Acute and Chronic Viral Hepatitis in South Africa — SC Robson

SC Robson

MBChB; MRCP (London); FCP (SA); PhD
MRC/UCT Liver Research Centre
Dept of Medicine
Medical School, UCT
Anzio Road
Observatory
7700

Curriculum vitae

Simon Christopher Robson was born in England in 1956, but completed his schooling in South Africa in 1972 as top scholar at the General Smuts High School, Vereeniging. At UCT he obtained the MBChB with distinction in 1978, and then worked and studied in various disciplines in Durban, Cape Town (Groote Schuur) and London (UK). Currently he is lecturer in the Department of Internal Medicine and Head of the Liver Clinic at Groote Schuur Hospital. He is keenly interested in research, liver transplantation and immunosuppression, and has a long list of publications and papers presented at local and international congresses.

Summary

Viral hepatitis is a common infectious disease and a major public health problem worldwide. The economic and human cost of these chronic hepatitis viruses is exacerbated by their association with hepatocellular carcinoma – one of the ten most common malignant tumors. This article reviews the relevant viruses in clinical practice in Southern Africa, attempts to condense some of the latest knowledge on the Hepatitis A and B, and the NANB hepatitis viruses. The NANBH virus group is further sub-classified and the author has solid serological data for the identification of 2 other viruses, Hepatitis C and Hepatitis E virus. The Delta agent seems to be rare in southern Africa. The major concern in southern Africa is to control hepatitis B virus and prevent the apalling sequelae of chronic infection with this virus. The high cost of vaccinating infants in high risk areas, is still a major problem.

S Afr Fam Pract 1991; 12: 263-72

KEYWORDS:
Hepatitis; Viruses; Primary Health Care; Physicians, Family.

Introduction

Viral hepatitis, an inflammatory and necrotic process in the liver, is a common infectious disease and a major public health problem worldwide. Acute viral hepatitis, although a generalised systemic infection, presents with clinical manifestations relating directly to inflammation of the liver with hepatocellular dysfunction and jaundice. The clinical severity of acute hepatitis is extremely varied. Most appear to present as asymptomatic or subclinical infection or with mild gastrointestinal symptoms and anicteric hepatitis. Infection with these viruses however may also result in an acute illness characterised by jaundice, malaise and prolonged convalescence. Acute fulminant hepatitis is fortunately rare and is associated with a high mortality.

Infection with certain of the hepatitis viruses may be associated with a persistent carrier state, chronic persistent hepatitis, chronic active hepatitis and the more serious complications, cirrhosis and portal hypertension.

Worldwide, these hepatitis viruses are responsible for the majority of all forms of chronic liver disease. The economic and human cost of these chronic hepatitis viruses is further exacerbated by their association with hepatocellular carcinoma – one of the ten most common malignant tumours worldwide.

The most frequently identified hepatitis viruses are the hepatitis A virus (HAV, infectious or epidemic hepatitis), the hepatitis B virus (HBV, previously termed serum hepatitis) and the hepatitis D virus (Delta agent or HDV). Other viruses that can cause acute hepatitis include the Epstein-Barr virus, cytomegalovirus (CMV), and the exotic haemorrhagic fever viruses such as yellow fever virus. The diseases caused by these latter viruses however are not generally included in the term viral hepatitis.

The non-A non-B viral hepatitis (NANB) hepatitis group, until quite recently, remained a diagnosis of exclusion of the above causes of viral

... Viral Hepatitis

hepatitis and other possible aetiological agents such as alcohol and drugs. The heterogeneity of this grouping was however quite apparent by the varied epidemiological and clinical presentations. Both parenteral and sporadic forms of infection were

The clinical severity of acute hepatitis is extremely varied

noted and a variable tendency of the NANB hepatitis virus group to produce chronic hepatitis and cirrhosis was identified.

