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Hepatitis B and Hepatitis C viral infection: A Review

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Abstract

Hepatitis B viral infection is an infectious-inflammatory disease of the liver caused by the hepatitis B virus (HBV). The course of hepatitis B infection varies greatly, with the clinical manifestations differing in patient with the age, immune status and the stage at which the infection is recognised. At the acute phase, infection may produce serious illness characterized by hepatomegaly, vomiting, jaundice, anorexia, fever, body aches and dark urine. Hepatitis C is an infectious disease of the liver caused by hepatitis C virus. HCV is an enveloped virus that belongs to hepacivirus genus in the flaviviridae viral family. Chronic HCV infection is typically asymptomatic during the first few decades and are mostly discovered following the investigation of an elevated liver enzymes or during routine screening in high risk individual. HBV and HCV share the same modes of transmission, thus infection with the two viruses is not uncommon especially in highly endemic areas and among subjects with high risk behaviors. Patients with dual HBV and HCV infection have more severe liver disease, and are at an increased risk for progression to hepatocellular carcinoma. The paper reviewed hepatitis B and C infection.

Keywords: Hepatitis B, Hepatitis C, Viral infection.

Introduction

Hepatitis B viral infection is an infectious-inflammatory disease of the liver caused by the hepatitis B virus (HBV) - a hepadnavirus (Zukerman, 1996). Originally, it was known as "serum hepatitis (Bakar *et al.*, 1996), and had caused epidemics in the world (Asia and Sub-Saharan Africa), with the disease now being endemic in China (Williams, 2006).

As noted by World Health Organisation (WHO, 2009) about one third of the World's population (> 2 billion people) have been infected with HBV virus at one part in their times including 350 millions who are chronic carriers (Schilsky, 2013) the virus is transmitted by exposure to infectious blood or body fluids such as semen, vaginal fluids (Fairley and Read, 2012), although the viral DNA has been detected in the saliva, tear and urine of chronic carriers.

According to Chang, (2007), the course of hepatitis B infection varies greatly, with the clinical manifestations differing in patient with the age, immune status and the stage at which the infection is recognised. At the acute phase, infection may produce serious illness characterized by hepatomegaly, vomiting, jaundice, anorexia, fever, body aches and dark urine. Approximately about 0.5% of acute cases terminate in fatal, fulminant hepatitis. Chronic hepatitis B often progresses to liver complications - (cirrhosis and hepatocellular carcinoma (hcc) in 25% of cases) accounts for the increased morbidity and mortality associated with the disease.

The pathophysiology of the disease shows that replication takes place in the liver (Locarnini, 2004), however, the virus spreads to the blood where virus specific proteins (viral antigen) and corresponding

antibodies are expressed. These proteins and antibodies forms diagnostic markers of infection and are utilized for the diagnosis of the disease. The treatment strategy consists of antiviral drugs supplemented with immune system modulators (interferon). Infection is prevented by vaccination (Pungpapong *et al.*, 2007).

Historic overview

According to Lurman, (1885), the differentiation of the various types of acute hepatitis began decades after world war 11, following a number of clinical and epidemiological studies. However in 1967, the existence of at least two types of hepatitis was firmly established after a study carried out by Krugman and his colleagues; one of which then called serum hepatitis was parenterally transmitted. Prince and co-workers also independently identified an antigen known as SH antigen that appears in the blood of patient suffering from transfusion associated hepatitis during the incubation period of the disease (Prince and Ganem, 1996), and further work established that Au and SH were identical. The antigens represented the hepatitis B surface antigen (HBsAg). In 1970, Dane and others discovered the viral particle (called Dane particle) by electron microscopy (Dane *et al.*, 1970). By the early 1980s, the genome of the virus has been sequenced (Galibert *et al.*, 1979), and the first vaccine were being tested and further developed.

The first vaccine approved by the American food and drug administration was called anti-cancer vaccine because the introduction of it resulted in the prevention of primary liver cancer due to the HBV virus (CDC, 2013).

