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Modern Principles of the Etiology and Pathogenesis of Viral Hepatitis

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Abstract: Viral hepatitis B (HBV) is one of the most significant modern health problems, affecting millions of people worldwide. This infectious disease caused by the hepatitis B virus can lead to serious health consequences, including chronic infection, liver cirrhosis, and primary liver cancer (hepatocellular carcinoma). Despite significant progress in the development of diagnostic and treatment methods, HBV remains a global problem that requires close attention and effective control measures.

Keywords: viral hepatitis, DNA virus, Dane particle, viral hepatitis B, Vaccines, hepatitis B prevention measures, spread of infection.

Relevance. The hepatitis B virus (HBV) virion, also known as the Dane particle, contains a partial double-stranded DNA genome, a core protein (HBcAg), viral DNA polymerase (reverse transcriptase), and a surface protein (HBsAg). HBV replication is unique in that it uses the enzyme reverse transcriptase to convert its pregenomic RNA into genomic partial double-stranded DNA. HBV is the cause of what was previously known as “serum hepatitis” to distinguish it from “infectious hepatitis” (HAV). HBV is transmitted by sexual intercourse, sharing needles and syringes, injecting drugs, blood and blood products, and mother-to-child transmission. The incubation period is 30-160 days, averaging 60-90 days.

In the liver, pathogenesis is mainly immune-mediated, including serum sickness such as rash, arthritis, and development of jaundice (symptoms similar to acute hepatitis A) due to circulating immune complexes that activate complement and cause liver injury. In addition, accumulation of immune complexes in the kidneys leads to renal injury. Antibodies to HBsAg are protective and promote disease resolution. About 90% of patients are cured of the infection after an acute illness, which may be asymptomatic; however, 10% of patients develop chronic infection, probably due to insufficient cellular immunity. If the virus is transmitted from mother to child, its chronicity is greater than 90%. Chronicity can lead to liver cirrhosis with an increased risk of developing HCC.

Acute diagnosis is based on the presence of HBsAg and IgM to HBcAg, and chronic diagnosis is based on HBsAg (more than 6 months) and IgG to HBcAg. Treatment of chronic infection includes alpha interferon and reverse transcriptase inhibitors. An effective subunit HBsAg vaccine is recommended for use in children aged 0 to 2 months, and in adults - in 3 doses at ages 0, 1 and 6 months, which provides long-term protection. Hepatitis B virus is widespread throughout the world.

According to WHO estimates, 240 million people worldwide are chronically infected with hepatitis B virus and more than 680,000 people die as a result of complications such as cirrhosis

and HCC. Prevalence rates vary markedly in sub-Saharan Africa and East Asia, where 5% to 10% of adults are chronically infected, most of whom may be asymptomatic. In addition, the Amazon region of South America, eastern and central Europe, the Middle East, and the Indian subcontinent have high rates of chronic infection. However, in North America and Western Europe, less than 1% of the population is chronically infected. About 10% of patients with HIV infection are chronic carriers of hepatitis B virus.

In the United States, the CDC reported that as of late 2014, there were an estimated 850,000 to 2.2 million people chronically infected with hepatitis B virus. HBV infection rates have declined since 1990 due to HBV vaccination and have remained stable since 2009. In 2014, there were 2953 new acute cases of HBV, an estimated 6.48 times the number of cases reported (19,200 cases, range 11,000–47,000). About 200 to 300 of these patients die from acute fulminant hepatitis, and 5% to 10% of infected patients become chronic carriers of the hepatitis B virus. An estimated 3000 to 4000 people die each year from hepatitis B virus-associated cirrhosis, and 1000 to 1500 people die from HCC.

The virus is spread vertically, parenterally, and sexually. Approximately 50% of infections in the United States are sexually transmitted, and the prevalence of serum HBsAg is higher in certain populations, such as men who have sex with men, patients on hemodialysis or immunosuppressive therapy, patients with Down syndrome, and injection drug users. Routine screening of blood donors for HBsAg and antibodies to HBcAg (anti-HBcAg) has significantly reduced the incidence of hepatitis B transmission following blood transfusions and plasma products. Cases still occur with the use of several types of blood products. Exposure to hepatitis B viruses through direct contact with blood or other body fluids, possibly from needlestick injuries, increases the risk of hepatitis B infection in health care workers. Transmission is also common among sexual partners of infected patients. Hepatitis B infection in infants is probably not transmitted trans placentally to the fetus in utero, but is acquired during delivery by ingestion of infected blood or fluids, or through abrasions. The incidence of viral infection is high (up to 90%) in infants born to mothers with acute hepatitis B infection or who are carriers of HBsAg and HBeAg BEAG.

