Immunization of babies of women who screen positive for hepatitis B

R. Vlădăreanu[1], C. Pop-Began[2], Simona Constantinescu[3]

1. "Carol Davila" University of Medicine and Pharmacy in Bucharest, Head of Department of Obstetrics and Gynecology, "Elias" Emergency University Hospital;
2. "Carol Davila" University of Medicine and Pharmacy in Bucharest, "Elias" Emergency University Hospital;
3. Head of Neonatology Department, "Elias" Emergency University Hospital

Correspondence:
Radu Vlădăreanu
e-mail: vladareanu@gmail.com

Abstract

To prevent the spread of HBV infection from mother to child in uterine and puerperal life it's considered opportune the administration of hepatitis B hyper immune globulin at birth followed by HBV vaccination to those newborns from mother with HBV infection. Also, in highly endemic areas of HBV, universal vaccination of all newborns was established. In order to prevent liver cirrhosis and hepato-cellular 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 markers which indicate an active replication of this virus (HBeAg), 80 to 90% of the newborns will become chronically infected; whereas if the mother is positive for anti-HBe, only some of the newborns will develop acute hepatitis or fulminant hepatitis. Therefore it is indicated to screen pregnant women for HBsAg in order to prevent mother-to-infant infection of HBV.
Keywords: *HBV infection, HBeAg, HBsAG, hyper immune globulin*

Introduction

Hepatitis B virus (HBV) is a blood-borne virus. Infection with HBV during infancy occurs through horizontal route, as well as vertically from HBV-infected mothers. Horizontal transmission of HBV to infants and children has become infrequent in many developed countries, mainly because of the routine screening of blood for HBV markers and the general use of disposable needles, syringes etc.[1].

Structure

Hepatitis B virus is a member of the Hepadnavirus family, and is one of the smallest enveloped viruses. These particles are not infectious and are composed of the lipid and protein that forms part of the surface, which is called the surface antigen (HBsAg), and is produced in excess during the life cycle of the virus[2].

Genome

The genome of HBV is made of circular DNA, but it is unusual because the DNA is not fully double-stranded. One end of the full length strand is linked to the viral DNA polymerase.

The core protein is coded for by gene C (HBcAg), and its start codon is preceded by an upstream in-frame AUG start codon from which the pre-core protein is produced. HBeAg is produced by proteolytic processing of the pre-core protein. The DNA polymerase is encoded by gene P. Gene S is the gene that codes for the surface antigen (HBsAg). The HBsAg gene is one long open reading frame but contains three in frame "start" (ATG) codons that divide the gene into three sections, pre-S1, pre-S2, and S.

Replication

Hepatitis B is one of a few known non-retroviral viruses which use reverse transcription as a part of its replication process. The virus gains entry into the cell by binding to a receptor on the surface of the cell and enters it by endocytosis. Because the virus multiplies via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus by host proteins called chaperones[3].

The morphology of this type of virus includes non-infective HBV proteins which can help the virulence of the HBV. Part of these proteins helps

us to identify the type of this infection (acute or chronic). Envelope proteins (HBsAg) demonstrate the presence of virus into body but only this presence can't demonstrate which type the infection is. Core protein (HBcAg), even hardly to identify - most frequently is used the identification of antibody protein IgG and IgM for this proteins (the HBc proteins expressed on the surface of the hepatocytes induce the cellular immune response) - show that the virus is in the replicated period. Soluble core proteins (HBe) and the responsive antigens (HBeAg) express the activity of the virus, justifying pregnant women screening.

HBeAg is a secretary small antigen produced by HBV. It can cross the placental barrier from mother to the infant. Trans-placental HBeAg from the mother induces a specific unresponsiveness of helper T cells to HBeAg and HBcAg in neonates born to HBeAg-positive HBsAg carrier mothers. This may be one explanation for the fact that 90% of the infants of HBeAg positive carrier mothers became chronic carriers, while only approximately less than 5% of the infants of HBeAg negative HBsAg carrier mothers become chronic carriers. The immune tolerance state persists for years to decades after neonatal infection.

Serotypes

There are virus serotypes (adr, adw, ayr, ayw), and eight genotypes (A-H) according to overall nucleotide sequence variation of the genome. The genotypes have a distinct geographical distribution and are used in tracing the evolution and transmission of the virus. Differences between genotypes affect the disease severity, course and likelihood of complications, and response to treatment and possibly vaccination[4].

Transmission

Transmission of hepatitis B virus results from exposure to infectious body fluids (unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, vertical transmission from mother to child). A mother who is positive for HBsAg theoretically confers a 20% risk of passing the infection to her offspring at the time of birth. Also, this risk is as high as 90% if the mother is also positive for HBeAg. HBV can be transmitted between family members within households, fact demonstrated by identifying the transmission of HBV in early life of infants from mother infected with HBV and to whom it wasn't demonstrated an intrauterine transmission. However, at least 30% of reported hepatitis B among adults cannot be associated with an identifiable risk factor[5].