Virological features

Hepatitis B virus (HBV) is the prototype member of the hepadnaviridae (hepatotropic DNA virus) family. HBV virion are double-shelled particles, 40-42nm in diameter, with an outer lipoprotein envelop that bears three related envelop glycoprotein (E-proteins) termed the surface antigens (Locarnini, 2004). Within the viral envelop is the viral nucleocapsid or the core which contains the viral genome - a relax- circular, partially duplex DNA of 3.2kb nucleotide long and a polymerase enzyme that is responsible for the synthesis of viral DNA in an infected host cell (Zuckerman, 1996). In addition to the virion, HBV infected cells produce two distinct sub-viral lipoprotein particles: a 20nm spherical (pleomorphic) bodies lacking a core and filamentous form of similar diameter. These particles are not infectious and are produced in excess during the life cycle of the virus (Howard, 1986).

According to Cheesbrough, (2006), the virus also carries hepatitis B core antigen (HBcAg) and secreted antigen (HBeAg).

Genome structure

Electron microscopy gave the initial view of the hepatitis B genome and according to Robinson *et al.*, (1974), the genome of HBV is a circular, yet partially double stranded DNA molecule which approximately is 3.2kb nucleotide long. The virus has a compact organisation because of the absence of non-coding frame (Kidd-Ljingen *et al.*, 2002), and also does not conform to the usual classification of virus in that the HBV virion contain both DNA and RNA with some regions of the genome packaged as single stranded and double stranded. This peculiar genome feature is due to the specific replication mechanism peculiar to the virus.

There are four defined overlapping open reading frames (ORF) in the genome (denoted C, X, P & S genes) which codes for seven different protein. The ORF-P occupies the majority of the genome and encodes for the hepatitis B polymerase protein (enzyme) while the ORF-S gene encode and direct the synthesis of three distinct hepatitis B surface protein (HBsAg). The core antigen (HBcAg) and the secreted antigen (HBeAg) are coded for by the ORF-C. The ORF -X gene encodes a 17kd protein known as hepatitis BX protein (HBX) whose function in HBV infection is yet to be elucidated.

Replication

The life cycle of HBV is complex. It is one of a few known non-retroviral viruses that uses reverse transcription as part of its replication process. At first, the virus gains entry into the cell through receptor-mediated endocytosis. Because the virus multiplies via RNA made by host enzymes, the viral genomic DNA is first transferred to the cell nucleus by host proteins called chaperones. The partially double-stranded viral DNA is then made fully double stranded and transformed into covalently closed circular DNA (ccc-DNA) that serves as a template for transcription of the four viral RNA (Beck and Nassal, 2007). The largest mRNA (which is larger than the viral genome) is used to make the new copies of the genome and to make the capsid protein and the viral DNA polymerase. These four viral transcripts undergo additional processing and go on to form progeny virions which are released from the cell or returned to the nucleus and recycled to produce even more copies (Bruss, 2007). The long mRNA is then transported back to the cytoplasm where the virion P-protein synthesizes DNA via its reverse transcriptase activity.

Classification

Serotypes

The hepatitis B virus polymerase enzyme lacks proof reading activity and thus sequence heterogeneity is therefore a common feature (Williams, 2006). Information from phylogenetic analysis has led to the

classification of HBV into eight genotypes designated A-H. The classification was based on the intergroup divergence of > 8% in the complete genome sequence and >4% in the S gene. On the basis of antigenic epitopes present on its enveloped protein, the following four serotypes (adr, adw, ayr, ayw) has also been documented (Norder *et al.*, 1994). According to Schaefer, (2007), the genotypes of HBV have different properties and also show heterogeneity in their global distribution: an attribute that may account not only for the prevalence of HBV mutants in the various geographical regions (Kurbanov *et al.*, 2010), but also responsible for the variation in the clinical outcome and response to antiviral treatment and possibly prevention strategy (Kranvus *et al.*, 2005).

Epidemiology

World Prevalence

Hepatitis B virus (HBV) infection is highly prevalent worldwide and is a major cause of morbidity and death. Globally, two billion people have been infected, with ten million cases (incidence case) occurring annually. There are about 350-400million chronic carrier out of which 15-40% may develop HBV associated complications (Drosten *et al.*, 2004).

Distribution: In developing countries of the world (Africa, Asia), there is highest HBsAg carrier rate (> 10%) and underspread infection occurs in infancy and childhood (Finlayson *et al.*, 1999). Kurbanov *et al.*, (2010) noted that about 2-7% of the population are chronically infected in moderately prevalence regions (Eastern Europe, Russia, Japan) with infection predominantly common in children. However, areas of low prevalence (USA, Western Europe) has about 2% of the population chronically infected and injection drug abuse, unprotected sex are common risk factors (Redd *et al.*, 2007).

