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Hepatitis C virus

Hepatitis C virus (HCV) is 1 of 6 (along with A, B, D, E, and G) that cause viral hepatitis that was discovered in 1989 during a study to discover the cause of post-transfusion hepatitis. It is a spherical, enveloped, single-stranded RNA virus measuring approximately 30-60 nm in diameter. It belongs to the genus *hepaciviruses*, under Flaviviridae family. The viral nucleocapsid consists of core protein and viral genomic RNA, which is enveloped by a lipid bilayer containing two glycoproteins. Its morphology is not exactly known.

HCV genome:
HCV has a positive-stranded RNA genome of about 9.5 kb. Structural components include the core and two envelope proteins (E1 and E2). Two regions of the E2 protein, designated hypervariable regions 1 and 2, have an extremely high rate of mutation. The envelope protein E2 also contains the binding site for CD-81, a receptor expressed on hepatocytes and B lymphocytes that acts as a receptor for HCV. The nonstructural components are proteins that function as helicase, protease, and RNA-dependent RNA polymerase.

Genotypes:
Heterogeneity is a characteristic feature of the hepatitis C virus. RNA-dependent RNA polymerase, an enzyme critical in HCV replication, lacks proofreading capabilities and generates a large number of mutant viruses known as quasispecies. Six distinct but related HCV genotypes and multiple subtypes have been identified on the basis of molecular relatedness. Some HCV genotypes are distributed worldwide, while others are more geographically confined. The major HCV genotype worldwide is genotype 1. Genotype 3 is found in Indian subcontinent.

Significance of genotypes:
Certain strains of HCV may have enhanced virulence than others. Viral genotyping helps predict the outcome of therapy and influences the choice of the therapeutic regimen. HCV genotype 1, particularly 1b, does not respond to therapy as well as genotypes 2 and 3. Genotype 1 also may be associated with more severe liver disease and a higher risk of hepatocellular carcinoma (HCC). Genotype 3 is more prevalent among intravenous drug users.

Transmission:
The factors most strongly associated with infection are IV drug abuse and receipt of a blood transfusion. Coinfection with HIV-1 appears to increase the risk of both sexual and maternal–fetal transmission of HCV. Nosocomial transmission from patient to patient can occur by infected and reused colonoscope, during dialysis, and during surgery. Needle-stick injuries in the health care workers can cause transmission of the virus. HCV may also be transmitted by means of acupuncture, tattooing, and sharing razors. The highest HCV antibody prevalence is found in haemophiliac patients who have received untreated blood or blood products.

Pathogenesis:

The natural targets of HCV are hepatocytes and, possibly, B lymphocytes. The exact mechanism by which HCV enters host cells to initiate infection is not well understood. HCV probably binds to hepatocytes via CD81 cell surface molecule expressed on their membranes. Replication occurs through an RNA-dependent RNA polymerase. Because HCV does not replicate via a DNA intermediate, it does not integrate into the host genome. HCV can produce at least 10 trillion new viral particles each day.
The core protein that gets translocated to the nucleus can interact with cellular proto-oncogenes, and thus play an important role in the development of hepatocellular carcinoma.

Clinical manifestations can occur, usually within 7 to 8 weeks after exposure to HCV, but the majority of persons have either no symptoms or only mild symptoms. The interval between infection and the development of detectable antibodies is estimated to be less than 12 weeks.

Acute infection: Symptoms of acute usually consisted of jaundice, malaise, and nausea. Rare cases of fulminant hepatitis have been described during this period. Acute disease may lead to recovery, fulminant hepatitis, relapsing hepatitis with intervening periods of normal liver function, inapparent chronic infection, chronic active hepatitis and cirrhosis.

Chronic infection: Chronic infection develops in 70-80% of patients infected with HCV, which is typically characterized by a prolonged period with no symptoms. Cirrhosis develops within 20 years of disease onset in 20% of persons with chronic infection. The development of cirrhosis can sometimes exceed 30 years. Once cirrhosis is established, the risk of hepatocellular carcinoma is approximately 1-4% percent per year. Coinfection with HBV or HIV-1, alcohol intake, male sex; and an older age at infection are factors that accelerate clinical progression.

