world population) people are infected with HCV worldwide with varied distribution in different geographical regions [4]. With 19% national wide prevalence Egypt stands a top in HCV burden [5].

Morphology and Genetics

HCV is a RNA virus possessing a positive (+) sense single stranded RNA as its nucleic acid, spherical, enveloped and measuring around 50 nm belonging to the family Flaviviridae and genus Hepaci virus1. HCV has two major envelope glycoprotein E1 and E2 and an additional NS2A (p7) protein and no comparable NS1 protein as observed in other flaviviruses [6] (Figure 1). Additional HCV has other nonstructural proteins including NS2B-NS3, NS4, NS4A, NS4B and NS5A, NS5B1. There are 6 genotypes (1-6) of HCV identified based on SS (+) RNA sequence analysis and around 100 subtypes which are distributed

throughout the world. Genotype 1a (60%) and 1b (20%) found in United states, genotype 4 is predominantly seen in the Africa and Middle East countries, genotype 5 and 6 prevalent in southeast Asia and South Africa and genotype 3 occurs in Asia [7]. A recent Indian study revealed prevalence of genotypes 1, 2 and 3 in India [8]. HCV replicates in Liver cells and peripheral mononuclear cells of lymphoid or bone marrow origin. Studies have confirmed that E2 protein of HCV binds specifically to CD81, a cell surface receptor that is present in different tissues and predominantly in liver cells [9]. HCV replicates rapidly and produces 1.0×10^{12} RNA copies per day which may be responsible for mutations within the genome. Studies have demonstrated the presence of quasi species (Swarm of closely related but genetically distinct nucleic acid sequences) of HCV in the same patient [10].

Pathogenesis

Human is the only reservoir for HCV and experimental infections in chimpanzees has been reported [11]. HCV is primarily transmitted by parenteral (exposure to blood and blood products) blood transfusion, Intravenous Drug Use (IDU) and vertical route (mother to child). Though less efficient, HCV can also be transmitted by occupational exposure, sexual contact, tattooing and body piercing as in acupuncture. Household exposure resulting in percutaneous or mucous membrane exposure to infected blood (sharing razors/sharpeners, toothbrush) blood can transmit HCV [1]. Infection with HCV leads to chronic liver disease which may be mild, moderate to severe depending on the extent of liver damage where in most of the cases virus elimination from blood is not possible. Acute infection with HCV may not show any specific symptoms and the virus replicates in liver cells and there is extensive inflammation. Fatigue, nausea, loss of appetite, inability to concentrate, weakness, chronic muscle and joint aches which can be assisted with fever are some of the non-specific symptoms. Though blood tests may reveal elevated liver enzymes, profound and more specific symptoms appear only after the scarring of liver tissue (cirrhosis). Increased blood pressure involving blood vessels of liver (portal hypertension) can attribute to ascites which in turn may lead to esophageal and gastric varices. Anaemia, thrombocytopenia, splenomegaly and kidney failure can be seen. In advanced liver cirrhosis, jaundice (yellowing of skin and Sclera) may be prominent. Chronic inflammation initiated outside the liver (extra-hepatic complications) due to viral replication may be responsible for Cryoglobulinaemia, vasculitis, arthritis,

HCV Viral Components

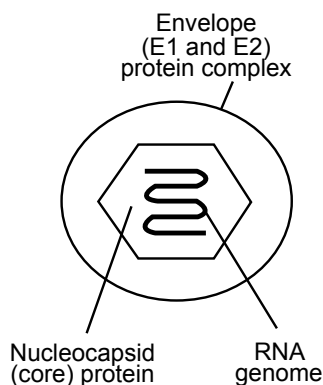


Figure 1: HCV topographic image.

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neuropathy, kidney disease and skin complications (lichen planus, porphyria cutanea tarda, purpura, urticaria) [12]. HCV is associated with development of hepatocellular carcinoma (HCC) (1-5%) [13]. A recent study in United states identified few co-morbidities in HCV infections other than liver disease including connective tissue disorders (37.5%), upper (35.6%) and lower respiratory tract infections (33.7%) which can influence treatment and there by disease management [14]. Recent studies have also established the relation between the HCV genotype and disease outcome [8].