In Nigeria and other subsaharan African countries, where there is a high level of blood transfusion demanding health conditions, about 70% of the (Nigeria) population has been exposed to the virus at one point in their life.

Transmission

Hepatitis B virus is highly contagious and relatively easy to transmit from one infected individual to another by exposure to blood or body fluids containing blood (Finlayson *et al.*, 1999). Possible routes of transmission includes unprotected sexual contact, blood transfusion, re-use of contaminated needles and syringes and vertical transmission from mother to child during birth (Buddeberg *et al.*, 2008). HBV virus has an incubation period of 2-6 months and has man as the natural reservoir (Cheesbrough, 2006).

Immuno-pathogenic mechanism of HBV infection

HBV is a hepatotropic, directly non-cytopathic hepadnavirus and thus immunologically mediated events play an important role in the mechanism and outcome of the disease (Glebe and Urban, 2007). According to Stefan & Chisari, (2005), the innate immune response does not play a significant role in the immune mechanism of the diseases; this is because HBV act as a stealth virus and establishes itself efficiently in the hepatocytes without alerting the innate immunity. This together with other virological factors (high level of HBsAg secretion, direct cytopathic effect of HBcAg) account for persistent infection associated with the virus. However, it is clear that antigen-non-specific inflammatory cells exacerbate the action of cytotoxic T-Lymphocytes (CTL) in the induction of liver pathology. The CTL eliminates HBV infection by killing infected liver cells and produces antiviral cytokines which are then used to purge HBV from viable hepatocytes (Iannacone *et al.*, 2007).

In addition to the exacerbated action of inflammatory cells on CTL, platelet activation at the site of liver injury also facilitates the accumulation of CTL and possible liver damage.

Pathology and clinical manifestations

Primary infection with HBV may be associated with little or no liver disease (sub clinical infection) or with disease severity ranging from mild to fulminant infection with icteric presentations. Chronicity with later extrahepatic complications also occurs in most cases.

Acute infection

Onset of clinical disease is insidious and is characterised by tiredness, anorexia, vague abdominal discomfort, nausea, vomiting, fever (may be mild or absent) and sometimes arthralgias and rash. Icteric phase of acute infection begins usually within 10 days of initial symptoms with dark urine, followed by pale stool, yellowish discoloration of mucous membrane, conjunctiva, sclera and skin (Terrault *et al.*, 2005).

Chronic infection

Chronic HBV infection is defined as the persistent of HBsAg for 6 months or longer and is characterised by continuous mild inflammatory activity in the liver with high risk of cirrhosis and hepatocellular carcinoma (McMahon, 2009). Chronic infection clinically is divided into three phases as noted by (McMahon *et al.*, 2001). At the inactive (Non-replicative) phase, markers of viral replication (viral proteins & antibody) are either absent or below detection level and inflammation of the liver is minimal. However, the immune tolerance phase is characterized by low rate of viral replication, presence of HBsAg and HBcAg in serum, high level of HBV- DNA,

with normal enzyme level and less pathological changes in liver biopsy. At the immune active phase, ALT levels up with detectable levels of HBsAg & HBV-DNA and necro-inflammatory conditions with or without cirrhosis and fibrosis occurs. There is loss of HBeAg and appearance of anti-HBe.

Fulminant hepatitis B

This is a rare condition that develops from massive necrosis of the liver substance in about 1% of HBV cases (Robinson *et al.*, 1995). There is a rapid fall in ALT and AST which may be erroneously interpreted as a resolving hepatic infection.

Extra-hepatic manifestations:

The extra hepatic complications of HBV occurs in 1-10% of patients and is directly associated with immune complex depositions in tissue (Dienstag, 1981). Basically, it includes serum-sickness-like syndrome, acute necrotising vasculitis (polyarthritis nodosa), membranous glomerulonephritis (MGN) and papular acrodermatitis (Gianoti-Crosti syndrome) in children (Liang, 2009).

Diagnosis of HBV infection

According to Zukerman, (1996), serological markers (though vary depending on the clinical stage) which includes viral antigens and antibodies produced by host cells are utilized in test assays for the detection of HBV infection.

