Annotations

Perinatal transmission of hepatitis B

Viral hepatitis is caused by four or more different viruses or groups of viruses: hepatitis A, hepatitis B; the more recently identified forms of hepatitis, non-A, non-B hepatitis which are caused by more than two viruses and probably by several different viruses; epidemic non-A hepatitis (previously referred to as epidemic non-A, non-B hepatitis); and the delta virus. Hepatitis A and hepatitis B can be differentiated by sensitive laboratory tests for specific antigens and antibodies and the viruses have been characterised. Specific laboratory tests are available for the delta agent, a defective virus which replicates in subjects infected with hepatitis B virus.

Hepatitis B virus and serological markers of infection

Hepatitis B virus is a 42 nm spherical particle made up of a core or nucleocapsid surrounded by a lipoprotein coat, hepatitis B surface antigen. The core of the virus contains a double stranded DNA, a DNA dependent DNA polymerase, and the e antigen. The surface antigen (previously referred to as Australia antigen) is generally produced in excess and it is found in blood in the form of 22 nm small spherical particles and tubular forms. Thus, the presence of the surface antigen in blood denotes that a subject is infected and may be infectious, especially if e antigen is also present. Antibody to the core component is found in these subjects and core antibody of the IgM class denotes recent infection. Antibody to e antigen indicates relatively low infectivity (although a better measure of infectivity is the presence of hepatitis B virus DNA in the serum). Hepatitis B surface antibody, which is the protective antibody, is found during convalescence, but it is not detectable if a carrier state is established. Antibodies reacting with other antigenic determinants on the complete virus have also been described. The various markers of infection with hepatitis B may be found in different permutations, and interpretation of laboratory tests may be complex.¹

Carrier state

Survival of hepatitis B virus in the population on a global scale is due to a huge reservoir of carriers, estimated conservatively to number over 200 mil-

lion. Prolonged shedding of the virus by a proportion of carriers and transmission by many varied routes account for the frequency of the infection. In many areas of the world infection at the time of birth and infection in early life are extremely important, leading to the carrier state. The timing and mechanism of transmission is, therefore, of great importance in developing intervention strategies by immunisation.

The carrier state is defined on the basis of longitudinal studies as persistence of the hepatitis B surface antigen in the circulation for more than six months. The carrier state may be life long and may be associated with liver damage varying from minor changes in the nuclei of hepatocytes to persistent hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. Many studies have provided compelling evidence of a consistent and specific association between persistent infection with hepatitis B virus and hepatocellular carcinoma, and it is likely that this association is causal in up to 80% of these cancers. Primary liver cancer is one of the 10 most common cancers in the world, with over 250 000 new cases each year.

Mother to infant transmission

Transmission of hepatitis B from carrier mothers to their babies may occur during the perinatal period and seems to be the single most important factor in determining the prevalence of the infection in some regions, particularly in China and South East Asia. The risk of infection to the infant may be very high, but it varies from country to country and seems to be related to ethnic groups. Infectivity is directly related to the presence of a high titre of hepatitis B surface antigen in the mother's circulation or hepatitis B e antigen, or both. When e antigen is present in the mother, as many as 90% of newborn children are infected, usually in the perinatal period. The prevalence of e antigen among surface antigen maternal carriers, and thus the infectivity of mothers for their infants, varies considerably in different geographical areas and in different ethnic groups. In some parts of Asia, particularly in eastern Asia, 30 to 50% of surface antigen carrier women of child-bearing age also carry e antigen in their blood, and the risk of perinatal transmission of hepatitis B to

infants born to mothers of Chinese origin, for example, may reach 80 to 90%.² Perinatal transmission is of intermediate frequency in mothers of west Asian or of Afro-Caribbean origin. In contrast, the carrier state and perinatal transmission is uncommon in Caucasian mothers. The pattern of mother to infant transmission and establishment of the carrier state is different in Africa. In Africa, e antigen is less frequent in carrier mothers and infection of infants occurs most commonly during early childhood. Another mode of transmission of hepatitis B is infection of children of non-carrier mothers by contact with children who had been infected by their carrier mothers.

It should also be noted that there is a substantial risk (about 70%) of perinatal infection if the mother has acute hepatitis B during the third trimester of pregnancy or within two months after delivery. Intrauterine infections are uncommon since the virus does not cross the placenta and the few infections which occur *in utero* are probably due to a leakage of maternal blood into the fetal circulation associated with a tear in the placenta. Finally, the precise mechanism of perinatal infection is uncertain, but it probably occurs during or shortly after birth as a result of a leak of maternal blood into the baby's circulation, or its ingestion, or inadvertent inoculation. Most of the children infected during the perinatal period become persistent carriers, and perinatal infections may account for about half the carriers in the population.³

The overall pattern of the global distribution of hepatitis B infection is as follows. The prevalence of the carrier state may be conveniently divided into three categories. Low endemic areas such as northern Europe, North America, and Australia where the carrier rate is less than 0.1%, areas with intermediate prevalence with up to five per cent carriers, which include eastern Europe, the Mediterranean, Central and parts of South America and South West Asia, high endemic areas such as China, South East Asia, the Pacific region, and tropical Africa where 15% or more of the population may be carriers. Evidence of infection by hepatitis B virus, as measured by the prevalence of hepatitis B surface antibody, shows similar geographical distribution, four to six per cent in low endemic areas, 20 to 55% in intermediate areas and 70 to 95% in high endemic areas. Infection with hepatitis B virus is thus a universal problem and prevention of infection by active immunisation would have a considerable impact on health, on the prevention of the carrier state and associated chronic liver disease in a proportion of carriers, and on the long term risk of progression to primary liver cancer.

