The Emergent Concern of Hepatitis B globally with special attention to Kingdom of Saudi Arabia

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Abstract

Chronic viral hepatitis is highly prevalent and creates a substantial burden to healthcare systems globally. The World Health Organization (WHO) estimates that over 350 and 250 million people worldwide are chronic carrier of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection respectively. These two diseases are the cause of significant global mortality and morbidity with approximately 1 million deaths each year attributable to them and their sequelae, liver disease and primary liver cancer. Although the efforts have been met with the long-lasting level of success and holds the promise for large reductions in disease burden in spite of the huge numbers of HBV infected population. The viral hepatitis has also been emerged as a leading public health concern and continues to be major disease burden in the Eastern Mediterranean. The WHO, estimates that approximately 4.3 million persons are infected with HBV in the Region each year. Saudi Arabia has been classified as a country with an intermediate prevalence of HBV showed up to 7% in Saudi children in late 1980s but declined to as low as 0.3% in 1997 since the introduction of universal vaccination of all Saudi children in 1989. In spite of this remarkable decline, the burden of decompensated liver disease secondary to hepatitis B is estimated to increase drastically in the next 40 years as the previously infected children start aging.

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Introduction

Hepatitis B virus has been considered to be one of the most serious and prevalent health problems, affecting more than 2 billion people worldwide. The availability of highly effective vaccine against HBV since 1982 could not avoid the current status of chronic carriers of the disease which has been reached to more than 350 million. HBV is carried in blood and in other body fluids including saliva, tears, semen and vaginal secretions and can be transmitted from person to person by a variety of means depending on the epidemiologic pattern within a geographic area. As suggested by WHO, the infection of HBV early in life is associated with the highest risk of chronic infection, and progression to liver cirrhosis and Heaptocellular carcinoma (HCC). About 90% of infants infected with hepatitis B virus around the time of birth, 30% of children infected in early childhood and 6% of those infected after five years of age will develop chronic hepatitis B virus infection. It has also been observed that the people with chronic hepatitis B (CHB) have a 15% to 25% risk of dying prematurely from HBV associated liver cirrhosis or HCC and 0.5 to 1.2 million people die annually from HBV infection (WHO 2010). [1]

Sustained reductions in hepatitis B seroprevalence and hepatitis B-related deaths have been observed in countries where universal infant vaccination against hepatitis B is in place. The benefits of infant immunization are most prominent in the countries, previously of high hepatitis B endemicity. [2] Still the viral hepatitis is the cause of significant morbidity and mortality, impose a great burden on country's health care system regardless of significant decline in the prevalence of HBV. In 2007, the Saudi Ministry of Health (MOH) ranked viral hepatitis as the second most common viral disease after chickenpox, with almost 9000 new cases diagnosed in that year. This review describes an overview of HBV infection, epidemiology, immunization, and prevention with special concern to Kingdom of Saudi Arabia.

Viral Epidemiology and Genome Organization of HBV

The prevalence of chronic HBV infection is about 5% globally, varies between regions could be categorized as high, intermediate and low endimicity. Around 45% of the total world population live in areas where chronic HBV is highly endemic [i.e.≥8% hepatitis B surface antigen (HBsAg) positivity], 43% live in intermediate-endemicity areas (2-7% HBsAg positive) and 12% live in low-endemicity areas (<2% HBsAg positive) (WHO Europe 2007). In the Middle East, Saudi Arabia and Jordan are currently classified by the WHO as areas of high endemicity. [3-5]

Hepatitis B virus belongs to hepadnaviridae family is double-stranded DNA virus enveloped, and contains genome of about 3200 bps within its core. The HBV genome is delivered into the nucleus infecting hepatocytes where relaxed circular DNA is converted to covalently-closed-circular DNA (cccDNA) before replication. The HBV replication cycle comprises reverse transcription using cccDNA as a template of RNA intermediates to prime DNA synthesis and translation of the hepatitis B proteins including hepatitis B surface antigen (HBsAg) and e antigen (HBeAg). [6] Thus, cccDNA plays an active role in the development of chronic hepatitis B infection. Evidently, a number of studies have suggested the impact of HBV genotype on disease pathogenesis and the clinical outcomes in patients with chronic HBV. [7,8] HBV genotypes evolved over the years have a distinct geographical distribution with 8% inter-group discrepancy in the complete nucleotide sequence of HBV. It also includes distinct nucleotide homology of the surface gene, which results in different hepatitis B surface antigen (HBsAg) serotypes. [9-11] Apart from genotypes E and G, the subgenotypes have at least 4% difference in nucleotide sequence, [12] Genotype A is prevalent in northwestern Europe, North America and Africa; genotypes B and C in South-eastern Asian population; genotype D is mainly found in the Mediterranean basin, Middle East, and India; genotype E in west Africa; genotype F in South and Central America; genotype G is determined recently in the USA, Germany and France while genotype H has been described in patients from South America. [6,13-17] However several studies have shown a strong relationship between HBV genotypes and mutations in the precore and core promoter regions that abolish or diminish the production of hepatitis B e antigen (HBeAg). [18]