Most infants do not develop clinical disease, but infection in the neonatal period is associated with a failure to produce antibodies to HBsAg and cell-mediated immune responses, probably due to an immature immune system, resulting in chronic carriage in more than 90% of infected neonates. Serologic testing and the detection of viral nucleic acid sequences integrated into tumor cell genomes have strongly associated HCC with persistent carriage of hepatitis B virus. In many parts of Africa and Asia, primary liver cancer accounts for 20% to 30% of all malignancies, but in the Americas and Europe, it is only 1% to 2%. The estimated risk of developing malignancy in individuals with chronic HBV infection is up to 10-fold and more than 300-fold in different populations. The risk of developing HCC is further increased in patients with chronic hepatitis B and a high viral load.

In the past, hepatitis B was known as post-transfusion hepatitis or as hepatitis associated with the use of parenteral drugs (serum hepatitis). However, in the last few years it has become clear that the main route of infection is close personal contact with the body fluids of infected people. HBsAg has been detected in most body fluids, including saliva, semen, and cervical secretions. In experimental conditions, infection was caused by exposure to as little as 0.0001 ml of infected blood. Thus, transmission is possible through such means as improperly sterilized hypodermic needles and instruments used in tattooing and ear piercing.

The factors that determine the clinical manifestations of acute hepatitis B are largely unknown; however, some of them seem to be related to the body's immunological reactions. Serum disease-causing rash and arthritis that may precede the development of symptoms and jaundice appear to be related to circulating immune complexes that activate the complement system. In addition, accumulation of these immune complexes in the kidneys leads to renal injury. Antibodies to HBsAg are protective and are associated with disease resolution. Cellular immunity may also

play an important role in the host response, as patients with deficient T-cell function are more likely to become chronically infected with HBV. However, CTLs cause liver injury by destroying infected cells. Antibodies to HBcAg, which are produced during infection, are present in chronic carriers with persistent production of hepatitis B virions and do not appear to be protective.

The morphologic changes in acute hepatitis B resemble those seen in other hepatitis viruses. In chronic active hepatitis B, the persistent presence of inflammatory foci of infection leads to hepatocyte necrosis, destruction of the reticular structure of the liver, and progressive fibrosis. Increasing fibrosis may lead to postnecrotic cirrhosis syndrome. Integrated hepatitis B virus DNA can be detected in almost all HCCs. It has not been proven that the virus has a transforming gene, but it may well activate a cellular oncogene. It is also possible that the virus does not play a direct molecular role in oncogenicity, since the natural history of chronic hepatitis B includes cycles of liver cell injury or death alternating with periods of intense regenerative hyperplasia. This significantly increases the likelihood of spontaneous mutational changes that can activate cellular oncogenes.

The hepatitis B virus transcription transactivator protein, HBx, is known to activate Src kinase, which may influence hepatitis B virus-induced carcinogenesis. HBx has been shown to interact with the tumor suppressor gene, p53, which may lead to the development of oncogenesis and HCC. Whatever the mechanisms, the association between chronic hepatitis B and hepatoprotection can be proven. Group B infection and HCC are obvious, and liver cancer is a major cause of morbidity and mortality in countries where chronic hepatitis B infection is common. The proven success of combination therapy with active and passive immunization to prevent hepatitis B infection in infancy and childhood makes HCC a potentially preventable disease.

The clinical presentation of hepatitis B is highly variable. The incubation period can range from 30 days to 180 days (average about 60-90 days). Acute hepatitis B usually presents with a gradual increase in fatigue, loss of appetite, nausea, and pain and distension in the right upper abdomen. Joint pain and swelling, and sometimes frank arthritis, may occur early in the disease. Some patients develop a rash. As liver damage increases, cholestasis increases, resulting in clay-colored stools, dark urine, and jaundice. Symptoms may persist for several months before finally resolving. Generally, the symptoms associated with acute hepatitis B are more severe and last longer than those associated with hepatitis A; however, icteric conditions and asymptomatic infection occur with acute hepatitis B. The infection to disease ratio, which varies with patient age and route of infection, is estimated to be approximately 3:1. Fulminant hepatitis, leading to extensive liver necrosis and death, occurs in less than 1% of cases.

