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Hepatitis B "A Global Burden"

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Abstract: **Hepatitis B virus (HBV) is a major worldwide cause of chronic hepatitis, cirrhosis, and Hepatocellular carcinoma, accounting for 1 million deaths annually. Cytopathic and liver injury is mostly caused on consistent response of host immune system against hepatitis B viruse. The prevalence of chronic HBV infection in different areas has been categorized as, high endemicity (8% prevalence), intermediate (2–7%) and low endemicity (2% prevalence). Pakistan falls under the endemic region with 3% HBV (Hepatitis B Virus) infected country population and lies in a zone of intermediate endemicity for these infections. Major symptoms appear in infected person are flu-like illness that includes fever, abdominal pain, fatigue, decreased appetite, nausea, and in some cases yellowing of the skin and eyes (jaundice). HBV is present in the blood, saliva, semen, vaginals excretions, menstrual blood, sweat, breast milk, tears and urine of infected individuals. The virus is transmitted efficiently by a number of routes including transmission from an infected mother to her child or by percutaneous and mucous membrane exposure to infectious blood or other body fluids. The incidence of clinically apparent illness is much higher (30–50%) in individuals infected after the age of 5 years. Introduction of PCR for detection of serum HBV DNA resulted in a significant improvement of sensitivity over that of other biochemical techniques. The availability of vaccination effectively prevented HBV infection in up to 95% of a group comprising infants through to young adults who completed a course of three vaccinations. Although mass vaccination programs have begun to control the spread of HBV, therapeutic intervention is the only option for those with established chronic HBV-associated liver disease. From high global epidemiology and increasingly spreading infections clearly indicates that Hepatitis B needs much more attention to reduce the risk of infection through awareness program.**

Keywords: **Hepatitis B, HBV infection.**

I. INTRODUCTION

Hepatitis B virus (HBV) is a major worldwide cause of chronic hepatitis, cirrhosis, and Hepatocellular carcinoma, accounting for 1 million deaths annually (Alter, 1981). The hepatitis B virus (HBV) was discovered in 1966 (Purcell, 1993). HBV infection is a serious global health problem, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. Of these, 75% are Asians (Alter, 1981 and Blumberg, 1977). A condition that evolves towards liver insufficiency and hepatocellular carcinoma in approximately 15 to 40% of cases (Lok, 2002). The global prevalence of chronic HBV infection varies widely, from high (8%, e.g., Africa, Asia and the Western Pacific) to intermediate (2–7% e.g., Southern and Eastern Europe) and low (<2%, e.g., Western Europe, North America and Australia) (Willis and Maddrey, 2000). In Europe, approximately 1 million people become infected each year and 200,000–300,000 infections occur annually in the US (McQuillan et al., 1999). Corresponding data are not available for the endemic regions of Asia and Africa, but infection rates are likely to be much higher (Margolis et al., 1991).Hepatitis B infection is the 10th leading cause of death worldwide, and results in 500,000 to1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and Hepatocellular carcinoma (HCC). HCC accounts for 320,000 deaths per year (Lavanchy, 2004). The virus causes acute hepatitis of varying severity and persists in 95% of children and 2–10 % of adult patients (Heerman et al., 1999 and Bower, 2000). Chronic HBV infection is defined as the presence of HBsAg in serum for at least

6 months or the presence of HBsAg and the absence of anti-HBc immunoglobulin M (IgM). The risk of developing chronic infection varies inversely with age and is highest (up to 90%) for infants (Hyams, 1995). Between 25 and 50% of children infected between 1 and 5 years of age develop chronic infection, compared to 6 to 10% of acutely infected older children and adults (Beasley, 1988). Persons with chronic HBV infection are at substantially increased risk of developing chronic liver diseases, including cirrhosis of the liver and primary hepatocellular carcinoma (Liaw and Lok, 1988). Prospective studies indicate that up to 25% of persons who acquire HBV infection as infants and young children develop either hepatocellular carcinoma or cirrhosis compared to 15% of adolescents and young adults who acquire chronic HBV infection (Beasley and Hwang, 1991). Chronically infected individuals, defined as those who carry hepatitis B surface antigen (HBsAg) for more than 6 months, represent the major source of HBV infection (Boag, 1991 and Margolis et al., 1991).