Hepatitis B virus pre-core mutations are most frequent in genotype D, followed by genotypes C and B, and are seen least frequently in genotype A. [19] Consequently, HBeAg-negative CHB occurs most frequently in genotype D dominant regions. Noticeably, 80-90% CHB patients were found HBeAg negative in Mediterranean areas, 30–50% in Southeast Asia, and less than 10% in the USA and northwestern Europe. [20] As reviewed by Abdo et al., the majority of Saudi patients infected with chronic HBV have genotype D and the same subpopulation of patients demonstrates higher HBeAg negativity by the age of 30. [21]

Transmission of HBV

HBV is transmitted through perinatal, sexual and parenteral/percutaneous exposure to infected blood or other body fluids. Perinatal transmission from carrier mothers to their babies is the most important factor in determining the prevalence of the infection in high endemic areas. It is estimated that approximately 90% of HBeAg-seropositive mothers (with high viral load) transmit HBV infection to their babies, compared with 10–20% of HBeAg-seronegative carrier mothers. [22] The data also suggests that the incidence of HBeAg is higher in Asian than in African HBsAg carrier mothers (40 *vs* 15%), so perinatal transmission is greater in Asians, but mainly horizontal in Africans. [23, 24]

In low endemic areas *i.e.* North America, the major source of HBV infection is sexual transmission which makes HBV to be considered as sexually transmitted disease (STD). As evident from studies that the highest risk of infection occurs in homosexual men. [25] The risk of HBV infection in heterosexuals is associated with duration of sexual activity, sexual partners of injection drug users, and numbers of sexual partners. [26]

The important mode of parentral transmission is sharing and/or reusing of syringes between injection drug users for drug with HBsAg-positive people. It is estimated that 23% patients were found positive for HBsAg through injection drug of all HBV infected patients in United States and Western Europe. [27] Parenteral/percutaneous transmission can occur during surgery, after needle-stick injuries, intravenous drug use, and the procedures such as ear piercing, tattooing, acupuncture, circumcision and scarification. [27] As with additional modes of transmission, working or residing in a health-care setting, living in a correctional facility, tattooing, renal dialysis and others who are likely to come into contact with potentially infected blood and blood products have been related to risk of transmission. Several studies show a high frequency of needlestick injuries and other percutaneous exposures to blood among health care workers in the eastern Mediterranean region including Saudi Arabia. [28-31] WHO reported approximately 10,000 HBV due to occupational exposure among health care workers in the same region. [32] As evident from the studies, there are high number of individuals have potential risk for transmission of blood-borne diseases to doctors, laboratory technicians, blood bank workers, nurses, personnel working in renal dialysis and transplant units, and other health care workers. [33] The sub-clinical cases of hepatitis are of main concern to the health care workers due to the absence of precaution measures when treating them, which eventually would lead to transmission of infection to persons in direct contact and subsequently to other patients. The risk of chronicity is low (less than 5%) for transmission through parentral mode as this acquires HBV infection during adolescence or adulthood without immune tolerance. Instead, the disease progress directly to the immune clearance phase and is of short duration, which possibly accounts for immediate recovery. [34]

Prevention

Keeping the routes and modes of HBV transmission into consideration, the prevalence can be interrupted. Obviously, routine serological screening of donor blood ensure considerable decline in transfusion-associated HBV. [35] It has been noted that free sterile syringes are provided in exchange for used syringes through Syringe-exchange programmes in the USA and other high-income countries to reduce transmission of blood-borne pathogens including HBV in injection drug users. It is also suggestible to run the syringe-exchange programme making contact with hard-to-reach population at fixed sites and on mobile van routes to deliver social and medical services, such as testing for HBV, counselling, and vaccination. [36]

The implementation of national programmes for infection control management have substantial challenges and regional efforts are needed to promote in the development of guidelines, training materials and a "health systems" approach to ensure high quality care. The civil society organization including Middle East and North Africa Harm Reduction Association (MENAHRA) and three sub-regional hubs continue to provide knowledge to injection drug users. WHO provide technical support, undertaking advocacy actions at country and regional levels to civil society organizations to establish or scale up harm reduction programmes. There are some provinces in Pakistan with highest prevalences of injection drug users where needle and syringe programmes are achieving the large scale coverage. The countries like Afghanistan, Egypt, Lebanon, Morocco and Oman also have support from WHO to provide harm reduction services to injection drug users. [37]

