Congenital Hepatitis B Virus (HBV) Infection

Konjenital Hepatit B Virus (HBV) Enfeksiyonu

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Summary
The hepatitis B virus (HBV) infection is the most prevalent chronic infectious disease in the world. Perinatal acquisition is the major cause of infection in infants and children. Without vaccine during infancy, 90 % of infants born to women positive for the virus will go on to become lifelong carriers. There are significant sequelae associated with HBV infection, ranging from fulminant HBV to chronic liver disease to an increased risk for carcinoma. In order to prevent liver cirrhosis and hepatocellular carcinoma in later life, it is essential to prevent HBV infection in infants. If the mother is chronically infected with HBV and is also positive for HBeAg, 8090% of the newborns become chronically infected, whereas if the mother is positive for antiHBe, only some newborns will develop acute hepatitis or fulminant hepatitis. It is necessary to screen pregnant women for HBsAg and prevent mothertoinfant infection of HBV, treating the infant with hepatitis B hyperimmune globuline at birth, followed by HBV vaccination.
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Key words: Hepatitis B virus, congenital infection, diagnosis, treatment, followup

Özet
Hepatit B virus (HBV) enfeksiyonu tüm dünyada en yaygın görülen kronik enfeksiyon hastalıklarından biridir. Perinatal olarak enfeksiyonun kazanılması infant ve çocuklarda görülen HBV enfeksiyonunun en sık nedenidir. HBV pozitif anneden doğan bebeklerin % 90`ı eğer yenidoğan döneminde aşılanmazsa yaşam boyu bu virus için taşıyıcı olarak kalırlar. HBV enfeksiyonu ile ilişkili belirgin sekeller bulunmaktadır ki bunlar fulminant HBV enfeksiyonundan kronik karaciğer hastalığına ve artmış hepatik karsinoma riskine kadar geniş bir aralıkda yer almaktadır. Bu çocuklar ileriki yaşamlarında karaciğer sirozu ve hepatoselluler karsinoma geliştirebilirler ve bu riski önlemek açısından yenidoğan döneminde HBV enfeksiyonunun önlenmesi çok önemlidir. Eğer anne HBV ile kronik olarak enfekte ve aynı zamanda HBeAg pozitif ise yenidoğanın kronik olarak enfekte olma oranı % 80-90` lara kadar çıkmaktadır. Anne eğer anti-HBe antikoru geliştirebilmişse bu durum bebek içinde koruyucu olabilmekte ve yalnızca bazı yenidoğanlar enfeksiyonu takiben akut hepatit veya fulminan hepatit tablosu geliştirmektedir. Anneden bebeğe HBV enfeksiyonunun geçişini önlemek amacıyla bebeğe doğumda hepatit B hiperimmunglobulin verilmesi ve bunu izleyerek aşı programına dahil edilmesi için tüm hamile kadınların HBsAg varlığı açısından rutin taranması çok önemlidir. *(Çocuk Enf Derg 2007; 1: 63-7)*

Anahtar kelimeler: Hepatit B virusu, konjenital enfeksiyon, tanı, tedavi, izlem

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Virology

HBV, the prototype member of the Hepadnaviridae family, has the distinguishing factors such as a circular, partially double-stranded DNA, and a lipid envelope formed of a unique antigenic protein called hepatitis B surface antigen (HBsAg). The antigen is found on the surface of the virus, the inner core of which contains a single copy of the endogenous DNA and a hepatitis B core antigen a(HBcAg), a third antigen initially related to infectivity and called hepatitis B e antigen (HBeAg), and a DNA-dependent DNA polymerase (1).

Pathogenesis

The only species infected by HBV seems to be human. Despite being hepatotropic, viral particles have been detected in various tissues and body

fluids. While HBV is not directly cytotoxic to liver cells, hepatocyte injury occurs as the body`s immunologic response to the virus (2).

The immunological events developing as a response to HBV infection and mediated by the cellular immune system include cytokine production (interferon alfa and interferon gamma), cytotoxic responses (natural killer [NK], cytotoxic T-cell, and antibody-dependent cellular cytotoxicity), and a T helper response to induce effective antibody production. Depressed T-cell responses constitute predisposing factors for chronic HBV infection (3).

