

HEPATITIS B VIRUS AND HEPATOCELLULAR CARCINOMA

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Abstract

Globally, WHO estimates that 350 million individuals are infected with HBV and that HBV is endemic in sub-Saharan Africa and regions of Asia. Hepatitis B is a major risk factor for hepatocellular carcinoma. Hepatitis B is treated with oral nucleoside reverse transcriptase inhibitors. **Bolognese J. Hepatitis B Virus and Hepatocellular Carcinoma. Med J Therapeut Africa. 2007;3:229-3.**

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INTRODUCTION

Hepatocellular carcinoma is a frequent complication of infection with the hepatitis B virus (HBV) and globally is the eighth most frequently diagnosed type of cancer. In the United States, where vaccination against HBV is more common, 1.25 million Americans are estimated to harbor the hepatitis C virus (HCV).(1) Globally, WHO estimates that 350 million individuals are infected with HBV and that HBV is endemic in sub-Saharan Africa and regions of Asia.(2,3)

Extensive inflammation of the liver contributes to fibrosis and eventual cirrhosis, or scarring of the liver.

HBV LIFE CYCLE

HBV life cycle described here has been summarized from ref 2. HBV is classified as a hepadnavirus, consisting of HBcAg, the nucleocapsid core and an outer lipoprotein coat that displays HBsAg, the surface antigen. Infection of the host is initiated when the HBV virion associates with a hepatocyte receptor, and the viral nucleocapsids permeate the cell. Subsequently, the viral DNA navigates to the nucleus, where it becomes integrated with the host DNA. Following transcription of the DNA into viral RNAs, translation events in the cytoplasm yield the viral nucleocapsid, precore antigen, polymerase, envelope protein, and transcriptional transactivating protein. Encapsulation of pregenomic RNA (pgRNA) into core particles, along with polymerase and protein kinase, allows the reverse transcription of RNA to DNA. Nascent viral nucleocapsids interact with envelope proteins in the endoplasmic reticulum. After entering the endoplasmic reticulum lumen, the nucleocapsids reach the Golgi apparatus and are ultimately released as virions which continue in the

infectious cycle.

Transmission

Perinatal or vertical transmission of HBV from mother to infant is typical in vulnerable areas of Asia. Horizontal transmission is more characteristic of African populations, where HBV is transmitted among young children under 5.(2)

Alternatively, HBV can be acquired parenterally through direct contact with blood or other bodily fluids. Recipients of blood transfusions in developing countries with more permissible screening of blood donors are at risk. Use of unsterile needles and unprotected sexual intercourse also places an individual at higher risk for HBV.(3)

Progression of HBV

Acute versus chronic infection with HBV assumes different courses, according to ref 2. Humans with acute infection may clear the virus within 2 months, but this is more common among those infected with HBV as adults. Infants and small children infected with HBV are more likely to have chronic HBV infection as they grow. HBV infection is estimated to be in 60 to 80% of all incidences of hepatocellular carcinoma. Persistent bouts of liver inflammation after infection with HBV increase the likelihood of developing hepatocellular carcinoma, or primary liver cancer. Cirrhosis may compound the prognosis of individuals with HBV by causing an elevated propensity for hepatocellular carcinoma. Cirrhosis impedes natural venous blood flow, where fibrotic tissue supplants apoptotic hepatocytes.(2) Consequently, overall liver function is compromised and the damage is typically irreversible.

Detection

According to the CDC, immediately proceeding infection with HBV, approximately 50 to 60% of individuals will be asymptomatic. In other individuals, symptoms may manifest as feelings of exhaustion and enervation, decreased appetite, jaundice, and abdominal discomfort.(1)

Symptoms that are possibly attributed to HBV can be confirmed through a series of liver assessment tests. Quantification of liver enzymes, such as ALT, AST, and alkaline phosphatase should be considered in conjunction with total bilirubin, prothrombin time, and albumin levels. Presence of specific antigens and antibodies, such as HBsAg and anti-HBsAg,

respectively can further solidify diagnoses.(2)

Vaccination

Aside from minor irritation at the site of injection, the HBV vaccine is reported to be well tolerated, according to an observational study of Gambian children.(4) It is given by intramuscular injection into the thigh of infants or the deltoid of children and adults.(2)

The vaccine can be derived from the plasma of donors who are positive for HBSAg, though more innovative technology has rendered that formulation more obsolete. In this method, the virion particles are inactivated by heat and therefore nonvirulent when injected into the recipient of the vaccine. Utilizing recombinant DNA from yeasts or mammalian cells hastens the preparation process. It is advantageous when infants born to mothers with HBV receive both passive and active immunization simultaneously. Passive immunization refers to supplementation with immunoglobulin, while active immunization is vaccination.(2)

Introduction of the hepatitis B vaccine in other areas of the world allows infants greater access to this preventative measure. In 1999, the Global Alliance for Vaccines and Immunization (GAVI) extended immunization access to 53 developing countries, including 23 in Africa. The following mathematical model was used to project that over 4,000 chronic HBV deaths were evaded in Mozambique after dissemination of the vaccine:(5)

$$\text{DEATHS} = \frac{\text{SURVIVORS} \times \text{PROBABILITY HBSAG CARRIERS} \times \text{RISKS FROM HCC OR CIRRHOSIS}}{\text{PROBABILITY HBSAG CARRIERS} \times \text{RISKS FROM HCC OR CIRRHOSIS}}$$

Researchers suggested that savings in health costs from the vaccine would be more apparent in the absence of premature deaths from HIV, occurring before the mean age (40 to 60 years) of HBV-related deaths.(5)

A vaccination campaign was initiated throughout China in an effort to combat initial infection with the virus, which typically occurs during early childhood or infancy. This is documented on the World Health Organization (WHO) website, as is the WHO observation that HBV is endemic in China.