The hepatitis B surface antigen (HBsAg) is most frequently used antigen screening test to detect infection with the virus, however, early in an infection and in the later stage (non-replicative carrier phase), HBsAg may be undetected because it may not have been expressed or is cleared by the host. During this period, IgM antibodies to the core antigen (anti-HBcIgM) may be the only serological evidence of the disease. If the host is able to clear the infection, eventually the HBsAg will become undetected and will be followed by IgG antibodies to the HBsAg and core antigen (anti-HBs and anti-HBc-IgG).

According to Lok and McMahon (2007), and individual who remain HBsAg positive for at least six months are considered to be chronic HBV carried. More recently, PCR tests have been developed to detect and measure the amount of viral nuclei acid (HBV-DNA) in clinical specimen. These tests assesses patient infection status and viraemic load and also is use to monitor treatment (Zoulin, 2006).

Treatment

Acute hepatitis B infection does not usually required treatment because most adults clear the infection spontaneously (Hollinger and Lau, 2006). Early antiviral

treatment may only be required in less than 1% of patients whose infection takes aggressive course (fulminant hepatitis) or who are immuno-compromise. Chronically infected individuals with persistently elevated serum alanine aminotransferase and HBV- DNA levels are candidates for therapy.

As of 2008, there are five antiviral medications and two immune-modulators licensed for the treatment of hepatitis B in the USA. This includes lamivudine (Epivir), adefovir (Hepsera), tenofovir (viread), telbivudine (Tyzeka), interferon alpha-2a and Pegylated interferon alpha-2a (pegasys).

Although none of these available drugs can clear the infection, they can stop the virus from replicating and minimizes liver damage such as cirrhosis and cancer (Dienstag, 2008).

Infant born to mothers known to carry hepatitis B can be treated with antibodies to HBV called hepatitis B immune globulin (HBIG) and when given within twelve hours of birth in combination with HBV vaccine, the risk of infection acquisition is reduced to 95% and this allows the mother to safely breastfed her child.

Prognosis

It has been shown that a person with self limiting acute infection clears the virus spontaneously within weeks to months (Dienstag, 2008). Children are less likely to clear the infection than adult without treatment. Hepatitis D infection can only occur with a concomitant infection with HBV because the Hepatitis D virus uses the HBV surface antigen to form a capsid (Taylor, 2006). According to Olueri *et al.* (1991), co-infection with hepatitis D increases the risk of liver cirrhosis and hepatocellular carcinoma.

Prevention and control

The hepatitis B vaccine is the mainstay of hepatitis B prevention and has been available since 1982. The vaccine was originally prepared from plasma obtained from patients who had chronic HBV infection. However, these are currently more often made using recombinant DNA technology, though plasma derived vaccine continue to be used; the two types of vaccines are equally effective and safe (Zuckerman, 2006). In the United States, the incidence of acute HBV infection reduced by more than 80% following initiation of immunization (Sorrell *et al.*, 2009). A universal immunization program in Taiwan, where vertical transmission of HBV was endemic, greatly reduced the death rate from hepatocellular carcinoma in young individuals (Chang and Chen, 1999). Hepatitis B surface antigen (HBsAg) may be detected in serum for several days following vaccination; this is known as vaccine antigenaemia (Martin-Ancel *et al.*, 2004). Vaccine is generally administered in either two, three or four dose

schedules; and can be received by both infants and adults and provides protection for 85-90% of individuals and lasts for 23 years (Mayo clinic staff, 2008)

Reactivation

Hepatitis B virus DNA persists in the body after infection and in some people the disease recurs (Vierling, 2007). Although rare, reactivation is seen most often in immunocompromised individuals (Katz *et al.*, 2008) Patients who undergo chemotherapy are at risk of HBV reactivation. The current view is that immunosuppressive drugs favour increased HBV replication while inhibiting cytotoxic T cell function in the liver (Bonacini and Maurizio, 2009).