Hepatitis B virus is one of the most common causes of chronic liver disease worldwide. Because HIV and HBV share transmission routes, up to 90% of HIV-infected patients have evidence of previous or current HBV infection[6].

Most people who become infected with HBV are able to clear the virus without treatment, and they subsequently become immune to HBV. A small proportion of individuals infected with HBV (approximately 10% in the general population) develop chronic HBV infection. Over time, chronic HBV can cause hepatic fibrosis and eventually cirrhosis, end-stage liver disease (ESLD), and hepato-cellular carcinoma (HCC)[7].

Mother-to-infant transmission of HBV from HBeAg positive mothers is the most common cause of acute or fulminant hepatitis B in infancy.

Reactivation

Hepatitis B virus DNA persists in the body after infection and in some people the disease re-occurs. Although rare, reactivation is seen most often in people with impaired immunity, it's established that male patients with baseline ALT of 200 UL/L are three times more likely to develop a reactivation than patients with lower levels. This demonstrates that persons with higher liver cell destructions (means a lower immune response to first HBV aggression) are most exposed to reactivation even reinfection[8].

Epidemiology of mother-to-infant transmission of HBV

If a mother is infected with HBV during pregnancy and develops acute hepatitis B, the infant's infection depends on the gestational age at the time of maternal hepatitis. Hepatitis in the first to second trimester rarely causes HBV infection of the newborn, whereas hepatitis in the third trimester or during the postpartum period frequently leads to HBV infection, which suggests that mother-to-infant transmission of HBV occurs mainly in the perinatal period, rather than in utero.

Approximately 20-30% of infants born to HBV-positive mothers become HBV-positive in early infancy and a few infants develop acute or fulminant hepatitis at 2-3 months of age.

Hepatitis B during pregnancy doesn't increase maternal mortality or morbidity, or the risk of fetal complication. Approximately 90% of the infants of HBsAg carrier mothers with positive hepatitis B e-antigen (HBeAg) will become carriers if no immune-prophylaxis is given. Trans-placental HBeAg may include a specific non-responsiveness of helper T cells and HBcAg. Spontaneous HBeAg sero-conversion to anti-HBe may develop with time but liver damage may occur during the process of the immune clearance of HBV and HBeAg[9].

Infants who are born from HBeAg-positive mothers and become HBV-positive are usually asymptomatic, but some of these develop chronic hepatitis during infancy. The histological findings of the liver biopsy in these infants are usually not so active and the liver function tests tend to become normal within several years, accompanied by a natural sero-conversion

from HBeAg to anti-HBe. However, there is a large number of newborn from mother with this type of infection that develops chronic liver diseases because of HBV presence. Most of the mother-to-infant infection of HBV appears to occur during delivery, because the HBs-antigenaemia of newborns in the first day of life is less than 1% and the appearance of HB surface antigen (HBsAg) is usually at the age of 1-2 months. Breast-feeding is not considered a major route of mother-to-infant infection of HBV, mostly if the mother is HBe-negative[5,7].

Prevention

According to our country situation, all infants should receive the hepatitis B vaccine. 12 Most of UE countries have national immunization programmes, including HBV vaccination. The complete vaccine series induces protective antibody levels in more than 95% of infants, children and young adults. After age 40, protection following the primary vaccination series drops below 90%. At 60 years old, protective antibody levels are achieved in only 65 to 75% of those vaccinated[3].

People in high risk groups are:

- persons with high-risk sexual behavior;
- partners and household contacts of HBV infected persons;
- injecting drug users;
- persons who frequently require blood or blood products;
- recipients of solid organ transplantation;
- those at occupational risk of HBV infection, including health care workers; and
- international travelers to countries with high rates of HBV.

The vaccine has an outstanding record of safety and effectiveness. Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide. In many countries where 8% to 15% of children used to become chronically infected with HBV, vaccination has reduced the rate of chronic infection to less than 1% among immunized children[10].

At the time being, more than 150 countries vaccinate infants against hepatitis B during national immunization programmes - a major increase compared with 31 countries in 1992, the year that the World Health Assembly passed a resolution to recommend global vaccination against hepatitis B[7,9].

Immunoglobulin and prevention

Although antiviral agents are available to treat and avoid the complications of chronic hepatitis B, prevention of HBV infection represent the most effective way to combat this virus. Screening for maternal HBsAg with or without HBeAg, followed by three to four doses of HBV vaccine in infancy and hepatitis B immunoglobulin (HBIG) within 24 hours of birth – represent an effective way to prevent HBV infection. In areas with a low prevalence of HBV infection or with limited resources, omitting maternal screening but giving three doses of HBV vaccine universally in infancy can also induce a good protection.