According to the United States Centers for Disease Control, 60% of the total population of China is infected with HBV. Additionally, the deaths of 263,000 inhabitants can be attributed to the progression of HBV into liver disease. Over 5 years, approximately 5.6 million children were given the vaccination. The National Vaccination Coverage Society strove to evaluate the effectiveness of this early intervention that entailed a 3-dose administration of the vaccine, with the first dose ideally given within 24 hours of birth.(6)

Treatment

Lamivudine (LMV), adefovir (ADV), telbivudine (Ldt), and entecavir (ETV) are oral HBV nucleoside reverse transcriptase inhibitors (NRTIs).

NRTIs are indicated for chronic HBV therapy, and inhibit viral polymerase (Pol).(8)

The NRTIs differ structurally according to the ribose isotope. Telbivudine includes L-configured riboses; entecavir contains a D-configured ribose and adefovir consists of an acyclic isotope. Extended use of NRTIs may cause the virus to confer resistance over time and cause unresponsiveness to continued antiviral treatment. Therefore, it is beneficial to have 4 distinct NRTIs as a way to offer multiple therapy options.(7)

Different structural configurations relate to functional variance between the NRTIs that are currently prescribed for chronic HBV. The mechanism of action of entecavir is thought to be by arresting HBV DNA elongation by becoming integrated into the lengthening chain following the addition of several base pairs. Entecavir has greater efficacy at lower concentrations than other NRTIs, which act to induce termination of the DNA chain. With its alkyl chain isotope, adefovir exists as a prodrug, meaning it must be metabolized into an active form before it can exert its therapeutic effects.(7)

A double-blind, placebo-controlled study was conducted to evaluate the efficacy of 100 mg daily doses of LMV in individuals who had been diagnosed with chronic HBV. The LMV treatment group consisted of 436 patients, while 215 patients were randomized to the placebo group. Ethical considerations and advisement of the safety monitoring board led to an interruption in the blinding procedures due to observed improvements in the treatment group receiving LMV. Subjection to an average course of LMV therapy of 32 months accounted for about a 50% decline in disease development.(8)

Aside from NRTIs, interferon is intended to lower HBV DNA levels, while also impeding the development of cirrhosis or hepatocellular carcinoma from HBV. In a pilot study involving 219 patients with HBV, 94 received interferon for over 6 months, while 219 refrained from interferon or antiviral treatment. After adjusting for covariables, the incidence rate of hepatocellular cancer after 10 years among patients who were administered interferon was 7.0%. Meanwhile, the incidence rate of hepatocellular cancer after 10 years among patients who did not receive treatment was 30.8%.(9)

Flu-like symptoms have been reported among individuals who take interferon, which may influence patient compliance.(10)

Peginterferon is thought to be associated with enhanced pharmacokinetic properties. Peginterferon consists of a branched polyethylene glycol attachment to interferon alfa-2a. In a study where patients

with HBV were assigned to receive peginterferon alfa-2a, lamivudine, or a combination of both treatments, a decline in HBV DNA levels to less than 20,000 copies per mL was more significant for patients receiving peginterferon alfa-2a monotherapy than lamivudine monotherapy. Of the 177 patients assigned to receive peginterferon alfa-2a monotherapy, 43% had a notable drop in HBV DNA. Of the 181 patients assigned to receive lamivudine monotherapy and the 179 patients assigned to receive combination therapy, 29% and 44% had decreased HBV DNA levels, respectively.(11)

Aflatoxin Exposure

Commonly stored food staples throughout Africa, such as groundnuts and maize, are potentially subject to fungal contamination. *Aspergillus flavus* and *Aspergillus parasiticus* are 2 species of fungi that generate aflatoxins. Aflatoxins are immunosuppressive and may have an ancillary affect on the development of hepatocellular carcinoma among individuals with HBV.(12)

In the liver, aflatoxins are converted by cytochrome P450 enzymes to AFB1-8,9-epoxide, a carcinogenic metabolite. AFB1-8,9-epoxide is capable of binding to DNA strands and inducing the transversion of guanine to thymine. Consistent with a study conducted by Kirk et al, genetic variability in the degree to which the resultant AFB1-N7-guanine adduct is metabolized can increase an individual's proclivity for hepatocellular cancer. Glutathione S-transferase facilitates conjugation of the unstable epoxide to reduced glutathione, thereby stymieing formation of the pro-mutagenic adduct. A deletion polymorphism in glutathione S-transferases, GSTM1 and GSTT1, will interfere with this protective mechanism.(7)

Levels of aflatoxin exposure vary perennially in tropical regions of Africa. Consumption of food that is stored during the dry season correlates with higher levels of aflatoxin in peripheral blood.(14) Meanwhile, fresh food is produced from the harvest at the end of the rains that constitute the rainy season from July to November.(12)

In Kenya, a severe hepatotoxicity outbreak coincided with a pervasive contamination of maize with aflatoxin in April 2004. Maize products were assessed to determine aflatoxin levels, which per health regulations are not to exceed 20ppb. Exposure to the contaminant was rampant, with over 55% of the samples peaking at levels higher than 100ppb.(15)

Conclusions

A combination of genetic and environmental factors influences infection by HBV and whether hepatocellular cancer follows. Early vaccination can prevent or delay HBV infection and education and awareness programs are likely to change behavior that decreases the quality and length of life. Additionally, more

standard inspections to evaluate food safety and replace any food suspect of mold infestation would help to limit extraneous exposure to aflatoxins in Africa.(14) An understanding of the interplay of causal variables in the onset of hepatocellular cancer is needed to alleviate its global burden.

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