Viral hepatitis B — an overview

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Worldwide the hepatitis B virus (HBV) is responsible for a large proportion of all forms of liver disease and is probably the most frequent cause of chronic viral disease in man. The economic and human cost of HBV is further exacerbated by its association with hepatocellular carcinoma (HCC), one of the ten most common malignant human tumours.

HBV

Structure

HBV is classified as a member of the family Hepadnaviridae (Fig. 1).[1-3] HBV is a small, spherical virus and has a diameter of 42 nm with a 27 nm inner core corresponding to the highly immunogenic hepatitis B core antigen (HBcAg).[4] The outer coat consists of a waxy lipophilic material and the three envelope proteins, termed hepatitis B surface antigen (HBsAg). These large, middle-sized and small HBsAg proteins are derived from a common open reading frame by alternate use of three stop codons.[5] Hepatitis B e antigen (HBeAg) is a soluble non-structural, enigmatic antigen which is often detected in the blood of patients infected with replicating HBV which results in massive viral load in the blood. Both HBe and HBc are derived from the same section of HBV DNA but the HBe transcript contains an additional 29 codons in phase and upstream of the HBc; these encode a secretory or signal peptide.[2,6] This addition facilitates entry into the hepatocyte endoplasmic reticulum where the HBe is processed and secreted.[7] Viral DNA mutations resulting in the cessation of HBeAg production are thought to occur by the insertion of a stop codon in the pre-HBc sequence.[5] The X protein is most probably a regulatory factor and may serve as a transcription activator.[8]

The virus also contains a circular DNA molecule which is partially double-stranded and is associated with a DNA polymerase protein. Possibly, as a consequence of the very small size of the HBV genome, the coding capacity has been enhanced by the use of overlapping open reading frames and multiple usage of the available DNA.[5,6] A happy consequence of this phenomenon is that the DNAs of several HBV isolates were sequenced over a decade ago and have subsequently been cloned in *Escherichia coli*, yeast and several mammalian cell lines.

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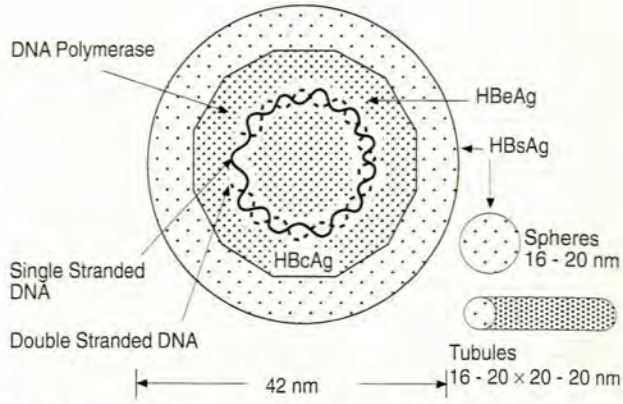

Fig. 1. Structure of the hepatitis B virus. Excess viral proteins are seen as spheres and tubules.

Replication of HBV within hepatocytes and other cells in man appears dependent on virion attachment via the pre-S region, entry, genome uncoating and the interaction of specific and nonspecific (e.g. steroid receptors) transcription factors of that cell which may interact with the HBV DNA binding sequences.[2,6] Unlike the retroviruses, the DNA of HBV does not need to be integrated into the host cell genomic DNA for viral replication to occur.[9] Transcription of mRNA is highly regulated and results in the formation of the various envelope, core, X, reverse transcriptases, RNAses, polymerases and the HBV pol protein.[6,7,9] These in addition generate the minus HBV DNA strand and the incomplete plus strand, which uniquely contains a segment of RNA. The polymerase and core proteins co-ordinate packaging within the cell nucleus.[6] Integration of usually defective or degenerate HBV DNA into the host genome occurs in a random fashion and may result in the generation of truncated viral proteins, 'neoproteins' or uncontrolled cell growth by the interaction with cell cycle control proteins.