Immune response: The primary immune response is mounted by cytotoxic T lymphocytes, which fails to eradicate infection in most people. It may contribute to liver inflammation and tissue necrosis. Viral clearance is associated with the development and persistence of strong virus-specific responses by cytotoxic T lymphocytes and helper T cells. The presence of lymphocytes within the hepatic parenchyma has been interpreted as evidence of immune mediated damage.
Seroconversion occurs in 8-9 weeks. Once persons seroconvert they usually remain positive. Although neutralizing antibodies to HCV have been detected in the serum of infected patients, these are short-lived. HCV infection does not induce lasting immunity against re-infection with different virus isolates, or even the same isolate.

Laboratory diagnosis:

Different diagnostic tests available are:

1. Antibody detection (anti-HCV)
    a. Screening by ELISA
        i. First generation ELISA
        ii. Second generation ELISA
        iii. Third generation ELISA
    b. Confirmatory RIBA
2. Antigen detection (HCVcAg)
3. Molecular techniques
    a. Qualitative and quantitative PCR
    b. bDNA signal amplification

A person can be considered to have serologic evidence of HCV infection only after an anti-HCV screening-test–positive result has been confirmed by a more specific serologic test such as, the recombinant immunoblot assay (RIBA) or a nucleic acid test.

First generation ELISA kits relied on a fusion protein antigen produced from an original clone and was denoted as the C100 antigen. Since the antigen used was non-structural one, many cases were not detected. Furthermore, antibodies against this antigen could not be detected until 15 weeks after the onset of hepatitis. The tests had poor specificity and many false positive cases were observed. **Second generation** assays and **third generation** assays incorporate core antigen as well as structural antigens. The currently used second- and third-generation enzyme immunoassays can detect antibodies within 4 to 10 weeks after infection. False negative tests can occur in persons with immune compromise, such as HIV-1 infection; patients with renal failure; and those with HCV-associated essential mixed cryoglobulinemia. These assays cannot distinguish acute from chronic infection. False-positive results are also known to occur. This is important especially when testing is performed on asymptomatic persons or when persons are being tested for HCV infection for the first time.

Recombinant Immunoblot assays (RIBA) are nitrocellulose strips coated with discrete bands of HCV antigens cloned in E. coli and yeast. This assay has been used to confirm positive enzyme immunoassays. A positive assay is defined by the detection of antibodies against two or more antigens. This test has higher specificity with equal sensitivity.

Antigen detection: ELISA tests to detect Hepatitis C virus core antigen is now available. Identification of hepatitis C antigen (HCAg) in hepatocytes of patients suffering from chronic HCV infection by immunofluorescence is also possible.

Molecular detection of HCV RNA: HCV RNA is usually detectable within 1-2 weeks of exposure. It is widely considered as gold standard in the diagnosis of HCV. These tests can be categorized as qualitative and quantitative. Qualitative HCV RNA tests are based on the PCR technique and can detect less than 100 copies of HCV RNA per milliliter. These are the tests of choice for the confirmation of viremia and the assessment of treatment response. Quantitative tests measure viral load. The viral load has been shown to be relevant to the outcome of anti-HCV therapy. Three commercial tests currently available to quantitate the degree of viremia are a branched-chain DNA assay and reverse-transcription PCR.

Treatment:
Treatment consists of interferon alfa administered subcutaneously and ribavirin orally. The virologic response to combination therapy should be assessed after 24 weeks. The attachment of polyethylene glycol to interferon alfa (peginterferon alfa) extends the half-life and duration of therapeutic activity of interferon alfa. Persons who cannot be treated with ribavirin can be treated with peginterferon alfa. Liver transplantation is the only available treatment option for patients with decompensated HCV-related cirrhosis and is also indicated for some patients with early stages of hepatocellular carcinoma. Reinfection of the graft with HCV almost always occurs.

Prevention and control:
There is no vaccine for hepatitis C. Control measures focus on reducing risk for contracting HCV. These include screening and testing blood, plasma, organ, tissue and semen donors. Various approaches include Inactivation of plasma derived products, counseling of persons with high risk, implementation of infection-control measures and public education.