Chronicity basically depends on the patient`s age at acquisition of infection. More than 90% of neonatal infections result in chronic infection, whereas only 5% of infections in adults become persistent. Cellular immune system immaturity or suppression of immune responses renders the neonate susceptible. Chronic infection due to immune suppression may be specific to HBV, possibly linked to the transplacental passage of soluble HBeAg, or be a nonspecific function of the fetal immune suppression normally occuring during gestation. After inoculation with infectious virions, HBsAg appears in the bloodstream of the susceptible host within 1 to 6 months during the acute phase of infection, with high levels of circulating virus and contagiousness. In that phase, there is a high risk of vertical transmission of HBV from mother to infant (4).

The specific risk depends on the timing of viral infection. HBV acquired during the first or second trimester poses a low risk of transmission (3%). Acute HBV during the third trimester of pregnancy increases the risk of transmission 78% without vaccine. In addition, all infants without vaccine will be infected if the mother has acute HBV at the time of delivery (5). While in older children and adults, production of virus is cleared by HBV-specific CD8+ and CD4+ lymphocytes through cytolytic and noncytolytic mechanism (6), in the neonate, following perinatal exposure, a chronic asymptomatic hepatitis with the histologic features of unresolved or persistent hepatitis the most common response (4).

The hepatocellular characteristics of infection in the newborn or during the first year of life have not been thoroughly defined. Early studies by Schweitzer and colleagues demonstrated that in 13 of 17 HBsAg-positive infants, no signs of acute clinical hepatitis were present (7). Although physical findings for 12 infants with persistent antigenemia remained normal, in one child, hepatomegaly and splenomegaly were detected at 15 months of age. Liver biopsy specimens obtained from 10 HbsAg-positive infants between 3 and 27 months of age revealed that 8 of the 10 infants had intact lobular architecture with no suggestion of nodular regeneration or fibrosis. Some liver cells were hydropic and polyhedral, creating a cobblestone appearance in the liver lobule. Liver cell nuclei were slightly enlarged, and liver cell necrosis with small foci were observed. Only one liver biopsy specimen had increased amounts of fibrosis, but there was no bridging between portal areas.

Transmission

Associated with a number of epidemiologic and immunologic factors, 3% to 50% of infants born to women who are HBsAg seropositive suffer from vertical transmission of HBV infection. The dramatic difference between geographic areas is likely to be related to the frequency of maternal HBeAg positivity, which is highly correlated with transmission (1). In the study of Burk et al, the level of HBV DNA in maternal serum during the prenatal period was shown to be the most important predictor of chronic infection in the newborn and the development of persistent infection was reported to be directly related to the quantity of DNA to which the infant was exposed (8).

Transmission may occur in the prenatal, perinatal periods, and rarely in the postnatal period (1). In one study, HBsAg was detected in 33% of amniotic fluid samples and in 95% of gastric aspirates from newborn infants (9). At birth, mother –to-child microtransfusions may occur during the labor, or contact with infectious body fluids may infect the baby. Because the child is in contact with maternal blood and swimming in a pool of serosities full of viruses during delivery, it can ingest them, leading to infection by physiological transfusion or by contact with maternal blood or genital secretions (2).

HBsAg has been detected in milk from HBsAg-positive women (10). Theoretically, infants may be infected through breast milk known to contain virus; however, this does not seem to add additional risk for the infant more than that constituted by a chronically infected mother. Thus, breastfeeding of infants who receive appropriate prophylaxis following delivery should be allowed. Fortunately, even in case of parents who refuse appropriate prophylaxis, or situations in which prophylaxis is not available, the added risks of neonatal infection beyond those from exposures to HBV during the pregnancy and birth are minimal, particularly with the nutritional and immunologic benefits provided by milk (2, 4, 11, 12).

Clinical Manifestations

HBV infection of the newborn infant results in a chronic, asymptomatic infection in a great majority of cases, strikingly contrasting HBV infection in normal adults, 90% of whom eventually have clinical and virologic recovery (3).

HBV-infected neonates usually are asymptomatic, while almost 10 percent may manifest clinical signs of infection between 2 and 6 months of age. Clinical presentation of persistent viremia in neonates varies in presentation from transient mild acute icteric hepatitis to fulminant hepatitis.Despite being rare, fulminant hepatitis results in the death of two thirds of infants without liver transplant (13, 14). A recent publication from England has reported that 73 infants diagnosed with perinatal infection were born to HBsAg-, HBeAg+ mothers (comprising 53 women from the Indian subcontinent and 9 Asian, 6African-Caribbean, and 5 white women) (15). They were either born before the era