Three types of particle may be seen on electron microscopy in serum from patients with acute or chronic hepatitis B infection. These are the Dane particles representing the complete viral particle, and the 22 nm diameter spheres and tubules which represent excess virally-coded substance proteins. The surface of the Dane particles display HBsAg and the spheres and tubules consist of HBsAg.[10] This excess HBsAg can be used to provide useful vaccine products.[11]

Laboratory diagnosis

As there are a number of tests available for the diagnosis of HBV infection and immunity, it is important to rationalise one's approach to the individual clinical setting.[12] Broadly speaking, there are tests for screening, for specific diagnosis and for prognosis. These laboratory tests include analysis of viral proteins (e.g. HBsAg) or the immunological humoral response against these antigens (e.g. anti-HBs). More sophisticated tests involve the analysis and determination of viral HBV DNA in biological fluids or tissues.

The analysis and measurement of HBsAg is the single most important test and is widely available. The standard methods employed are radio-immunoassay (RIA) and enzyme immunoassay (EIA); both are available in

commercial kit form and are suitable for automation. These tests are cheap, rapid and accurate. The detection limit for most assays is around 0,02 - 1 ng/ml. The confirmed finding of HBsAg in the blood or other biological fluids is diagnostic of HBV infection but does not indicate the duration of infection or the replicative state of the virus. HBV vaccines which are administered intramuscularly contain HBsAg bound to aluminium hydroxide and thus do not produce detectable antigenaemia. It is important to remember that the absence of detectable HBsAg does not exclude the potential for HBV infection. This is particularly important in the context of fulminant liver failure.

The next most important from a clinical perspective is the anti-HBc test which is an excellent confirmatory test in the individual who is HBsAg positive; it can also serve as an additional screening test to determine past exposure or immunity to HBV. The presence of IgM anti-HBc is highly suggestive of acute infection but may also be positive (albeit in lower titre) in individuals with active replicative chronic HBV infection. The major indication for the use of the anti-HBs assay is to determine the efficacy of immunisation; when performed in a quantitative manner, this test also provides information on the need for booster immunisations.

Tests for HBeAg are used as a surrogate marker for active HBV replication and thus potential viral infectivity. This surrogate marker is, however, unreliable in certain parts of the world (e.g. Mediterranean areas) where 'HBeAg minus' mutants are a significant problem.[7,13] The most accurate and definitive tests are the determinations of HBV DNA by dot/slot blotting, liquid hybridisation assays or polymerase chain reaction (PCR). A positive result in any of the above is a precondition of HBV infectivity. Results are expressed either as picograms of HBV DNA per ml or as HBV genome equivalents — where 1 pg corresponds to roughly 3×10^5 genomes. Optimised and reliable assays allow detection down to the range of 5 - 10 pg/ml of HBV DNA. PCR techniques have much lower levels of detection with sensitivities down to 10 - 100 HBV DNA genome equivalents per sample. Endogenous HBV DNA polymerase activity may be assayed on well-preserved plasma samples, from which HBV has been concentrated through sucrose gradients, and should be regarded primarily as a research tool.[14]

The assays are further explained and illustrated in the context of both acute and chronic HBV infection later in this article.

Epidemiology

The incubation period of HBV infection is 60 - 180 days. Laboratory tests for hepatitis B have confirmed the importance of parenteral transmission and the infectivity of blood products. However, hepatitis B is not spread exclusively by blood and blood products. HBV infection is more prevalent in individuals living under poor socio-economic conditions. Long-term asymptomatic carriers of the virus are the main source of infection in the community. There is a huge reservoir of carriers worldwide.[15,16]

Sexual transmission of hepatitis B is well recognised. At very high risk are male homosexuals and individuals with multiple sexual partners. HBsAg has been found not only in blood, but also in saliva, menstrual and vaginal discharges, seminal fluid and serous exudates. These have all been implicated in the spread of infection. Transmission of HBV may result from accidental inoculation of minute amounts of blood or fluids contaminated with blood (such as may occur during medical, surgical and dental procedures), use of inadequately sterilised syringes and needles, intravenous and percutaneous drug abuse, tattooing, earpiercing, nose-piercing, acupuncture, laboratory accidents and accidental inoculation with razors and toothbrushes.[15,16]

In certain parts of the world, additional factors may play a role. These include traditional tattooing, scarification, ritual circumcision and perhaps repeated bites by blood-sucking insects, although the latter mode of transmission remains unproven and of uncertain epidemiological significance.