II. MATERIALS AND METHODS

Current review is concluded by searching and studying various literature and research papers available from various studies of scientific communities. Many search engines like journal of virology, infectious diseases, pak MediNet, pubmed, google scholar and other many open access journals were used for data available by using keywords hepatitis B prevalence, transmission, symptoms, diagnostic methods, treatment etc. One hundred and thirty four different articles and reports were taken from the online available sources, out of which mostly studies were found to be published in 2000 and onward were included in the present review. We also previously conducted a study on institutional based prevalence of hepatitis B detected through RT PCR. We used ALT methods and then PCR based diagnosis was done for all collected samples in four months. We used many parameter in our study e.g agewise, genderwise, regionalwise prevalence and also made a comparison of the results obtained from various diagnostic techniques. The data about the prevalence of HBV was found to be in three categories low, middle and high endemic regions, Pakistan is considered in mid endemic region by the studies been conducted in past by various Pakistani researchers. they have also found that major reasons of transmission of HBV is due to none secured Blood donation, careless healthcare workers, surgical patients exposure, shave by barbars, discarding medically used apparatus in open environment, drug injection usage.

The global prevalence of Hepatitis B

The global prevalence of chronic HBV infection varies widely. The prevalence of chronic HBV infection in different areas has been categorized as high, intermediate or low HBV endemicity. Areas of high endemicity (prevalence 8%) account for a total of 45% of the global population and include Africa, Asia (East of the Indian subcontinent but excluding Japan), the Pacific Basin, the Amazon Basin, the Arctic Rim, the Asian Republics previously part of the Soviet Republic, and parts of the Middle East, Asia Minor and the Caribbean. Additionally, in parts of Eastern Europe, such as Bulgaria, Romania, Albania and Moldavia, the carrier prevalence of HBV is 5–10% of the general population. Areas of intermediate endemicity have a prevalence of chronic HBV infection of 2–7% and account for a total of 43% of the global population (Maddrey, 2000).Southern and Eastern Europe, the Middle East, Japan, Western Asia through the Indian subcontinent, and parts of Central and South America, are regarded as areas of intermediate endemicity (Maynard, 1990). By contrast, chronic HBV affects fewer than 2% of the population of most of Western Europe, Australia and North America that are generally categorized as areas of low endemicity (Margolis et al., 1991). Even within these areas, however, there may be differences in HBV prevalence based on race and ethnicity (Coleman et al., 1998).

Prevalence of Hepatitis B in Pakistan

It is estimated that in Pakistan about 4 million people are infected with hepatitis B virus **(**Abbas et al., 2010**).** According to WHO (World Health Organization), Pakistan falls under the endemic region with 3% HBV (Hepatitis B Virus) infected country population (Hakim et al., 2007). Pakistan lies in a zone of intermediate endemicity for these infections (Shepard et al., 2006). Countries with high endemicity are those where HBsAg seroprevalence is greater than or equal to 8 percent; countries with intermediate endemicity are those where seroprevalence is 2–7 percent; and those with low endemicity are those where seroprevalence is less than 2 percent. (Peter and Carla, 1992).

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Transmission of Hepatitis B Virus

HBV is present in the blood, saliva, semen, vaginals excretions, menstrual blood, sweat, breast milk, tears and urine of infected individuals (Boag, 1991). The virus is transmitted efficiently by a number of routes including transmission from an infected mother to her child (perinatal or vertical transmission), or by percutaneous and mucous membrane exposure to infectious blood or other body fluids (horizontal transmission) (Alter, 1996). The predominant routes of HBV transmission vary according to the prevalence of HBV infection. In regions of high endemicity, transmission from an infected mother to child is the main mode of transmission, with the lifetime risk of acquiring HBV greater than 60% (Maynard, 1990 and Alter, 1996). Perinatal transmission rates from HBsAg-positive mothers are as high as 90% (Margolis et al., 1991). Infections are generally acquired early in life, either at or shortly after birth, or early in childhood from exposure to members of the extended family who may be carriers of HBV (Gust, 1996). In regions of intermediate endemicity, individuals of all age groups can be infected, although chronic infection is generally caused by transmission during infancy or early childhood. The lifetime risk of infection is 20– 60% (Alter, 1996). In regions of low HBV prevalence, where the lifetime risk of HBV infection is less than 20%, transmission is primarily horizontal (between individuals). Sexual transmission (either homosexual or heterosexual) in high-risk adults is a main mode of transmission in Europe and North America (Gust, 1996), although needle sharing amongst intravenous drug abusers or occupational exposure to contaminated blood and blood products continues to be important (Lee, 1997). Individuals aged 15–24 years are generally considered to have the highest rate of infection (Zuckerman, 1999).