After extensive research into possible aetiological agents of NANB hepatitis, two further hepatitis viruses have been identified and their genomes fully cloned. Diagnostic serological tests are available in research institutions. The hepatitis C virus (HCV) appears to be the major aetiological agent of transfusion-associated NANB hepatitis and to account for a proportion of sporadic community acquired NANB hepatitis. The hepatitis E virus (HEV or E-NANB) appears to cause the enterally transmitted NANB hepatitis (or epidemic non-A viral hepatitis) which appears to result in epidemics and in sporadic disease in endemic communities.

There is also increasing epidemiological evidence for a further hepatitis virus, the so-called hepatitis F virus (F-NANB), which would appear to be transmitted in a sporadic community acquired form. This may account for some cases of fulminant and sub-fulminant liver failure in NANB hepatitis infection. This virus however has not been identified and there are no established serological tests for its detection.

This review will concentrate on the relevant viruses in clinical practice in Southern Africa and will attempt to condense some of the latest knowledge on HBV and the NANB hepatitis virus.

1. Hepatitis A Virus (HAV)

Epidemiology

Hepatitis A is said to occur endemically in all parts of the world and the exact instance is difficult to estimate because of the high proportion of asymptomatic and anicteric infections, differences in surveillance and different patterns of the disease. This notifiable disease is grossly under-reported and only one sero-type of hepatitis A has been identified. In developing countries, infection is almost universal in childhood and most cases appear to be subclinical and anicteric. In the industrialised countries, the prevalence of hepatitis A antibodies is lower at about 30-50% of the adult population. This implies that localised outbreaks in creches and other institutions may result in a

Acute fulminant hepatitis fortunately is rare

significant number of adults contracting the illness from members of their family and from other close contacts.

HAV is spread predominantly by the faecal oral route, most commonly by person to person contact. Therefore infection is particularly common under conditions of poor sanitation and overcrowding. Common-source outbreaks result most frequently from faecal contamination of drinking water and food, but water-borne transmission does not appear to be a major factor in industrialised urban communities. The consumption of raw or inadequately cooked shellfish, cultivated in polluted water, may be associated with a high risk of hepatitis A infection. Hepatitis A infection is also

Worldwide these hepatitis viruses are responsible for the majority of all forms of chronic liver disease

common in male homosexuals. In general this virus is not transmitted parenterally by blood and blood products except under experimental conditions.

Clinical Features

The incubation period of hepatitis A is from 3 - 5 weeks with a mean of about 28 days. Although the disease has a low mortality, adult patients may be incapacitated for many weeks. Complications of HAV infection include fulminant hepatitis in a small proportion of patients. This is characterised in the early stages by protracted vomiting, dehydration, confusion and encephalopathy. These patients are also prone to haemorrhagic complications, cerebral oedema, renal failure and hypoglycaemia. Further complications of HAV infection include a protracted cholestatic illness which may be exacerbated by

early onset of normal daily activities and premature exercise. There is no evidence for persistence of the infection and progression to chronic liver damage does not occur.

Diagnosis

Specific serological tests for HAV antigen and antibodies include radioimmunoassay and enzyme-linked immunosorbent assays. Anti-HAV is always demonstrable during the early phase of the illness and titres increase rapidly. The antibody usually persists for many years and its presence indicates immunity. Serological diagnosis of recent infection can be established conveniently by the demonstration of anti-HAV of the IgM class. HAV IgM is detectable in serum for 45-60 days after the onset of symptoms. The presence of HAV IgG alone indicates previous exposure, but not current infection.

Management

Control of infection is difficult since faecal shedding of the virus is highest during the late incubation and prodromal phases of the illness. Therefore strict isolation of cases at the time of illness is not a useful control measure as the spread of the hepatitis viruses is maximum before this time. The spread of hepatitis A in focal outbreaks may be reduced by simple hygienic measures and by the sanitary disposal of excreta.

Passive Immunisation

Normal pooled human immunoglobulin (containing titres at least 100 international units per ml of anti-HAV) may be given intramuscularly before exposure to virus or during the early incubation period to prevent or attenuate the clinical illness. The dosage should be at least 2 international units of anti-HAV per kilogram body weight. In cases of pregnancy or in patients with liver disease, the dose may be doubled. The immunoglobulin does not always prevent infection and excretion of HAV with non-apparent hepatitis may develop.