Hepatitis B may also be transmitted by carrier mothers to their babies during the perinatal period. This vertical transmission appears to be important in south-east Asia where the risk of infection may reach 50 - 60% or more. There is also a substantial risk of perinatal infection if the mother has acute hepatitis B in the second or third trimester of pregnancy or within 2 months of delivery. Although hepatitis B virus can affect the fetus *in utero*, this is uncommon and appears to occur in less than 5% of cases. In contrast to countries like Taiwan, the incidence in Africa, Greece and Hong Kong is higher in children than neonates. In this horizontal spread, infection in the first year of life is rare. However, in certain rural areas of South Africa large numbers of children are infected between 3 and 10 years of age. The same areas have extremely high incidences of HCC with an average age of onset in the late twenties.

Geographical distribution

An estimated 300 million people are chronically infected with HBV. HBV infection is present on all continents and almost every country in the world. Sub-saharan Africa, south-east and far-east Asian countries and the coastal belt of Greenland are most affected. The rate of serum HBsAg expression in screened individuals varies from a low of 0,1 - 0,5% in western Europe to a high of 8 - 15% in Africa and the Far East. The prevalence of past and present HBV virus infection as determined by the presence of antibody to HBsAg is higher, ranging from 4 - 6% in the low-prevalence areas to 70 - 95% in Asia and Africa. Several seroprevalence studies undertaken in South Africa show distinct racial and social stratification of risk. Rural communities appear to be at greater risk of exposure and chronic viral infection. Figures for exposure are around 70% and chronic HBsAg carriage approximately 5 - 10%.

HBV in children

Although the predominant clinical manifestations are usually observed in adulthood, infection with HBV in areas of high endemicity is most commonly established in the neonatal period, infancy or early childhood,[15,16] the latter being most important in South Africa.

The risk of chronic HBV infection in children appears to be inversely related to the age of initial infection. Transmission of HBV from an infected mother to her baby during birth (perinatal or so-called 'vertical transmission') results in a risk of persistent infection of between 70% and 90%. This declines with increasing age, when children have a risk of horizontal transmission of 60% during the second year of life and 10% by the age of 6 years.

In the far eastern Asian area of high endemicity, perinatal infection is common and accounts for a significant proportion of chronic infection in adults. In these areas, up to one half of pregnant women have high levels of circulating HBV as indicated by the presence of HBeAg or HBV DNA. Infection of the neonate is thought to occur at the time of delivery either by percutaneous entry through skin abrasions or by the ingestion of blood; transplacental transmission is uncommon. In other areas of high endemicity, such as Africa and the Middle East, perinatal transmission is much less common. This may be a consequence of decreased serum HBeAg expression in chronically infected, parturient mothers.

In Africa, toddlers and young children are at high risk of contracting HBV. The exact mechanism of transmission at this young age remains obscure; various postulated percutaneous and oral routes remain to be proven. Infection may occur within families, usually either from siblings or the mother, by percutaneous or other forms of exposure. In several studies, transmission from outside the family may have accounted for up to one half of the total infection rate, which is frequently over 60%. Infection in infants and young children is usually subclinical, making them a source of infection for other young children.

In areas with intermediate rates of HBV infection (India, South America and eastern Europe), transmission occurs in all age groups but is more common among older children and adolescents. Icteric acute hepatitis B with arthralgia is more usual with adult-onset infection and may result in severe illness and, occasionally, death. However, early childhood infection is considered to contribute most significantly to the pool of 2 - 7% of adults with chronic HBV infection.

With the established improvements in socio-economic factors and advanced health care in the developed Western world, the prevalence of chronic infection in adults is around 1 - 2%. Here spread of HBV occurs primarily among adolescents or adults as a consequence of intimate sexual contact or other activities that result in transmission of biological fluids, such as intravenous drug use. Although only a small fraction of infection in areas of low endemicity occur in infants and young children, these still account for about one-third of cases of chronic infection in adults in these populations.