Hepatitis C virus (HCV)

Brief history

According to Ryan & Ray (2004), Hepatitis C virus (HCV) which currently infect an estimated 120-180 million people (i.e 2-3% of the world population) has been present in some human population for several centuries notably HCV genotype 1 & 2 in West African and genotype 6 in South East Asia. The discovery of the disease was made not until Cho in 1987 demonstrated that numerous post-transfusion blood samples that caused hepatitis in the recipient were negative for both hepatitis A and B viruses (Cho *et al.*, 1987), and were classified initially as non A, and B hepatitis (NANBH). In 1989, at the center for disease control and prevention, the virus was identified through a novel molecular cloning, and a diagnostic procedure developed.

The screening of donors for HCV was introduced in blood bank in 1990, which greatly reduced the risk of HCV infection globally and with the introduction of the first alpha interferon (Schering's Intron A) treatment in 1991 complication and death from the virus has been greatly reduced (Morgan *et al.*, 2013).

HCV Infection

Hepatitis C is an infectious disease of the liver caused by hepatitis c virus (Ryan and Ray, 2004). It is widely believed that the outcome of both infection and the pathogenesis of the associated liver disease are determined by host-virus interaction mediated by the immune response (Houghton, 2009). Although Shores and Teri, (2011), had noted the difficulty in elucidating the viral-host factors at play in the infection which he attributed to the limited host range (human & chimpanzees) and non existence of cell culture or animal model for the virus.

According to Sugden *et al.*, (2012), the current state of knowledge of the biology and pathogenic mechanism of the virus infection reflect what has been learned about their natural history and immunobiology in humans and

chimpanzees as well as information from functional genomics and virologic-immunological analysis of closely related flavi-viruses infection in their natural host.

The Organism

Structure

HCV is an enveloped virus that belongs to hepacivirus genus in the flaviviridae viral family. Structurally, the viral particle is enveloped in a lipid-glycoprotein bi-layer in which are anchored the envelop proteins (E₁ & E₂ proteins) (Linderberch *et al.*, 2005). The lipid envelop surrounds the nucleocapsid which is composed of multiple copies of small basic proteins (the core protein) that contains the RNA genome (Linderberch and Rice, 2007).

Basically, the HCV-RNA genome is a positive-single stranded RNA (+SSRNA) molecule that consists of a single open reading frame (ORF) of 9600 nucleotide base.

The core proteins (c-proteins) and the envelope proteins (E₁ & E₂) forms the structural proteins, functions in viral replication and are encoded by the N-terminal part of the ORF while the non-structural proteins (P₇ viroporin, NS₂, NS₃, NS_{4A}, NS_{4B}, NS_{5A}, NS_{5B}) are encoded by the other half of the ORF with the replicative enzymes and plays part in viral morphogenesis and assembly. It has been noted that HCV proteins exert multiple functions during the viral life cycle and this may be governed by different structural conformation interaction with viral and cellular partners (Dufour, 2006).

Classification

Based on genetic difference between HCV isolates, the HCV virus species is classified into six genotypes (1-6) with several subtypes within each genotype (represented by a small letter). On their genetic diversity, subtypes are further broken down into quasispecies (Burh *et al.*, 1995).

The preponderance and distribution of HCV genotypes varies globally. For example in North America, genotypes 1a predominate followed by 1b, 2a, 2b and 3a. In Europe, genotype 1b is predominant followed by 2a, 2b, 2c and 3a. However in Africa, genotypes 4 and 5 are found almost exclusively (Farci and Purcell, 2000). Clinically, there is need to establish the genotype of HCV infecting an individual before commencement of treatment, reason being that it determines both the type and duration of treatment and also predict the livelihood of clearance (cure) following treatment.

Viral cycle

Blanchard *et al.* (2003) stated that numerous cellular receptors (CD81 & CD209 molecules, scavenger

receptor B type 1 (SRB1), low density lipoprotein receptors (LDL-R), asialoglycoproteins receptors and glycosaminoglycans) interact with the HCV envelop glycoproteins (E₁ & E₂ proteins) to mediate viral fusion and attachment. By receptor-mediated endocytosis, the nucleocapsid is released into the cell cytoplasm (Linderbach & Rice, 2007). Following decapsidation, the viral genome (+SSRNA) is translated to generate a large precursor HCV protein. The replication of HCV virus is thought to be semi-conservative and asymmetric involving several steps. Due to lack of proof reading by HCV-RNA polymerase, there is high probability of mutation rate in the virus- a factor utilized by the virus to elude the host immune response (Dufour, 2006). It has been noted that replication of HCV occurs in the hepatocytes, although a controversial evidence of replication in lymphocytes exists.