Passive immunoglobulin immunisation is used most commonly for close personal contacts of patients with hepatitis A and for those exposed to contaminated food.

Prevalence of HBV virus infection differs remarkably in different parts of the world – below 1% in Western Europe to as high as 15% in Africa

---

This mode of control may also be used in limiting outbreaks in institutions. Prophylaxis with immunoglobulin is also recommended for people without antibodies to hepatitis A virus who are visiting endemic areas. The period of protection is about 6 months. Hepatitis A vaccines are still experimental.

2. Hepatitis E (Epidemic Non-A hepatitis or E-NANB)

Epidemiology

Epidemic hepatitis resembling hepatitis A but serologically distinct from it has been reported from the subcontinent of India, Central and South East Asia, the Middle East, North Africa, Mexico and in travellers returning from these regions. The infection is acute, self-limiting and occurs predominantly in young adults. The incubation period appears to be 30-40 days and the illness appears more severe in pregnant women in whom it is associated with a mortality of up to 20%, especially during the last trimester. The infection is spread by the ingestion of contaminated water, and probably, food. The source of the infection is either human or animal faeces. Few secondary cases are recognised but when household contacts of the index case are examined, serial biochemical tests of liver function are abnormal in about 20% of these contacts.

The aetiological agent of E-NANB hepatitis appears to have biophysical and biochemical characteristics of a non-enveloped RNA virus similar to the caliciviruses. E-NANB hepatitis is observed in developing countries; both in local outbreaks and in a sporadic form.

Clinical Features and Diagnosis

The clinical and histopathological characteristics of the disease are comparable with those of acute viral hepatitis, although cholestatic or toxic-like features with morphological changes in the liver are frequently encountered. E-NANB hepatitis specific antigen (HEV Ag) immunologically related to the virus-like particles of HAV is expressed in the cytoplasm of hepatocytes during the early acute phase of infection and is also found to induce specific antibodies in infected primates. These specific anti-HEV antibodies are found in acute and convalescent sera from patients with E-NANB hepatitis in geographically isolated outbreaks. The seroprevalence in Southern Africa is yet unknown as these recently developed tests have not yet been adequately evaluated.

... Viral Hepatitis

3. Hepatitis B Virus

Structure

HBV (also called the Dane particle) is classified as a hepadna virus type I. It has a diameter of 42 nanometers with a 27 nanometer inner core corresponding to the hepatitis B core antigen (HBcAg). Hepatitis B e antigen (HBeAg) is the soluble part of the core antigen and is detected in the blood of patients infected with hepatitis B virus. The virus also

HAV is grossly under-reported and only one type of hepatitis A has been identified

contains a unique circular DNA molecule which is partially double stranded and is associated with a DNA polymerase protein. Three types of particles may be seen by electron microscopy in serum from patients with acute or chronic hepatitis B infection. These are the large, complex Dane particles, and the spheres and tubules which represent excess virally-coded proteins. The surface of all three particles displays the major protein known as hepatitis B surface antigen (HBsAg). The entire DNA of HBV has been cloned in E coli, in yeasts and in several mammalian cell lines.

Hepatitis B Subtypes And Geographical Distribution

Four principal phenotypes of hepatitis B are recognised but other complex permutations of these variants have been described.

In many parts of the world the prevalence of HBV virus infection is much higher than elsewhere. An estimated 300 million people are carriers of HBV virus. The rate of antigen expression in patients 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 antibody to hepatitis BsAg is higher ranging from 4 - 6% in the low prevalence areas to 70 - 95% in Asia and Africa.