Delta super-infection and other liver diseases

Chronic infection with HBV predisposes that individual to chronic infection with the hepatitis D virus (HDV or delta agent) which may result in severe hepatitis and progression to liver disease.[17] HDV infection appears to have comparable modes of transmission to HBV but inexplicably has a very low prevalence in southern Africa. Alcohol abuse and iron overload are likewise associated with more accelerated liver disease in those individuals who have HBV markers.

Further considerations on modes of HBV transmission

HBV is an extremely hardy virus and can survive extremes of temperature and exposure to many chemical agents. The virus is found in almost all body fluids or secretions, often in high concentrations and may survive up to 6 months at room temperature. The virus is readily transmitted via the percutaneous route in minute quantities of blood, e.g in scarification practices or ear-piercing, both of which are frequent procedures. Less obvious instances include the passage of HBV through skin abrasions or rashes. Non-cutaneous routes of transmission have been difficult to document but the majority of cases are presumed to be secondary to ingestion of contaminated secretions possibly as a consequence of hand-mouth contact. Even airborne particles may contain HBV and infection via the respiratory tract is theoretically possible.

Acute hepatitis B

The clinical expression of acute HBV infection is extremely variable and ranges from a fulminant disease (which is rare) to subclinical infection, which is very common. Hepatocyte damage appears to be mediated by the host immune response, predominantly by cytotoxic T cells and natural killer cells. HBV, *per se*, is probably not cytopathic but this point is controversial.[18] Jaundice, preceded by nausea, anorexia and vomiting, appears in about 20 - 50% of patients, and a minor influenza-like syndrome may occur, particularly in children. Clinical features which may point to HBV include a long prodromal period, arthralgia and skin rashes. The diagnosis of HBV infection entails the use of laboratory tests which show increased serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity, and must be confirmed in every case by demonstration of the appropriate hepatitis B serological markers.

The serological profile of a typical case of acute hepatitis B is shown in Fig. 2. HBsAg is detectable for about 3 months. Following the disappearance of HBsAg, anti-HBs appears after a lag period of 3 weeks. Antibodies directed against HBc appear and remain positive early on in the disease. Anti-HBs and anti-HBc persist for years after the patient has recovered and constitute the most lasting evidence of previous HBV infection. IgM anti-HBc disappears at or before 6 months, when the patient recovers from acute hepatitis B. Total and IgM anti-HBc are present during the 'window' period after HBsAg is lost but before anti-HBs antigen appears. Anti-HBe develops after the disappearance of HBeAg. In cases of presumed acute HBV infection where the standard viral markers are negative during the 'window' phase, the IgM anti-HBc test becomes invaluable in establishing the diagnosis and thus indicating the family members' need for prophylactic therapy.

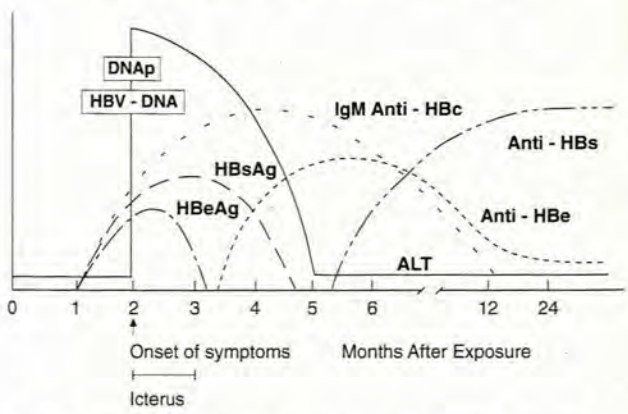

Fig. 2. Serological profile of a typical case of acute hepatitis B.

Outcome of acute HBV infection

Most adults with acute HBV infection recover fully within 6 months. Approximately 5 - 10% progress to chronic HBV infection. In contrast, 30 - 40% of children and about 90% of neonates with acute HBV infection become chronically infected.

Risk factors for chronicity of infection include gender (males are at greater risk), age at the time of infection and whether immunosuppression is concurrent. HBV infection manifests as clinical hepatitis more commonly in adults than children. Since age is also associated with the risk of chronicity, subclinical HBV infection is also associated with an increased risk of chronicity. Chronic carriers of HBV may typically have a mild or asymptomatic initial episode of disease and therefore often do not give a history of previous acute hepatitis.