Epidermiology

Incidence, Prevalence & Mortality rate

Hepatitis C virus is worldwide in distribution and from the study by Hannafiah, (2013) as based on the systemic review of anti-HCV sero-prevalence data, the global incidence and number of people with anti-HCV antibody has increased from 2.3% to 3.0% and >122 million to > 185 million cases between 1990 and 2005. Available data indicates that infection varies considerably by country and region, with prevalence rate of <2% in USA, 3% in Eastern Europe, Latin America, Middle East and certain African countries with Egypt (> 10%) having the highest value.

HCV infection particularly in its chronic form is associated with sizable mortality.

Transmission modes

Whereas HCV virus transmission in developing countries frequently results from exposure to infected blood and blood products in healthcare and community setting Other mode of transmission (tattooing, sharing of items e.g. manicuring/pedicuring equipments, traditional practices) etc has also been documented (Shors and Teri, 2011).

Hepatitis C virus is not found consistently in bodily secretions, thus sexual transmission is usually low (Tohme and Holmberg, 2010) although sexual activity involving high degrees of trauma do present a greater risk. Vertical transmission of the virus (from infected mother to her child) occurs in less than 10% of pregnancies (Shors and Teri, 2011).

Pathogenesis

HCV virus is hepatotropic in nature. Ryan and Ray, (2004), has noted that the pathogenesis of hepatitis C virus remains a medical challenge 15 year post

discovery, with persistent infection, chronic necro-inflammatory conditions (cirrhosis/fibrosis) and liver cancer having been established as sequels complications from primary infection.

HCV strongly induces (yet cunningly evade) the innate immune response and also defeat the adaptive immunity by functional inactivation and mutation. There is also a high level of dys-regulation of several signal transduction pathway by the virus and this direct mechanisms that promote viral persistence, hepatocytes apoptosis and oncogenic transformation (Mueller *et al.*, 2009).

Clinical presentations

Acute hepatitis C infection is referred to as the first 6 months after infection with the virus. Between 60% to 70% of those affected develop no symptom. In the minority of patients who experience acute phase symptoms, they are generally mild and non-specific and include decrease appetite, fatigue, abdominal pain, jaundice, itching and flue-like symptoms. Approximately 15-40% of persons infected clear the virus from their body during the acute phase, the remaining 60-85% of patients infected develop chronic hepatitis C. Treatment with interferon alpha and ribavirin at the acute stage has a high success rate (over 90%) with half the treatment time required from chronic infections (Jackel *et al.*, 2001).

Chronic hepatitis C infection is defined as a persistent infection for more than six months. The natural course of chronic hepatitis c varies considerable from person to person with disease progression being influenced by age, gender, alcohol consumption, HIV confection and fatty liver (Paradis and Bedossa, 2008). Fortson *et al.* (2005) described the general signs and symptoms associated with chronic hepatitis C to include fatigue, flu-like symptoms, joint pains, itching, sleep disturbance, appetite change, nausea and cognitive problems (depression).

Extra- hepatic complications

According to Zignego *et al.* (2006), HCV virus infected patients has a high propensity to developing extra-hepatic complications. These may include cryoglobulineamia (a form of small vessel vasculities), cutanea tarda (Franco and Dommacco, 2013), and membrano-proliferative glomerulonephritis (MPGN). Most of the complications arise from the deposition of porphyrin in tissues due to loss of liver function.

A variety of central nervous system disorders, cardiomiopathy and increased risk of pancreatic cancer has also been documented (Matsumori, 2006). Louis *et al.* (2011) noted that thrombocytopenia occurs in 0.16 - 45% of those with chronic HCV and 20-30% may have a B-cell lymphoproliferative disorder.

Diagnosis

The diagnostic test for HCV can be divided into two categories (a) serological assays that detect antibody to the virus (Anti-HCV) (2) molecular assay that detects, quantify/characterize RNA genome (Wilkins *et al.*, 2010). Antibody to HCV virus (anti-HCV) is the principal screening test for HCV exposure (Dufour, 2006) and it can be detected in 80% of patient within 15 weeks of exposure, in >90% within 5 to 6 months after exposure. Ray *et al.* (2009) stated that HCV antibody test have a strong positive predictive value, although false-negative values can be obtained in newly infected patient in which sero-conversion is yet to occur and in those who clears the virus spontaneously, or have insufficient level of antibody to be detected by the test method (Alter, 2007).