One important difference between hepatitis A and hepatitis B is the development of chronic hepatitis, which occurs in approximately 10% of all patients with hepatitis B infection, with a much higher risk in neonates (~90%), children (~50%), and the promise of immunocompetent treatment. In immunocompetent adults, a strong cellular immune response leads to acute hepatitis and only rarely (~1%) to chronic hepatitis. Chronic infection is associated with ongoing viral replication in the liver and, as a rule, the presence of HBsAg in the serum.

Chronic hepatitis may progress to cirrhosis, liver failure or HCC in 25% of patients. During the acute episode of the disease, when active viral replication occurs, large amounts of HBsAg and HBV DNA, as well as fully formed virions and high levels of DNA polymerase and HBeAg, can be detected in the serum. Although HBcAg is also present, antibodies against it (anti-HBc) are always present and prevent the detection of HBcAg. After recovery from acute hepatitis B, HBsAg and HBeAg disappear from the serum with the production of antibodies (anti-HBs and anti-HBe). There is a short “window” period or equivalence zone characterized by the disappearance of HBsAg and preceding the appearance of anti-HBs. During this winter period, HBsAg and anti-HBs are absent, but anti-HBc (IgM) is present (anti-Hbe may also be present). Anti-HBs production is associated with the clearance of infection and protection against

reinfection. Anti-HBc is detectable early in the course of the disease and persists in serum for many years. It is an excellent epidemiological marker of infection, but is not protective.

Laboratory diagnosis of acute hepatitis B is best made by measuring serum antibodies to HBsAg and IgM to HBcAg, since these antibodies disappear within 6 months after acute infection. Almost all patients who develop jaundice are anti-HBc IgM positive at the time of clinical manifestations. Past hepatitis B infection is best determined by detecting IgG antibodies to HBcAg, HBsAg, or both, whereas the vaccine induces only antibodies to HBsAg. While HBV antigens and antibodies are detected by enzyme immunoassay, HBV DNA is detected by PCR.

Patients with chronic hepatitis B may show evidence of viral persistence in the serum. HBsAg may be detectable throughout active disease, and anti-HBs is not produced, which probably explains the chronic course of the disease. However, anti-HBc (IgG) is detected. Two types of chronic hepatitis can be distinguished. In one type, HBsAg is detected but not HBeAg; these patients usually have progressive liver dysfunction. In the other, both antigens are detected; the development of antibodies to HBeAg is associated with clinical improvement. Chronic hepatitis B infection is best identified by the presence of HBsAg in the blood for more than 6 to 12 months.

Progression of liver disease is associated with HBV DNA levels greater than 1,000 IU/mL (5,600 copies/mL). Individuals with hepatitis B virus levels below 1,000 IU/mL and normal liver function have a low risk of disease progression. Hepatitis B virus DNA testing is used to determine the effectiveness of antiviral treatment. In addition, a new test has recently been approved that will quantify HBsAg levels in patients infected with HBV, which can be used as a prognostic marker for antiviral drug effectiveness, disease progression, risk of liver damage, and signs of recovery.

Viral hepatitis B (HBV) remains a serious public health threat despite significant advances in diagnosis and treatment. The pathogenesis of HBV infection illustrates the complex relationship between the virus and the host immune system, which explains the diversity of clinical manifestations and the difficulty in achieving a complete cure.

Diagnosis of HBV requires a comprehensive approach combining serologic tests and imaging techniques to accurately assess the liver. Treatment is aimed at suppressing viral activity and preventing disease progression using antiviral drugs and supportive therapies. However, complete cure is achieved only in a small percentage of cases, which emphasizes the importance of prevention.

Effective prevention of HBV is possible through vaccination, which plays a key role in reducing morbidity and preventing the spread of infection.

Vaccination against hepatitis B should be carried out everywhere, especially among newborns, health care workers and people at risk.

In conclusion, the fight against HBV requires a multifaceted approach, including public awareness, regular screening, access to quality health care and an active vaccination campaign. Only through joint efforts can significant progress be made in controlling this disease and reducing its negative impact on public health.

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