Chronic hepatitis B

By definition, patients with HBsAg persisting for longer than 6 months and HBeAg persisting for longer than 3 months are chronic carriers. Carriers may be symptomatic (fatigue, malaise) or healthy. In symptomatic carriers with chronic disease, HBsAg and HBeAg, and DNA from HBV are usually present in serum or liver. So-called 'healthy' carriers usually produce HBsAg alone and, on most occasions, do not have evidence of active viral replication.

The serological profile of a typical case of symptomatic chronic hepatitis B is shown in Fig. 3. In this patient markers of active viral replication, HBeAg and HBV DNA were present for almost 5 years. At about 5 years after the onset of disease seroconversion to the non-replicative state occurred. Seroconversion is associated with disappearance of HBeAg and HBV DNA. The development of anti-HBe may suggest the cessation of active viral replication although, as in this case, HBsAg may still be produced. This is, however, an unstable situation. Individuals may relapse and again develop markers of viral replication. Abortive seroconversions are also documented with transient flares of hepatitis, unaccompanied by loss of HBeAg.

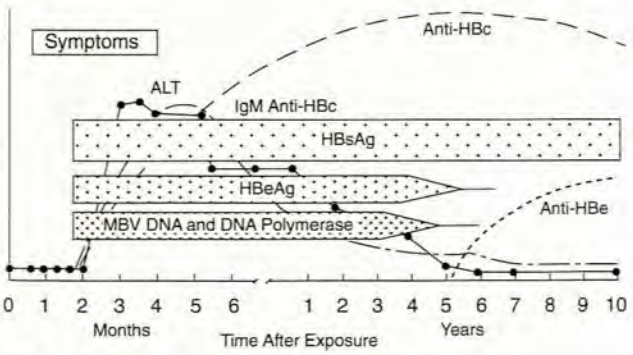

Fig. 3. Typical case of chronic hepatitis B infection.

Outcome of chronic HBV infection

Chronic HBV infection may produce an asymptomatic carrier state (with an increased risk of HCC) or chronic hepatitis with the potential to develop cirrhosis in up to 55% of patients with severe histological changes, including active inflammation and hepatocellular necrosis. The terms 'persistent' or 'active' hepatitis are often misleading and are being phased out in favour of a new approach, in which the nature of the chronic hepatitis is characterised by a description of the histological changes in the context of the serological and molecular biological evidence for HBV replication as described above.

Another potential complication of chronic HBV infection is primary liver carcinoma or HCC. Several studies have shown integration of HBV DNA into the genome of human hepatoma cells. The risk of developing liver cancer with chronic hepatitis B virus infections is 42 times greater than that of the general population in Western countries. In the East, the lifetime risk of developing liver cancer may be up to 50% in patients with chronic hepatitis B virus infection.[18-21]

A small percentage of patients with chronic HBV infection may develop extrahepatic manifestations such as polyarteritis nodosa, glomerulonephritis, cryoglobulinaemia, peripheral neuropathy and marrow hypoplasia or even aplasia. These conditions are thought to be related to the formation of immune complexes or to other poorly characterised reactions.

Treatment of chronic HBV infection

The rationale for antiviral treatment of chronic HBV infection is that even mild forms of liver injury may progress during episodes of reactivation,[22] that there is an increased risk of hepatocellular carcinoma[18-21] and that untreated patients serve as a reservoir of infection.[15,16] The goals of treatment therefore are to diminish infectivity of the host, to normalise liver inflammation and improve symptomatology. This effect may be predicted by the sustained disappearance of markers of HBV virus replication.[23]

Of all the agents which have been used to treat chronic type B virus hepatitis, alpha interferon (IFN) offers the most promise. While IFN is usually well tolerated in clinically compensated patients with chronic hepatitis B, there are insufficient data about its efficacy and safety in patients with decompensated forms of the disease. Steroid priming should never be used in this group of patients because of the risk of further decompensation. Such variables as the pretreatment level of circulating HBV DNA and amino-transferase levels, degree of histological activity, sexual lifestyle and HIV status of the patient influence the response to treatment.[23]