HCV-RNA can be detected by PCR typically one to two weeks after infection (Ozaras & Taham, 2009). A positive antibody test (immuno-assays) is confirmed by recombinant immune-blot and the viral load monitored by HCV- RNA polymerase chain reaction.

Diagnostic markers of HCV

Chronic HCV infection is typically asymptomatic during the first few decades and are mostly discovered following the investigation of an elevated liver enzymes or during routine screening in high risk individual (Alter, 2007). Liver enzymes are variable during the initial part of the infection (Ray *et al.*, 2009), and begins to rise at seventh week (AST often < ALT). High AST (value > ALT) with the elevation of ALP and GGTP indicates progression to liver cirrhosis and possibly hepatocellular carcinoma. Although Ray *et al.* (2009) had also opined that elevated liver enzymes do not closely follow disease severity. Liver biopsy and elastography has been shown to be of high accuracy in determining the extent of liver damage.

Treatment

It has been noted that HCV induces chronic infection in 50-80% of the infected persons, however approximately 40-80% of these cases clears the virus following treatment. Treatment is more effective at the acute stage. There is a very small chance of clearing the virus spontaneously (i.e. without treatment) in chronic carriers (Scott *et al.*, 2006). Currently, the treatment of HCV is based on the combination of pegylated interferon alpha and the antiviral drugs ribavirin for a period of 24 or 48 weeks depending on the genotype. Evidence from prognostic studies as measured by sustained viral response to treatment has shown that sustained cure rates of 70-80% has been recorded in those with genotype 2 and 3 and 45-70% cure rate for other genotypes (Liang and Ghany, 2013).

Characteristic flu-like symptoms and emotional problems is seen in half and one third of patient under treatment (Wilkins *et al.*, 2010).

Morgan *et al.*, (2013) noted that successful treatment decreases the future risk of hepatocellular carcinoma by 75%. In those with cirrhosis and hepatocellular carcinoma, liver transplantation is recommended, though cases of recurrence (infection of graft) have been noted in 10% of graft cases within 5 years (Cirria *et al.*, 2013).

Prevention and control

Currently, vaccine capable of protecting against hepatitis C virus is not available; however there are few number that are under development up to trial stage. Dufour, (2006) has attributed the difficulty in vaccine development to high variability and genetic diversity among strains (genotypes and sub-genotypes) of hepatitis C virus. A combination of preventive strategies such as proper screening of blood, use of new syringes, not sharing of needles, safe medical practices etc are the hallmark of prevention and control (Hagan *et al.*, 2011).

Hepatitis B virus and Hepatitis C virus co-infection

HBV and HCV share the same modes of transmission, thus infection with the two viruses is not uncommon especially in highly endemic areas and among subjects with high risk behaviors. Patients with dual HBV and HCV infection have more severe liver disease, and are at an increased risk for progression to hepatocellular carcinoma (HCC) (Benvegnu *et al.*, 1994). Co-infected patients also represent a diverse group with various viral replication and immunity profiles. Because of their distinct clinical course and heterogeneity, identification of patients who are candidates for therapy and selection of the optimal antiviral therapy is a challenge for clinicians. The exact number of patients co-infected with HBV and HCV is unknown. IN a study carried out in Eastern Europe, a dual infection rate of 0.68% was obtained in randomly selected healthy population of 2200 individuals. (Atanasova *et al.*, 2004) In patients with chronic hepatitis B, estimates of the rate of HCV co-infection vary from 9% to 30%, depending on the geographic region (Liaw, 1995). In another study carried out in Italy, it was found that rate of dual infection increased with age, and was more common in patients over 50 years of age (Gaeta *et al.*, 2003). These data notwithstanding, the exact number of HBV and HCV co-infected individuals is yet to be established. This is partly attributed to the fact that these studies may underestimate the true number of patients with both viral infections because no large- scale studies have been performed, and partly also to the fact that there is a well-described phenomenon of "serologically silent" occult HBV infection (i.e. patients with negative hepatitis B surface antigen (HBsAg) but detectable serum HBV

DNA) in patients with chronic hepatitis C (Zignego *et al.*, 1997).