Acute Hepatitis B

The clinical expression of acute HBV virus infection is extremely variable and ranges from a fulminant disease (rare) to a 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 appears to be non-cytopathic. Jaundice appears in about 20 - 50% of patients and a minor flu-like syndrome may occur, paticularly in children. Clinical features which may point to hepatitis B virus include a long prodromal period, arthralgia

Outbreaks of HAV in creches may result in large numbers of adults contracting it from members of their families

and skin rashes. It must be stressed that the diagnosis of HBV infection relies primarily on appropriate laboratory tests which confirm elevated serum aspartate amino transferases and alanine amino transferases and hepatitis B serological markers.

HBsAg is detectable at the onset of illness. Following the disappearance of HBsAg anti-HBs appears after a lag period of three weeks. Antibodies directed against HBcAg appear and remain positive. Anti-HBs and anti-HBc persist for years after the patient has recovered and constitute the most

About 300-million are carriers of the HBV virus

lasting evidence of previous HBV infection. IgM anti-HBc disappears at or before six months, when the patient recovers from acute hepatitis B. Total and IgM anti-HBc are present during the 'window' period after MBsAg is lost but before anti-HBs antigen appears. Anti-HBe develops following the disappearance of HBe antigen.

Outcome of acute HBV infection

Most adults with acute HBV infection recover fully within six 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 being male, young at the time of infection and immunosuppression. Chronic carriers of hepatitis B virus typically have mild or asymptomatic disease initially and therefore often do not give a history of previous acute hepatitis.

Chronic Hepatitis B

Patients with HBsAg persisting longer than six months and HBeAg

persisting longer than three months are by definition chronic carriers who may be symptomatic (fatigue and malaise), or asymptomatic - a healthy carrier state. In chronic disease, HBsAg and HBeAg, and DNA from HBV, are usually present in serum or liver. Healthy carriers usually produce HBsAg alone and do not usually have evidence of active viral replication.

Most adults with acute HBV infection recover fully within 6 months, but about 35% of children (and 90% of neonates!) become chronically infected

In chronic active hepatitis B infection markers of active viral replication (HBeAg and HBV DNA) remain elevated for years. Sero-conversion to the non-replicative state occurs years after onset. This is associated with disappearance of HBeAg and HBV DNA. The development of anti-HBe implies the cessation of active viral replication, although HBsAg is still being produced, signifying that the HBV has become integrated into hepatocyte genome. This is an unstable situation as patients may relapse and again develop markers of viral replication. Abortive sero-conversions are also documented with transient flares of hepatitis unaccompanied by loss of HBeAg.

Outcome of chronic HBV infection

Chronic HBV infection includes asymptomatic carriers (who may develop primary hepatocellular carcinoma) and patients with either chronic persistent (CPH) or chronic active hepatitis (CAH). CPH is most often a relatively benign condition which may develop into CAH with histological development of severe portal inflammation and piecemeal bridging necrosis of the liver. Patients with CPH have a good prognosis with less than 10% progressing onto cirrhosis. Patients with CAH have a five year survival rate of 86% in comparison to those with CAH who develop cirrhosis of 55%.

Another potential complication of chronic HBV infection is primary liver carcinoma. Molecular biological evidence has revealed that persistent infection with HBV results in liver cancer with integration of HBV DNA into the DNA of hepatoma cells. The risk of developing liver cancer with chronic hepatitis B virus infection is of the order of 42 times greater than 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.

In 10 - 20% of patients with chronic HBV infection, extra-hepatic manifestation develop which include polyarteritis nodosa, glomerulonephritis, peripheral neuropathy and marrow hypoplasia. These conditions are felt to be related to immune complex diseases.

Epidemiology

The incubation period of hepatitis B infection is 60 - 180 days.
Laboratory tests for hepatitis B have confirmed the importance of parenteral routes of transmission and the infectivity of blood products. However hepatitis B is not spread exclusively by blood and blood products. Under certain circumstances the virus may be infective by mouth, and is endemic in institutions for the mentally handicapped. The virus is also more prevalent in adults and in individuals living under poor socio-economic conditions. There is a huge reservoir of carriers world-wide.