Laboratory diagnosis

Detection of anti-HCV antibodies by Enzyme linked Immunosorbent Assay (ELISA) and Recombinant Immunoblot Assay (RIBA) is the most common diagnostic method. Molecular diagnostic techniques including Transcription Mediated Amplification (TMA), branched DNA (b DNA) test and Real-time Polymerase Chain Reaction (RT-PCR) which can be used for qualitative and quantitative evaluation of HCV RNA are available for diagnosing and monitoring HCV disease [1,15,16]. RNA sequence analysis and reverse hybridization techniques are available for genotyping and sub typing of HCV. Non-invasive (enzyme levels-Alanine aminotransferase (ALT) and Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) and Gamma Glutamyl Transpeptidase (GGTP)) and invasive (liver biopsy) methods are available for assessing the extent of liver damage in chronic liver disease caused by HCV [17].

Treatment and HCV Related Chronic Liver Disease Management

Ribavirin and peginterferons (alpha-Interferon (IFN- α 2a and IFN- α 2a 2b) chemically modified to increase its half-life) in combination has proven to be the choice of treatment in chronic liver disease caused by HCV [18]. The treatment in HCV infection is primarily aimed at reducing the HCV RNA viral load (<50 IU/mL) to undetectable levels (Sustained Virological Response(SVR)) after withdrawal of antiviral therapy thereby preventing HCV related hepatic and extra-hepatic complications including Hepatocellular Carcinoma (HCC) [5,19]. Studies have been in progress in developing newer treatment strategies targeting NS3 and NS4 protease inhibitors with Direct Acting Antiviral Agents (DAAs) including telaprevir and becaprevir in combination to conventional therapy [20]. Treatment decision is made depending on the extent of liver damage. Patients with moderate to severe liver condition are indicated specific HCV therapy. Decision on whether to treat individuals suffering from chronic HCV infection with mild liver condition, co-infected with HIV or other infections, pediatric age group and those over 60 years of age has to be cautiously measured on the benefits of therapy and its side effects [5]. Antiviral therapy in HCV needs a cautious approach as there is a possibility of potential drug-drug interactions which may be associated with severe and/or life threatening complications. Contraindications of HCV therapy include individuals with anemia, neutropenia, thrombocytopenia, Chronic Obstructive Pulmonary Disease (COPD), Chronic Kidney Disease (CKD), Cardiovascular Disease (CAD), autoimmune conditions, solid organ transplant patients and endocrinological disorders (Thyroid condition). Depression, psychosis and pregnancy are also contraindications for HCV treatment. Monitoring treatment response in HCV infection includes periodic check on biochemical parameters, virological monitoring to achieve SVR and histological examination of liver wherever needed. Patients on treatment are categorized as responders (those who achieve SVR), partial-responders (HCV RNA levels decline but remain detectable), non responders (sustained HCV

RNA viral load) and relapse cases (initial elimination of HCV RNA with reappearance after discontinuing therapy) [21].

Current Perspectives and Future Implications

Epidemiological studies on prevalence of HCV infection and distribution of genotypes in various geographical regions, planning and implementation of specific guidelines in diagnosis of acute and chronic HCV infection is the need of the hour. As there is no available vaccine recommended against HCV, prevention of HCV transmission remains mainstay in reducing newer infections. Genotyping is important to guide treatment because some viral genotypes respond better to therapy than others. The genetic diversity of HCV is one reason that it has been difficult to develop an effective vaccine since the vaccine must protect against all genotypes. As HCV infection initiates both hepatic and extra hepatic inflammation, and that antiviral therapy against HCV may lead to toxic side effects, studies must be encouraged on pre-therapeutic assessment and continuous and regular monitoring of patients on treatment. Identification of co-morbidities (co-infection with HBV, HIV, alcoholism, extreme age) can help in reducing the morbidity and mortality associated with HCV infection.

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