Approximately 40% of patients lose HBeAg-positivity and become anti-HBe-positive following standard courses of treatment, compared with a spontaneous seroconversion rate of approximately 10% per annum.[24] The long-term benefits of this treatment are still being assessed but in several instances total clearance of the HBV infection has been claimed.[23]

More information is needed on the treatment of patients who are HBeAg-negative and are infected with mutant forms of HBV. Individuals with mild to moderate decompensated disease, HBV carriers with chronic delta infection and children present their attending physicians with difficult therapeutic decisions. Studies are also needed to address whether early treatment of individuals with persistent viral replication 6 - 12 weeks after the onset of acute hepatitis, where HBeAg is still detectable, may prevent evolution to chronic infection.

Prevention

Although there is still uncertainty about modes of HBV infection in areas of high endemicity, epidemiological studies indicate that full immunisation with plasma-derived or recombinant HBsAg vaccines, as part of national immunisation programmes, viz. EPI, prior to 1 year of age, should interrupt the major horizontal routes of infection. The prevention of perinatal infection also requires the administration of HBV hyperimmune globulin at birth. Booster immunisations may also be required to prevent infection in late childhood and in young adults.[11]

Current recommendations by the World Health Organisation and the Centers for Disease Control are for the universal immunisation of infants in all geographical areas, irrespective of endemicity. It is unfortunate that, despite the availability of safe and increasingly cheaper vaccines there is still widespread apathy and even reluctance to implement these recommendations for non-economic factors. For example, despite the availability of safe and effective vaccines for over a decade, the incidence of hepatitis B infection in the USA has increased by one-third with a postulated 300 000 new infections annually. In developing countries, particularly in Africa, economic factors and population numbers probably preclude the implementation of effective mass immunisation against HBV at current HBV vaccine prices. It is hoped that the anticipated redistribution of medical resources and the greater emphasis on primary health care in the 'new South Africa' facilitate the earlier introduction of HBV immunisation.

Surveillance

Passive surveillance of hepatitis B through routine notification has been a legal requirement for more than a decade in South Africa. In 1990, the asymptomatic HBsAg-positive carrier state was also made notifiable. Hepatitis B is substantially under-reported but the reporting rates in some parts of South Africa have been remarkably steady, enabling the reliable interpretation of trends in the incidence rate of HBV infection.[25] Some countries have successfully implemented sentinel surveillance programmes for HBV infection.

Laboratory data on HBV infection serve as a useful adjunct to notification data. Laboratories which are able to identify repeat specimens on patients can provide useful data on the number of cases of acute hepatitis B occurring in their catchment area. In addition, histopathology laboratories can provide data on the number of cases of hepatocellular cancer.

Finally, serological screening programmes in high-risk settings, e.g. mental institutions and in the general population, can provide estimates of the prevalence of exposure to HBV and the HBV carrier rate.

Immunisation

Passive immunisation

Hepatitis B immunoglobulin is prepared from plasma samples with high titres of anti-HBs. This preparation may confer temporary passive immunity and is useful for post-exposure prophylaxis. The major indication for the administration of this immunoglobulin is a single exposure to HBV, e.g. in cases where blood containing the virus is inoculated, ingested or splashed onto mucous membranes and the conjuctiva. Doses of 250 - 500 international units have been used effectively. The immunoglobulin should be administered as early as possible after exposure, preferably within 48 hours. There appears to be little benefit from the administration of the immunoglobulin more than 7 days after exposure to the virus. It is recommended that two doses be given 30 days apart. The recommended adult dosage is about 3 ml and the dose in the newborn infant 1 - 2 ml. The immunoglobulin is given by deep intramuscular injection. Active immunisation is essential for long-term protection.