There is much evidence for the sexual transmission of hepatitis B. At very high risk, are male homosexuals and promiscuous individuals. HBsAg has been found not only in blood, but also in saliva, menstrual and vaginal discharges, seminal fluid and serous exudates. These have been implicated in the spread of infection.
Transmission of infection may result from accidental innoculation of minute amounts of blood or fluids contaminated with blood, such as may occur during medical, surgical and dental procedures, immunisation with inadequately sterilised syringes and needles, intravenous and percutaneous drug abuse, tatooing, earpiercing, nosepiercing, acupuncture, laboratory accidents and accidental innoculation with razors and toothbrushes.

The risk of liver cancer with chronic hepatitis B infection is 42 times greater than the general population in Western countries

In certain parts of the world, additional factors may play a role. These include traditional tatooing, scarification, ritual circumcision and,

perhaps as a result of repeated bites by blood sucking insects, although this remains unproven.

Hepatitis B may also be transferred from carrier mothers to their babies during the perinatal period. This appears to be an important factor in determining the prevalence of infection in south east Asia, where

Hepatitis B may be transferred from carrier mothers to their babies during the perinatal period

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 two months after delivery. Although hepatitis B virus can affect the foetus in utero, this is uncommon and appears to occur in less than 5% of cases. In contrast, the peak occurrence in Africa, Greece and Hong Kong is in children rather than in neonates. Here the virus is thought to spread within the family by other unknown mechanisms. This implies that immunisation against hepatitis B within the first or second year of life, may protect against subsequent infection in our southern African populations.

Immunisation

Passive Immunisation

Hepatitis B immunoglobulin is prepared from pooled plasma with a high titre of anti-HBs. This preparation may confer temporary passive immunity for post-exposure prophylaxis. The major indication for the administration of this immunoglobulin is a single acute exposure to HBV such as where blood containing the virus is innoculated, ingested or splashed onto mucous membranes and the conjunctiva. Doses in the range 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 immonoglobulin more than 7 days after exposure to the virus. It is recommended that two doses of the immunoglobulin be given 30 days apart. The recommended adult dosage is about 3ml and the dose of hepatitis B immunoglobulin in the newborn infant 1 - 2ml. The immunoglobulin is given by deep intramuscular injection.

Active Immunisation

Active immunisation is essential for long-term protection. Active immunisation against hepatitis B is required for groups who are at high risk and do not have serological evidence for past or present HBV infection. These include individuals requiring repeated transfusions of blood or blood products, prolonged inpatient treatment, frequent tissue penetration or repeated access for circulation, patients with natural or acquired immunodeficiency or with malignant disease. Viral hepatitis is also an occupational hazard amongst health care personnel and the staff of institutions for the mentally retarded. High rates of infection with hepatitis B occur in narcotic drug addicts, drug abusers, homosexuals and commercial sex workers. Individuals working in high endemic areas are also at an increased risk of infection. Young infants, children and susceptible people living in certain areas where socio-economic conditions are poor and the prevalence of hepatitis B is high should be immunised. The immune response to current hepatitis vaccines is poorer in immuno-compromised patients and the elderly.

The current indications for the use of hepatitis B vaccines in low prevalence areas are noted in Table I.

Specific issues in HBV vaccination

The current commercially available vaccines with plasma-derived or recombinant yeast-derived contain HBsAg but lack HBcAg. These vaccines are safe, immunogenic and effective. Vaccines are usually administered at 0,1 and 6 months and are given by intramuscular injection into the deltoid muscle. There is no risk of HIV or other hepatitis virus transmission with HBV vaccines. In protective efficacy studies, the plasma-derived and yeast-derived vaccines appear to be equivalent. A variable proportion of

Also a substantial risk of perinatal infection if the mother has acute hepatitis B during certain periods of pregnancy

healthy individuals may lose protective levels of anti-HBs at about five 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 for all individuals who have lost protective

... Viral Hepatitis

Table I. Current indications for the use of hepatitis B vaccines in low prevalence areas