of routine prenatal prophylaxis (n=51) or were prophylaxis failures (n=22). In that study, the mean duration of follow-up was 10 years (range: 2 to 20 years). All children were clinically well with normal height and weight; none had evidence of liver enlargement by palpation or ultrasound examination. Three of the 73 children had cleared HBsAg and had become seropositive for antiHBs at follow-up testing. Sixty-five percent of children were seropositive for HBeAg, and 30% had seroconverted to become anti HBe positive by an average of 10 years of age (range: 4 to 19 years). Unlike 18 of the 50 (36%) children from the Indian subcontinent, with no seroconversions noted in the 9 Asian children, four of the five (80%) white children seroconverted. Different rates of HBeAg seroreversion in different ethnic groups also has been reported in other studies (16). In the Boxall et al's study, half of the Indian subcontinent children and two thirds of Asian children had normal values for serum ALT. Elevated aminotransferase values remained stable over follow-up evaluation period. Liver biopsy samples of 48% of the children indicated that 30% of biopsy specimens had minimal or no inflammation, 63% had mild hepatitis, and 6% demonstrated moderately severe hepatitis, as graded by Ishak scoring (17). Two children with moderately severe changes had "incomplete cirrhosis". The severity of the histopathologic changes and age, gender, ethnic origin were not associated, while a weak association was found between elevation of liver function test and the degree of inflammation. Children who were HBeAg positive also had the highest levels of circulating HBV DNA.

Whereas almost 50 to 90% of infants and children with acute HBV infection will become chronic carriers, 10 % of adults will suffer from chronicity. The persistent low level of active viremia in chronic infection is always the largest reservoir for transmission of HBV. Despite being asymptomatic, most children with chronic HBV infection may develop fatigue, right upper quadrant abdominal pain, and glomerulonephritis secondary to immune complex deposition. Symptoms of chronic HBV infection usually develop simultaneously with cirrhosis or hepatocellular carcinoma (HCC); however, this generally does not occur until the patient reaches late adolescence or adulthood, even in those with perinatally-acquired infection (18).

Diagnosis

HBsAg and HBeAg are the first viral markers to appear in the serum of HBV-infected individuals. Although HBV DNA may also be present, its assays are not widely available. HBV DNA assay test most often are used to monitor response to antiviral therapy, rather than to the diagnose an HBV infection (4). At clinical onset, HBeAg decreases and anti-HBc antibody appears. HBsAg may either decrease during infection or persist for a longer period. Clinical recovery is achieved when HBsAg disappears and anti-HBs antibody and anti-HBe antibody appear. Anti-HBs antibody presence is correlated with durable immunity, whereas HBeAg presence suggests active infection and high infectivity, particularly through maternal-fetal transmission (3). Although HBsAg does not usually cross the placental barrier, it can be acquired at birth or shortly afterwards. Thus, the presence of HBsAg in cord blood may indicate intrauterine infection (16).

Due to lack of sufficient specific data on the kinetics of HBV antigens and DNA during the first year of life, testing of the exposed infant can be challenging because transplacental passage of HBeAg can occur even in the absence of infection (19). Although HBsAg and HBV DNA can be intermittently positive in infected infants during the first 6 months of life, but persist after that point. The infants that were exposed but not infected may sporadically tests positive for various HBV antigens but should be consistently negative after 6 months of age. Chronic HBV infection is confirmed if HBsAg is positive two tests at least 6 months apart (4).

Treatment

Monitoring protocols for chronic liver disease, cirrhosis, and hepatocellular carcinoma have not been defined for young HBV-infected patients. The role of antiviral treatment for these patients also remains controversial and requires confirmation of liver damage with biopsy. Interferon alpha (IFN-α, Intron-A®) and lamivudine (Epivir-HBV®) are the only licensed medications available in the United States for the treatment of chronic HBV in children. Response rates to IFN-α treatment have been ranged between 20 and 58 % compared with 8 to 17 % in untreated controls (20, 21). In some studies, Lamivudine (2', 3'-dideoxycyosine) also cleared HBV DNA in 23 percent of HBeAg-positive children compared with 13 percent in the control group (22). Children with elevated liver enzymes (ALT) and low levels of HBV DNA replication were most likely to respond (23, 24). Chronic HBV carriers such as perinatally infected children do not benefit from medical therapy significantly unless they have active immunologic responses to HBV.