Clinical Outcomes

Not only does the age at which the individual becomes infected with HBV correlate with the route of transmission (Maynard, 1990), but it is also an important determinant of clinical outcome (Chang, 1998). Clinical disease occurs when the immune system of the host attacks HBV-infected hepatocytes causing liver injury (Lee, 1997). Up to 95% of neonates and children under 5 years of age who are infected with HBV become chronic HBV carriers, although infection is generally subclinical because of their immature immune systems (Alter, 1996 and Lee, 1997). The incidence of clinically apparent illness is much higher (30–50%) in individuals infected after the age of 5 years (Alter, 1996). In adults, HBV infection is most likely to cause clinically apparent acute hepatitis B, with only 1–5% of adults remaining chronically infected (Lee, 1997). Chronic hepatitis B is a serious consequence of HBV infection. Between one-third and one-quarter of people chronically infected with HBV are expected to develop progressive liver disease (including cirrhosis and primary liver cancer) (Zuckerman, 1999). An estimated 15–25% of all age groups infected with chronic will die prematurely from these conditions (Alter, 1996).

Diagnosis of Hepatitis B

Monitoring of hepatitis B virus (HBV), DNA in serum has become the standard method of assessing the replicative activity of HBV. The clinical importance of this method has been reported for the assessment, management, and antiviral treatment of patients with chronic HBV infection (Lok, 1994). Hybridization assays for detection of serum HBV DNA have been used since the beginning of the 1980s. Introduction of PCR for detection of serum HBV DNA resulted in a significant improvement of sensitivity over that of hybridization techniques (Brechot, 1993). Home-brew PCR-based assays employed radioactive or nonradioactive hybridization techniques (Lehtovaara et al., 1993). Those assays, however, lack standardization and reproducibility, as has been shown by the results of the EUROHEP proficiency study, where more than 50% of participating laboratories failed either the sensitivity or the specificity criteria (Pawlowsky et al., 1997).

The standardized quantitative Amplicor HBV Monitor Test (Roche Diagnostic Systems, Pleasanton, Calif.), which has been introduced recently, is based on a previously described quantitative PCR with colorimetric detection (Ranki et al., 1995). This assay includes a simplified sample preparation procedure, a PCR amplification, a hybridization step, and colorimetric detection on a micro well plate. The Amplicor HBV Monitor Test proved to be relatively easy to use, and the whole procedure can be carried out in 7 h (Gerken et al., 1998). The lower detection limit of this assay was found to be 10^2 to 10^3 HBV DNA copies/ml, thus making the assay 1,000 to 10,000 times more sensitive than a widely used commercially available hybridization assay (Jardi et al., 1996). According to the manufacturer's package insert, the Amplicor HBV Monitor Test shows linearity from 4.0×10^2 (lower detection limit) to 4.0×10^7 HBV DNA copies per ml.

The reproducibility data of the Amplicor HBV Monitor Test indicate that this test is very reliable, with coefficients of variation being mostly below 20% (Kessler et al., 1998).