1. All health care personnel in frequent contact with blood and needles.
2. Patients who are likely to acquire a large number of blood transfusions at major elective surgery. Patients treated by maintenance haemodialysis, or those being admitted to residential institutions for the mentally handicapped where there is a known high incidence of hepatitis B.
3. Spouses and sexual contacts of patients with acute or chronic hepatitis B. Other family members in close contact should receive the vaccine.
4. Infants born to mothers who are persistent carriers of HBsAg or are positive as a result of recent infection.
5. Individuals who frequently change sexual partners, particularly promiscuous male homosexuals and commercial sex workers. Narcotic and intravenous drug abusers. Long-term prisoners and prison staff, ambulance and rescue services and selected police personnel. Military personnel also require immunisation in certain countries.
6. Immediate protection may be required under certain circumstances following potential and recent exposure to HBV. In this setting, active immunisation with the vaccine is combined with simultaneous administration of hepatitis B immunoglobulin at a different site.

anti-HBs titres but should be strongly considered for individuals who remain in high risk categories. Hypo-responders, which may be identified by post-vaccination anti-HBs testing, may respond with the development of protective levels of anti-HBs on re-vaccination.

Intradermal HBV vaccine administration of one tenth the usual dose, induces anti-HBs in most recipients but the peak response and duration of protection are reduced in comparison to intramuscular administration. Intradermal administration for booster innoculation remains to be evaluated.

The rapid induction of anti-HBs with an accelerated HBV vaccination schedule has potential for post-exposure prophylaxis.

Other vaccines include polypeptide vaccines containing specific HBV antigenic determinants. Clinical trials of these polypeptide vaccines are in progress. Hybrid virus vaccines utilising recombinant vaccinia viruses have been constructed for HBV. However at present there are no accepted markers to prove adequate attenuation of the vaccinia virus for man and known adverse reactions to vaccinia virus vaccines are well documented. Other recombinant viruses are being investigated as vectors for vaccines, in particular oral adenoviruses and polioviruses.

Treatment of chronic HBV infection

The rationale for the anti-viral treatment of chronic hepatitis type B is that even mild forms of liver injury may progress due to episodes of reactivated infection and that untreated patients serve as a reservoir for infection. The risk of hepatoma is about 200-fold greater in HBV carriers. 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.

Of all the agents which have been used to treat chronic type B virus hepatitis, interferon (IFN) either alone or in combination with an immunopriming pulse of steroids offers the most promise. While IFN is usually well tolerated in clinically compensated patients with chronic hepatitis B, there is insufficient data concerning the 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 pre-treatment level of circulating HBV DNA and aminotransferase levels, degree of histological activity, sexual lifestyle and HIV status of the patient influence the response to treatment. The choice of a combination of a short course of steroids and interferon, or interferon alone, may depend upon consideration of these variables in each patient.

Approximately 40% of patients

seroconvert from HBeAg positive to HBeAg negative and anti-HBe positive following treatment, as compared with a spontaneous seroconversion rate of approximately 10% per annum. The ultimate benefits of this treatment are still under study.

More information is needed on the treatment of patients who are HBeAg negative, individuals with mild to moderate decompensated disease, HBV carriers with chronic delta infection and children. Studies also need to address whether the treatment of individuals with persistent viral replication 12 or more weeks after the onset of illness may prevent evolution to chronic infection.

4. Hepatitis D Virus (Delta Agent)

Structure

The hepatitis Delta virus (HDV) is a small defective RNA virus, the only known human pathogenic virus which cannot infect cells or replicate on its own. HDV requires the hepatitis B virus as a 'helper' DNA virus, for its survival. HDV has an outer coat composed of HBsAg, of HBV origin; its own delta antigen and small genome. HDV resembles the so-called satellite viruses of plants which are likewise coated by capsid material of obligatory helper viruses. The virus appears to be directly cytopathic in contrast to hepatitis B where damage appears to be immune mediated.