Following the introduction of effective vaccine for HBV in early 1980s, the addition of HBV vaccination was recommended to all national immunization programmes by WHO. Universal immunisation programme for new born babies, international financial support and reduced cost of vaccine in low-income have resulted in a dramatic reduction in HBV transmission in many countries with historically high endemicity. [38] The strategy of selective vaccination is applied for individuals at high risk of infection in high-income countries with low endemicity of HBV such as northern Europe. [39]

Since the introduction of HBV immunization, infection has been fallen down across the world. For example, the HBsAg carrier rate in Taiwanese children reduced from 10% to less than 1% from 1984-2004, with a 68% decrease in fulminant hepatitis in infants (0–1 year), and a 75% decline in HCC in children (aged 6–14 years). [40,41] Amazingly, the incidences of acute HBV were fallen by 81% from between 1990 and 2006 in USA and not many cases were found in blood recipients, dialysis patients, and health-care workers as well. [6] The recombinant DNA vaccine contains HBsAg from genetically engineered yeast (Saccharomyces cerevisiae). The vaccine has showed potential effect of more than 95% in preventing chronic infection with HBV up to 8 years after immunization of children born to hepatitis B carrier mother. [42-45] This study assessed long term antibody persistence and immune memory 20 years after primary vaccination during infancy with HBV vaccine (Engerix TM-B). [46] The cohort studied included individuals born to hepatitis B carrier mothers.

The epidemiology of HBV infection is very convoluted in the Eastern Mediterranean Region. There was the wide range of HBV prevalence from 2%-3% in several member states, to >10% in Somalia and Sudan prior to the introduction HBV vaccine into the expanded programme on immunization (EPI). Noticeably, the transmission of HBV continues among unvaccinated older children and adults irrespective of the introduction of HBV vaccine into EPI. [3, 47-49] Several studies indicate that >90% patients infected with acute HBV were born before the introduction HBV vaccine. [49, 50] It was estimated that 7 % of Saudi children were found positive for HBsAg in late eighties. The incidence of HBV infection was reduced to 0.3% in 1997, after the introduction of universal vaccination of all Saudi children in the year 1989. Despite this significant reduction, the burden of decompensate liver disease secondary to HBV is likely to increase drastically in the next 40 years as the previously infected children start aging. [51, 52]

As the follow-up of post-vaccination, the studies were executed on cohorts of children 2 years of age and the children of 1-12 years old who had received the HBV vaccine at birth. Amazingly, the significant reductions in the prevalence of HBsAg to minor numbers were observed, establish the efficacy of HBV vaccine. [51,52] Consequently, In 2008, Al-faleh et al. reported the absolute absence of HBsAg or anti-hepatitis B core antigen (HBc) detection among a cohort of students of 10-12th grade selected randomly from high (Aseer), low (Al-Qaseem), and moderate (Madinah) HBV endemic regions, 18 years after the vaccination. [53] According to data compiled by General Directorate for communicable Diseases, Ministry of Health, Riyadh, it was found only 1.31% HBV positive subjects among the individuals who were willing to get married undergoing premarital screening from January to May 2008. [54] Evidently, the monitoring of childhood HBV vaccination in cross-community data illustrates the

prevalence of 0.05% and 0.22% among children and adults respectively. The average reported incidence was 0.15% with wide variations occurring between regions that ranged from 0.03% to 0.72%. [55,56] Recently, I observed the increasing prevalence of HBV in males (0.9 to 2.0 %) and females (0.5 to 0.8 %) both (0.7 to 1.4 %) for the calendar years 2008 to 2010 who visited King Fahad Hospital, Buraidah for premarital screening [57] for it is also suggested to conduct such type of surveys in the countries *i.e.* Egypt, Sudan, Djibouti where the prevalence of HBsAg is high but do not provide a birth dose and settings. The application of HBV vaccine at birth is very important where the prevalence of HBsAg is high though it is recommended by EPI in all countries.

Conclusions and Recommendations

As suggested from various studies the prevention of viral hepatitis in KSA has contributed to the great reduction in prevalence rates of HBV on some aspects which needs to be continued. The control and prevention of HBV infections require continuous monitoring as well as evaluation of prevention and surveillance strategies. Despite significant improvements in hygiene practices, screening, education messages, sterile needles, as well as blood transfusion safety and blood product treatment, the incidence of HBV infection continues to rise in Saudi Arabia. The increasing development cannot be easily interpreted as it may also partly reflect the results of intensified screening activities, improved surveillance, and accurate testing methods. Keeping these views into consideration, HBV to be an increasing public health concern in Saudi Arabia in the coming decades, calls for appropriate public health action. Therefore, public should have awareness concerning consequences, effect, treatment and precaution through health promotion programs and community service education. Health promotion programs for public need to be targeted and based on a thorough understanding of their knowledge, belief and cultural practices regarding viral hepatitis. Proper education for people, especially young individuals, will be an effective tool in reducing the spread of HBV within the kingdom.

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