Prevention of Hepatitis B Virus Infection

Active and passive immunization against HBV have been used to try and combat the substantial global problem caused by transmission of the virus. Before the era of HBV vaccination, passive immunization with hepatitis B immunoglobulin was useful in preventing perinatal infection in infants (Chang et al., 1997). The first vaccine against HBV reached on the market in late 1981, and was followed, 5 years later, by an alternative recombinant vaccine (Davey, 1996). By 1995, vaccination effectively prevented HBV infection in up to 95% of a group comprising infants through to young adults who completed a course of three vaccinations (VanDamme et al., 1995). The first country to implement a mass vaccination programme against HBV was Taiwan in 1984 (Chang et al., 1997 and Chang, 1998). For the first 2 years, the programme covered only neonates born to HBsAg positive mothers; thereafter it was extended to cover all neonates, then children and gradually adults. As a result both perinatal and horizontal HBV transmission decreased, and the carrier rate was reduced more than 10-fold. Furthermore, 6–10 years after the initiation of Taiwan's mass immunization programme, the incidence of childhood hepatocellular carcinoma had decreased significantly. These findings led Chang [1998] to suggest that immunization against hepatitis B should be included in the World Health Organization (WHO) Expanded Programme of Immunization (EPI) In Children organized by the World Health Organization (WHO).In 1991, the EPI Global Advisory Group called for all countries to add the hepatitis B vaccine to their national immunization programmes (Davey, 1996 and Kane, 1998). By 1998, 80 countries had achieved this goal, and a further 10–20 countries plan to do so over the next few years. Hepatitis B vaccines are now included in the national immunization programmes (Kane, 1998).

Treatment of Hepatitis B

Although mass vaccination programs have begun to control the spread of HBV, therapeutic intervention is the only option for those with established chronic HBV-associated liver disease. Acute hepatitis B does not require specific treatment because more than 90% of adults will spontaneously clear their infection, although symptomatic treatment may be indicated (Gitlin, 1997). The primary objective of therapy for chronic hepatitis B is eradication of the virus that will, in turn, lead to remission of necro-inflammatory liver disease and an improved long-term prognosis. Two therapeutic approaches have been used to prevent hepatitis B viral replication: immune modulators, such as interferon (IFN) alpha, and antiviral agents in the form of nucleoside analogues (e.g., lamivudine). Patients with chronic hepatitis B have deficient responses to endogenous IFN alpha (Lee, 1997). The aim of therapy with IFN alpha is to stimulate the immune system to attack HBV-infected hepatocytes, thereby inhibiting viral protein synthesis. Until recently IFN alpha was the only potentially successful treatment for chronic hepatitis B (Vail, 1997), and indeed, the mainstay of treatment (Rosenberg and Dienstag, 1999). Treatment with IFN alpha, however, has several disadvantages. The criteria for increasing the likelihood of a good response to therapy with IFN alpha include adult-acquired disease, high baseline alanine aminotransferase (ALT) concentrations, low baseline HBV DNA concentrations, absence of liver cirrhosis, and female gender (Gitlin, 1997 and Lee, 1997). Most chronic hepatitis B patients, however, particularly in endemic regions, do not fit this profile and thus have a reduced probability of responding to treatment. Because of its mode of action, use of IFN alpha is also only successful in patients with active immune responses, making it ineffective in patients infected with human immunodeficiency virus (HIV) and dangerous in those who have undergone organ transplantation. Furthermore, Asian patients, who make up three-quarters of the world's HBV carriers, respond relatively poorly to IFN alpha (Lai et al., 1998). Treatment is expensive and must be administered by injection. Moreover, IFN alpha is poorly tolerated, with side-effects including influenza like symptoms, injection-site reactions, rash, weight loss, anxiety, depression, hair loss, thrombocytopenia, leukopenia and thyroid disorders (Vail, 1997). The development of modern nucleoside analogues, such as lamivudine and famciclovir, has launched a new era in the treatment of hepatitis B (Rosenberg and Dienstag, 1999). These agents block viral replication directly by inhibition of the HBV polymerase. To date, lamivudine is the only nucleoside analogue to have been approved for the treatment of chronic hepatitis B; other nucleoside analogues have been shown to have much less efficacy (famciclovir), or to be poorly tolerated (lobucavir) (Dusheiko, 1999). Studies with lamivudine have shown that it reduces rapidly HBV replication and suppresses HBV DNA to undetectable levels after