Clinical Features

When acute delta hepatitis occurs in a chronic HBsAg carrier, this is known as superinfection. Simultaneous acute delta and acute hepatitis B infection is called co-infection. Superinfection often leads to chronic delta infection whereas co-infection rarely does. Superinfection may be asymptomatic or may be serious, leading to fulminant hepatitis. Therefore delta hepatitis, although not as common as the other hepatitis viruses, is important because of its severity.

Epidemiology and Control

The geographic prevalence of hepatitis D virus in carriers of HBsAg suggest that this infection is important in the Middle-East, parts of Africa and South America. The studies performed in southern Africa to date, suggest that delta agent is absent or very rare despite the large pool of HBsAg carriers. There is, however, no cause for complacency as the rapid spread of HIV virus throughout our subcontinent illustrates. A similar process may occur with HDV in view of the large reservoir of HBV carriers in our subcontinent. The mode of transmission of HDV is similar to that of HBV and is predominantly parenteral, but non-percutaneous spread also occurs. Immunisation against hepatitis B will also protect against infection with the delta agent by depriving HDV of its protective HBsAg coat.

Treatment

Established delta hepatitis is currently treated along the same lines as chronic hepatitis B infection, with interferon. There is presently no alternative treatment for this serious disease and improvement may only occur in about 25% of patients. This however seems to require ongoing treatment and may not be related to a direct antiviral action nor to an inhibition of HDV replication.

5. Hepatitis C Virus (HCV)

Structure

The hepatitis C virus (HCV) appears to be an RNA virus with a lipid envelope about 18 nanometres in diameter and belonging to the toga or flavivirus family. Interestingly, both these families are arboviruses, a group of viruses usually transmitted by insect bites.

Epidemiology

According to published reports, HCV is a major cause of transfusion associated non-A non-B (NANB) hepatitis throughout the world and may play a role in community acquired NANB hepatitis as well. Approximately 75% of chronic post transfusional hepatitis (PTH) cases from the United States, Japan and Italy were found to have markers of HCV infection. In addition, about 58% of community acquired chronic NANB hepatitis cases with no identifiable source of parenteral exposure appear to be positive for anti HCV. There also appear to be more than one NANB virus responsible for PTH.

Predominant modes of transmission for HCV virus include contact with blood or blood products, the sharing of contaminated needles or syringes and sexual or intimate contact with a HCV carrier. At highest risk are recipients of multiple units of blood and especially recipients of commercial factor VIII concentrates. We have recently shown that 60% of haemophiliacs at Groote Schuur Hospital have markers for hepatitis C virus, in agreement with the international literature. Likewise, we have shown that about 20% of a randomly selected patient population with auto-immune chronic active

hepatitis and alcohol-induced cirrhosis, have markers for HCV. Healthy pregnant women do not appear to have markers for HCV in our institution. A survey of blood donors at the Transfusion Services is in progress.

Clinical Features

Acute NANB hepatitis secondary to HCV virus appears to run a mild anicteric course in about 75% of patients. Because of the frequency of asymptomatic mild disease, many cases of HCV hepatitis remain undetected. Despite its relatively mild, often asymptomatic course, acute NANB hepatitis secondary to hepatitis C virus has a tendency to progress to chronic liver disease in about 50% of patients. Fluctuating transaminase patterns most often persist although the magnitude of ALT elevation decreases. Despite mild or absent symptoms, chronic NANB hepatitis may progress very rapidly with the early onset of chronic hepatitis and cirrhosis. There are associations with hepatocellular carcinoma.

Diagnosis

Antibodies against HCV serve as markers for this infection. Although 54% of acute phase sera taken within 30-60 days of onset test positive, this figure increases to 67% of chronic phase sera taken 6 - 36 months from onset. Therefore in the acute setting the diagnosis of HCV will still be one of exclusion. Additional data which aid in the diagnosis are epidemiological factors (history of exposure to blood or blood products, intravenous drug addiction and the episodic fluctuating ALT patterns.