Passive immunisation

Passive immunisation against hepatitis B by the administration of hepatitis B immunoglobulin has been available for about a decade, and it has been used with substantial effectiveness for prophylaxis after a single acute accidental inoculation and for interrupting maternal to infant transmission. The results of small non-randomised studies and more recently controlled studies have shown that it is possible to prevent perinatal transmission of hepatitis B virus from surface antigen and e antigen carrier mothers to 70 to 80% of infants by the administration of hepatitis B immunoglobulin at birth and at varying intervals thereafter. Infection still occurs, however, in many instances (range 20 to 40%). The importance of administering the first dose of immunoglobulin within a few hours of birth should be noted.⁴

Active immunisation

The development of hepatitis B vaccine from the excess surface antigen protein coat of the virus collected from the plasma of asymptomatic carriers is an ingenious, though highly unusual solution to the repeated failure to grow the virus in tissue culture. The surface antigen is purified by several physical and biological procedures and inactivated. The currently licensed plasma-derived vaccines which meet World Health Organisation requirements have been shown to be safe and effective, and have not been associated with a risk of transmission of AIDS or other infectious agent.⁵ Vaccines produced by recombinant DNA techniques in eukaryotic cells, particularly yeast, are at a stage of clinical evaluation, and progress is being made with the development of chemically synthesised hepatitis B peptide vaccines.

Although the priorities for immunisation against hepatitis B are not the same for each country or geographical region, since the needs are dictated by differing epidemiological patterns, cultural and sexual practices, socioeconomic factors, and the environment, it is evident that the prevention of perinatal transmission has the highest priority for children born to mothers in 'high risk' groups and for susceptible women of childbearing age and their newborn infants in endemic areas. This was clearly shown by the pioneer studies carried out in Senegal by Maupas *et al*⁶ and in Taiwan by Beasley *et al*.² The plasma-derived vaccines were highly immunogenic and there was no interference by circulating maternal antibodies. Nevertheless, the protection afforded by the vaccine alone was about 70% (and at best 80%), a rate which is similar to the

efficacy of passive protection using multiple injections of hepatitis B immunoglobulin.

Passive-active immunisation

Various temporal combinations of hepatitis B immunoglobulin and hepatitis B vaccine have now been extensively evaluated in Taiwan² and in Hong Kong,⁷ and smaller studies were conducted in Japan, Holland, and elsewhere. A number of trials are still in progress. Analysis of the results of the trials in Taiwan and Hong Kong, which are high endemic areas, has shown that combined passive-active prophylaxis improved the protective efficacy in infants born to hepatitis B e antigen carrier mothers to over 90%, whereas in the untreated group development of the carrier state ranged from 73 to 88%.⁸

Although it is difficult to recommend precise immunisation schedules at present, since an international standard preparation of the vaccine is not yet available to permit direct comparisons between different vaccines, it is clear that combined prophylaxis is the method of choice for protection of infants born to e antigen positive mothers, and this should be extended to babies born to surface antigen carrier mothers who are e antibody negative.

Ideally, it has been suggested that infants born to all surface antigen positive mothers including those with e antibody should be immunised, although it is recognised that the risk of perinatal infection in the latter group is very small. It should be noted, however, that unless these children are actively immunised they are at a continuing risk of infection by horizontal transmission later in life.

The relative scarcity of hepatitis B immunoglobulin and its cost, however, and the current high cost of the licensed hepatitis B vaccines preclude large scale prophylaxis at present. Nevertheless, the fact that multiple doses of immunoglobulin as compared with a single dose at birth did not offer significant advantage when combined with a course of vaccine is encouraging. Secondly, the vaccine is highly

immunogenic in infants and the dose could be reduced substantially (although paediatric doses are not yet ampouled or licensed in, for example, Great Britain). Thirdly, vaccines produced by recombinant DNA techniques should prove to be equally effective and substantially cheaper; and there is also the longer term prospect of cheap chemically synthesised vaccines.

Given sufficient resources, protection by combined immunisation against hepatitis B of all newborn infants at risk is within reach. The principal health benefits will include dramatic reduction of the persistent carrier rate, reduction in morbidity and mortality from chronic liver disease, and prevention of a substantial proportion of hepatocellular carcinomas.

References

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