only a few weeks of treatment (Tyrrell et al., 1993; Dienstag et al., 1995; Nevens et al., 1997 and Lai et al., 1997). Longer-term trials (1–2 years) have shown that lamivudine reduces significantly hepatic necro-inflammatory activity and the progression of fibrosis, and normalises serum ALT concentrations in both Asian and western patients (Dienstag et al., 1998; Lai et al., 1998 and Liaw et al., 1998). Because lamivudine acts by inhibiting the synthesis of new viral DNA, and not by destroying directly the covalently closed circular HBV DNA that is already present in the hepatocytes (Rosenberg and Dienstag, 1999), HBV DNA will often recur after cessation of therapy. Lamivudine, however, is well tolerated (Lai et al., 1998) and long-term therapy will probably address this limitation. Although treatment with lamivudine for 1 year is as effective as a standard course of IFN alpha with respect to rates of hepatitis B e antigen (HBeAg) loss and seroconversion (defined as HBeAg-negative, antibodies to HBeAg [anti-HBe]-positive, HBV DNA-negative) (Rosenberg and Dienstag, 1999), lamivudine has advantages over IFN alpha in terms of better tolerability and mode of administration (oral). Probably the most important advantage of lamivudine over IFN alpha, in terms of global treatment of chronic hepatitis B, is that it seems to be effective in suppressing HBV replication irrespective of the patients' sex, ethnicity, disease severity or mode of acquisition of HBV infection. Lamivudine thus offers a promising new treatment option for patients with chronic hepatitis B, with particular utility in those for whom previous therapies were unavailable, contraindicated or ineffective. As with all antiviral therapies, lamivudine is associated with the emergence of strains of HBV that are less sensitive to treatment. The YMDD (tyrosine-methionine- aspartate-aspartate) motif is located in the nucleotide-binding pocket of the viral DNA polymerase, and mutations in the gene coding for this region cause reduced sensitivity to lamivudine (Allen et al., 1998 and Lai et al., 1998). Despite the emergence of YMDD variants, however, patients maintain clinical benefit from sustained lamivudine therapy (Rosenberg and Dienstag, 1999). It has been suggested that combination therapy with two or three nucleoside analogues or combination with IFN alpha treatment might delay or prevent the emergence of viral resistance (Lee, 1997, Rosenberg and Dienstag, 1999).

III. RESULTS AND DISCUSSION

Hepatitis B virus (HBV) is responsible for a substantial proportion of cases of post-transfusion hepatitis, liver cirrhosis and hepatocellular carcinoma (Torbenson et al., 2002). An estimated 2 billion people are infected with HBV worldwide, among them 350 millions are chronic carriers: hepatitis B surface antigen (HBsAg) positive (WHO, 2000). HBsAg positivity in developed countries varies from 0.6 percent in Wales, England, to 1.2 percent in Texas, USA. However, higher prevalence of infection with HBV has been reported from various parts of the developing world including 3.5% in Gaza, Palestine (Yassin et al., 2002). 1.6%–7.7 % in Brazil (Arboleda et al., 1995), 19.6 % in Egypt (el-Sayed et al., 1997), 2%–10 % from various parts of India (Chowdhury et al., 1999).In Pakistan, it is estimated at around seven million,that is about 5% of the world wide 350 million carriers of hepatitis B (Wasim et al., 2006). The World Health Organization (WHO) Assembly endorsed the recommendation of its Global Advisory Group that all countries should implement a hepatitis B immunization program (WHO, 1992).These vaccines contain non-glycosylated HBV small S protein as the envelope antigen which must be released from the yeast during the manufacturing process (Stephenne, 1990).The transmission risk of these diseases increases among persons who are given unsterilized therapeutic injections, patients with thalassaemia, patients on haemodialysis and persons who have their faces or armpits shaved by street barbers (Bhatti, 1995).

IV. CONCLUSION

It has been concluded from the present literature survey that in Pakistan, Hepatitis B is an emerging disease. Polymerase chain reaction (PCR) based diagnostic test are now used for the diagnosis of Hepatitis B for accurate and precise results. Many research institutes in pakistan including, Institute of Biomedical and Genetic Engineering Islamabad (IBGE) are performing research on molecular level of HBV which should be further accelerated to make it common to prepare recombinant vaccine against HBV and to make it easily accessible and economical throughout the country to reduce the risk of infection. Awareness programs about HBV infection and transmission are needed to be launched by the government especially in rural areas of Pakistan where the prevalence is much more high and increasing day by day due to unawareness.

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