Active immunisation

Active immunisation against hepatitis B is required for groups who are at high risk and do not have serological evidence of past or present HBV infection. These include individuals requiring repeated transfusions of blood or blood products, prolonged inpatient treatment, frequent tissue penetration or repeated arterial or venous access, and patients with natural or acquired immunodeficiency or with malignant disease. Viral hepatitis is an occupational hazard among health care personnel and the staff of institutions for the mentally disabled. High rates of HBV infection occur in intravenous drug abusers, homosexuals and commercial sex workers. The immune response to current hepatitis vaccines is good in the young but may be poor in immuno-compromised patients and elderly persons.[25,26]

Specific issues in HBV vaccination

Vaccines currently available in South Africa consist of plasma-derived or recombinant yeast-produced HBsAg. These vaccines are safe, immunogenic and effective. Ideally, vaccines are administered by intramuscular injection into the deltoid muscle at 0, 1 and 6 months. There is no risk of HIV or of other hepatitis virus transmission. In protective efficacy studies, the plasma-derived and yeast-derived vaccines appear to be equivalent. A variable proportion of healthy individuals may lose protective levels of anti-HBs about 5 years after the first vaccine dose. Most, but not all, of these individuals appear to be protected against HBV infection. Booster doses are not currently recommended routinely but should be strongly considered for individuals who remain in high-risk categories. Hypo-responders, who may be identified by post-vaccination anti-HBs testing, may respond to revaccination.

Intradermal administration of one-tenth the usual dose of HBV vaccine induces anti-HBs in most recipients, but the peak response and duration of protection appear to be less than those achieved by intramuscular administration. Intradermal administration of booster inoculation remains to be evaluated. The rapid induction of anti-HBs with an accelerated HBV vaccination schedule at 0,1 and 2 months may have potential for post-exposure prophylaxis. A schedule of vaccination applicable to the EPI programme is suitable for mass immunisation in the developing world. Here HBV vaccine would be given together with DPT at 6 weeks, 10 weeks and 14 weeks of age.

Other vaccines include polypeptides containing specific HBV-antigenic determinants. Clinical trials of polypeptide vaccines are in progress. Hybrid virus vaccines for HBV utilising recombinant vaccinia viruses have been developed. These vaccines have certain theoretical advantages in that a single strain of vaccinia may be designed to present antigens characteristic of several viral diseases simultaneously. However, at present, the use of vaccinia virus remains experimental. Other recombinant viruses being investigated as vectors for hepatitis vaccines include adenoviruses and polioviruses, which may be effective when given by mouth.

The potential for the generation of vaccine-induced escape mutants in neonates born to HBV-infected mothers exists[27] but may be preventable by alterations in the recombinant vaccines.

Conclusion

A major concern in southern Africa is to control hepatitis B virus infection and thus prevent the appalling sequelae of chronic infection. Universal vaccination of infants in high-risk areas in South Africa will be an important step in the reduction of liver disease in our country.

The introduction of a national hepatitis B vaccination programme in South Africa is imminent. This policy must be supported by the political will to control HBV infection. This entails the provision of adequate resources for vaccination and surveillance, as well as general public health measures aimed at preventing transmission.

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Hepatitis C — a South African perspective

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The existence of non-A, non-B (NANB) hepatitis was established in the 1970s, when accurate serological tests allowed exclusion of hepatitis A and B viruses as the cause of most cases of post-transfusion hepatitis.[1] The term 'hepatitis C' was coined after molecular cloning of nucleic acid from highly infectious sera of chimpanzees[2] identified an RNA virus as the primary cause of post-transfusion hepatitis (PTH). Sequence analysis and expression of the RNA has shown it to be closely related to the flavi- and pestiviruses. It has marked genomic variability which may affect its biological and immunological characteristics, is transmitted parenterally and sporadically, by as yet unidentified routes, and causes chronic indolent liver disease in 50 - 75% of infected patients. It is associated with hepatocellular carcinoma, glomerulonephritis, cryoglobulinaemia, auto-immune liver disease, lymphocytic sialadenitis and porphyria cutanea tarda. Up to 500 million people worldwide may be infected with hepatitis C virus (HCV),[3] and many questions about the disease remain unanswered. Therapy is still largely ineffective and our current understanding of the long-term natural history, our methods of diagnosis, therapy, prevention and immunisation are suboptimal.

Virology of HCV

HCV was first obtained by screening the products of approximately 1 million c-DNA clones expressed in bacteriophage vectors, with serum from patients with NANB PTH.[2] The sequence of the first clone identified (5-1-1) encoded a 55 amino acid peptide containing an

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