Adefovir (Hepsera™) is a nucleotide analog used for treatment of chronic HBV infections at low doses in adults. Newer agents, pegylated interferon and other nucleotide analogs such as tenofovir (Viread™) and entecavir (Baraclude®), have not been studied in children with chronic HBV infections. Because tenofovir has shown activity against HIV-1 viruses, it is being investigated for the treatment of adults who are coinfected with HIV and HBV (25). Although currently, a pediatric formulation for tenofovir is being developed, specific dosage guidelines are not available yet (26).

Prevention

Prenatal testing for HBsAg is recommended for all pregnant women (18). Prevention of vertical transmission of HBV has improved after unsuccessful early efforts using only single doses of hepatitis B immunoglobulin (HBIG) to successful efforts using repeated HBIG doses during the infant's first

6 months of life (27). The development of the hepatitis B vaccine has led to protocols incorporating the combination of the two interventions, eventually resulting in the current HBV prevention strategies (28, 29). Because, immunoprophylaxis significantly reduces the rate of vertically acquired HBV, all term infants born to HBV positive mothers should receive hepatitis B vaccine and HBIG within 12 hours of delivery. While this combination reduces the vertical transmission rate by almost 90 percent, the failure of passive-active immunization in the other 10% may represent the proportion of in utero transmission. In these cases, the virus is incorporated into hepatocytes before the administered passive antibody can neutralize its infectivity (3).

When maternal hepatitis serology (HBsAg) cannot be determined, the term infant should be given HBV vaccine within 12 hours of birth and maternal HBsAg status should be established immediately. However, because HBV vaccine alone is effective at preventing perinatal transmission and HBIG is expensive with its possibly limited added value, the administration of HBIG is delayed until confirmation of maternal infection (30). When the mother is confirmed HBsAg positive, the infant should receive HBIG as soon as possible, i.e. no later than 1 week of age. Infants of these mothers should be given the second and third doses of HBV vaccine at 1 to 2 months and 6 months of age, respectively (31).

The testing of these infants at 1 year of age (3 to 9 months after completion of the vaccine series) for the presence of infection (HBsAg) as well as anti-HBs antibody is highly recommended. However, nearly 5% of those vaccinated will not develop anti-HBs antibody. An adequate antibody is produced after revaccination of nonresponders in 15% to 25% of infants after one additional dose, and in 30% to 50% after three additional doses (32). Levels of anti-HBs higher than 10 mIU/ml are considered protective. The presence of HBsAg beyond 8 months of age is suggestive of a failure of immunization, and its presence at 15 months confirms a chronic carrier state. Transmission from HBeAg negative mothers to their infants have been attributed to mutations of the precore region of the virus in isolated cases (33). Cesarean section does not reduce the incidence of immunoprophylaxis failure (2).

For the preterm infant, Hepatitis B immunoprophylaxis is slightly different. The American Academy of Pediatrics recommends hepatitis B vaccination shortly after birth for preterm infants of HBsAg-negative mothers who weigh more than 2000 g (31). If the preterm infant weighs less than 2000 g and maternal HBsAg is negative, it is recommended that hepatitis B immunization be delayed until the infant is 30 days of chronologic age or discharged from the hospital. Nevertheless, regardless of weight, all preterm infants born to HBsAg-positive mothers, should receive both HBIG and hepatitis vaccine within 12 hours of birth. While these infants should receive a second, third, and fourth dose of hepatitis B vaccine at 1, 2 to 3, and 6 to 7 months of chronologic age, respectively, preterm infants of mothers with unknown HBsAg status should also receive both HBIG and vaccine and be treated as though the mother is HBsAg-positive until proven otherwise. Not only the term infants but preterm infants of HBsAg-positive mothers as well should be tested for anti-HBs and HBsAg at 9 to 15 months of age to determine their carrier status (34).

In addition to providing immune prophylaxis with HBIG and vaccine to infants, lamivudine also has been used for treatment in mothers with high viral loads during the last month of pregnancy in an effort to reduce the risk of vertical transmission (35). At this time, antiviral therapy during the last month of pregnancy cannot be routinely recommended (4).

Follow-up

Unfortunately, guidelines for monitoring children who develop chronic HBV infection for development of cirrhosis and HCC have not been established yet. Consequently, children who acquire HBV infection early in life are at a higher risk of developing HBV related sequela in their late teenage and early adult years (25). Regular evaluations of liver enzymes, hepatic ultrasound, and serum alpha-fetoprotein as a marker for HCC are useful. Liver enzymes in early childhood may be assessed on a yearly basis, with periodic imaging or other studies based on these results added by clinical findings over the course of time (18).

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