Treatment of HBV and HCV co-infection patients can represent a challenge. This is because no standard recommendations exist for treatment of HBV/HCV co-infection, and therefore treatment must be individualized based on patient variables such as hepatitis blood test results and DNA or RNA levels, patient prior exposure to antiviral treatment, and the presence of other similarly transmitted viruses such as hepatitis D virus and human immunodeficiency virus (HIV). Assessment of the dominant virus is helpful in determining a treatment strategy. In co-infected patients with HCV dominant disease, interferon (IFN) plus ribavirin treatment has been well studied and has proven efficacy, whereas IFN with or without lamivudine is a reasonable option for patients with HBV dominant disease.

HBV and HCV Interaction

Several studies have shown that the HBV and HCV interact with each other affect the immune responses. HCV infection can suppress HBV replication, as demonstrated by studies showing that patients with chronic hepatitis B who are coinfecting with HCV have lower HBV DNA levels, decreased activity of HBV DNA polymerase, and decreased expression of HBsAg and hepatitis B core antigen in the liver. Furthermore, patients with chronic HBV infection who become superinfected with HCV can undergo seroconversion of hepatitis B e antigen (HBeAg) and HBsAg to respective antibodies (Liaw *et al.*, 1994). In a longitudinal follow-up study of a large series of HBV infected patients carried out by Sheen *et al.*, 200, it was found that the annual incidence of HBsAg seroconversion was 2.08% in co-infected patients compared to 0.43% in patients with HBV monoinfection, and a subsequent study confirmed these results (Utili *et al.*, 1999).

Relationship between HBV and HCV infections and blood group

ABO blood groups are set of agglutinogens (antigens) which are genetically determined carbohydrate molecules carried on the surface of red blood cells. The relationship of these blood groups of different populations and their susceptibility to diseases like plague, small pox, malaria, cholera suggests the possible role of blood group antigen in the occurrence of diseases. During the past twenty years, many reports have documented the role of blood group antigens as receptors for parasites, bacteria and viruses (Garratty, 2005) However, the role of ABO blood group in the susceptibility to viral hepatitis has always been under controversial discussion and is yet to be elucidated as stated by Umit *et al.* (2008). In contrast, association of blood groups with HBV infection and fibrosis severity in HCV infection has been reported (Bahel *et al.*, 2009). Ahmad *et al.* (2008) also noted that there exists a high

variability in the susceptibility to most infectious organisms due to variation in red cell adherence function in the various groups, with non-secretors being more susceptible-an attribute to the fact that soluble antigens bind and block the adherence of infectious agents to cell receptors thus limiting the susceptibility.

Conclusion

Hepatitis B viral infection is an infectious- inflammatory disease of the liver caused by the hepatitis B virus. The course of hepatitis B infection varies greatly, with the clinical manifestations differing in patient with the age, immune status and the stage at which the infection is recognised.

The life cycle of HBV is complex. It is one of a few known non-retroviral viruses that uses reverse transcription as part of its replication process. At first, the virus gains entry into the cell through receptor-mediated endocytosis. Because the virus multiplies via RNA made by host enzymes, the viral genomic DNA is first transferred to the cell nucleus by host proteins called chaperones.

Hepatitis B virus (HBV) infection is highly prevalent worldwide and is a major cause of morbidity and death. Globally, two billion people have been infected, with ten million cases (incidence case) occurring annually.

The hepatitis B vaccine is the mainstay of hepatitis B prevention and has been available since 1982. The vaccine was originally prepared from plasma obtained from patients who had chronic HBV infection. However, these are currently more often made using recombinant DNA technology, though plasma derived vaccine continue to be used; the two types of vaccines are equally effective and safe.

Hepatitis C is an infectious disease of the liver caused by hepatitis c virus. HCV is an enveloped virus that belongs to hepacivirus genus in the flaviviridae viral family. Chronic HCV infection is typically asymptomatic during the first few decades and is mostly discovered following the investigation of elevated liver enzymes or during routine screening in high risk individual.

HBV and HCV share the same modes of transmission, thus infection with the two viruses is not uncommon especially in highly endemic areas and among subjects with high risk behaviors. Patients with dual HBV and HCV infection have more severe liver disease, and are at an increased risk for progression to hepatocellular carcinoma.

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