Control

Testing for anti-HCV substantially improves the safety of transfusion of blood and blood products, likewise steps taken to reduce the transmission of HIV have led to the exclusion of patients most likely to carry HCV infection. Passive immunisation against HCV has not been entirely effective but may be tried following parenteral exposure to contaminated blood products. There are no vaccines for HCV at this present time.

Viral hepatitis is an occupational hazard amongst health care personnel of institutions for mentally retarded

---

Treatment

The treatment of HCV CAH remains a vexed problem. Because of the lack of markers until recently, all clinical studies have been performed on heterogenous groups of patients. The only recognised effective mode of treatment is again that of alpha interferon. In NANB hepatitis a much lower dosage regimen is required but for a much longer period. Priming with steroid treatment does not appear to be essential in this form of hepatitis.

6. Hepatitis F Virus (HFV or F-NANB)

This is an epidemiological entity with no specific markers. It may arise sporadically or in outbreaks, and results in fulminant and sub-fulminant hepatitis in a large proportion of patients. Patients usually develop encephalopathy up to 12 weeks following the onset of jaundice, and have a fluctuating clinical course characterised by periodic elevations of transaminases. The presence of jaundice, marked coagulation disturbances, renal impairment and age over 40 years appear to indicate a poor prognosis with a mortality in excess of 90%. The only recognised modalities of treatment here are liver transplantation.

Conclusion

In this clinical review I have attempted to summarise current information on the hepatitis A, B and NANB viruses. The NANBH virus group, although heterogenous, is being further sub-classified and we have solid serological data for the identification of two other viruses, hepatitis C virus and hepatitis E virus. The delta agent appears to be rare in southern Africa but further epidemiological surveys are required to confirm this finding.

The major concern in southern Africa is to control hepatitis B virus and prevent the apalling sequelae of chronic infection with this virus. Universal vaccination of infants in high risk areas is important but will only be possible once the costs of vaccine are reduced locally to such an extent that this can be an affordable practice.

Acknowledgements

Richard Hift reviewed the manuscript and gave useful comments and criticisms. Thanks to Lavinia Petersen for her meticulous secretarial assistance in preparation of this paper.

... Viral Hepatitis

Bibliography

Hepatitis A

Lemon SM. Type A viral hepatitis. N Eng J Med 1985; 313: 1059-67.

Hepatitis B

Sutherland S. Update on viral hepatitis. The Practitioner. 1986; 230: 237-46.

Sarver D. Hepatitis in clinical practice. Postgrad Med 1986; 79 (4): 194-214.

Hoofnagle JH. Towards universal vaccination against hepatitis B virus. N Eng J Med 1989; 321: 1333-4.

Kirsch RE, Robson SC. Prevalence of Hepatitis B in Southern Africa. S Afr Med J. Editorial. 1989; 75: 461.

Hoofnagle JH, Peters M, Mullen KD et al. Randomized, controlled trial of recombinant human alpha interferon in patients with chronic type B hepatitis. Gastroenterology. 1988; 95: 1318-25.

Hepatitis C and other NANBH

Zuckerman AJ. The elusive Hepatitis C virus. Br Med J 1989; 299: 871-3.

Kuo G, Choo Q-L, Alter HJ et al. An assay for circulating antibodies of a major etiologic virus of human non-A, non-B hepatits. Science 1989; 244: 362-4.

Alter HJ. Non-A, Non-B Hepatitis: Sorting through a diagnosis of exclusion. Ann Int Med 1989; 100 (8): 583-5.

Dienstag JL, Alter HJ. Non-A Non-B Hepatitis: Evolving epidemiologic and clinical perspectives. Seminars Liv Dis 1986; 6: 67-81.

Hepatitis D

Hoofnagle J. Type D (Delta) Hepatitis. JAMA 1989; 261 (9): 1321-5.

Rizzetto M, Verme G. Delta Hepatitis – Present status. J Hepatol 1985; 1: 187-93.

Hepatitis E

Ramalingaswami V, Purcell RH. Waterborne non-A, non-B hepatitis. Lancet 1988; T: 571-3.