Acute hepatitis B or exacerbation of chronic HBV disease may occur during pregnancy. Although the early literature reported an increased risk of mortality or morbidity of the fetus, later data denied this. It's demonstrated that pregnancy neither increased maternal mortality or morbidity from hepatitis B nor the risk of fetal complications during the pregnancy, such as fetal death, abortion, or congenital anomalies. However, pre-term labor was reported to be increased in the mothers with acute hepatitis B during pregnancy. Although infection is rarely symptomatic, 70 - 90% of newborns infected from their mothers will remain chronically infected into adult life if immune-prophylaxis is not given[11].

Prevention is also the most cost effective method for successfully controlling HBV infection and its complications[12].

Immunoglobulin is designed to be administrated in the following conditions:

- Prophylaxis against hepatitis B in adults and children over two years of age who have not been vaccinated against hepatitis B
- Prophylaxis against hepatitis B in adults and children whose vaccination certification is incomplete or missing
- Prophylaxis against re-infection of a transplanted liver in patients who carry the surface antigen of the hepatitis B virus
- Immunoprophylaxis of hepatitis B in the newborn of a hepatitis B virus carrier mother
- After exposure to material containing hepatitis B surface antigen
- As soon as possible but not later than 72 hours after birth, injection of immunoglobulin after investigation of the at-risk person for HBsAg and anti-HBs. Unless the anti-HBs antibody determination at monthly intervals (which also acts as a control of the success of vaccination following the simultaneous vaccination) indicates that earlier administration is necessary, repetition of the dose at intervals of 2 months. Passive administration is no longer necessary once active rising of anti-HBs antibodies has commenced.

For prophylaxis against re-infection of a transplanted liver in HBsAg-positive patients, immunoglobulin is infused intravenously during surgery in the anhepatic phase and re-infused daily over a period of 7 days after surgery. During the subsequent long-term treatment, a serum level should be maintained with monthly checks of the anti-HBs serum level[5].

- Immunoprophylaxy for the prevention of hepatitis B in the newborn, of a hepatitis B virus carrier mother. Immunoglobulin should be administrated from birth - onward, until active immunity has developed. Vaccination against hepatitis B virus is highly recommended. The first vaccine

dose can be injected on the same day as immunoglobulin however in different sites[9].

Costs

In Hungary was made a study based also on the protection of HBsAg positive mother's newborns against HBV infection that is organized on nation-wide level. According to this, each pregnant woman attending prenatal care has been obligatorily screened for HBsAg since 1995. The newborns of positive mothers received vaccination in order to assure a response from their immune system and passive prophylaxis, within 12 hours after birth. If the mother hasn't attended prenatal care, the baby is immunized actively and the mother is immediately tested for HBsAg. If her test is positive, the baby is passively immunized. As a result of this conduit, founds used in the last five years were less than 20.000 EUR; yearly on the prevention of the newborn's infection of HBsAg positive mothers using hepatitis B immunoglobulin. The newborns at risk were actively immunized at the same time. The cost of HBsAg screening tests was averaged 145.000 EUR yearly. The prevention of newborn HBV infection has cost an average of 135.000 EUR yearly.

Virus carriers can develop chronic infection and due to this an end stage hepatic disease (EHD) or hepato-cellular carcinoma (HCC). Considering the infection already present at birth data, without screening and prevention, yearly 5-10 cirrhosis's and 1-2 HCC or EHD would evolve. In Hungary an EHD patient who was ill for 20 years until hepatic transplantation and then lives another 20 years, costs 175.000 EUR.

Immunoglobulin precautions

Hypersensitivity to any of the components from immunoglobulin, especially those very rare cases of IgA deficiency (the patient has antibodies against IgA) is an example. Treatment with immunoglobulin in the prophylaxis against hepatitis B is not indicated if the person at risk has been fully vaccinated against hepatitis B and his immune response has been adequate[7].

Interactions

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

It has been shown by clinical studies that an anti-HBs titer of 100 units per liter protects from HBV reinfection. As the degradation rates vary widely between individuals, it is not possible to specify a standard treatment period. It should be individually determined for each patient after transplantation. Most transplantation centers aim at a maintenance dose of 200 units per litre in order to be sure that the dosage does not fall below the minimum value of 100 units per litre.

Conclusion

Most studies support the concept of combined passive - active immunization against HBV infection in newborns from HBsAg-positive mothers with or without HBeAg-positive.

The specific immunoglobulin was well tolerated and appears to effectively prevent viral infection after single administration.

Protection of HBV infected mothers' newborns from cirrhosis or HCC with active and passive immunization is cost-effective if one EHD is prevented yearly.

Prophylaxis of all newborns from HBsAg-positive mothers, including immunoglobulin administration, within 24 hours from birth and 3 doses of HBV vaccine, is recommended. ■

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