CONTINUING MEDICAL EDUCATION

Viral Hepatitis

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Introduction

The term hepatitis indicates liver inflammation primarily involving ongoing hepatocellular necrosis. It is typically characterised by a disproportionate elevation of serum alanine aminotransferase (ALT) compared with serum alkaline phosphatase and bilirubin levels. So far, seven viruses (A, B, C, D, E, F and G) have been described as agents of acute or chronic hepatitis. Of these hepatitis viruses A, B, C, D, and E are all well-characterised, molecularly defined agents with unequivocal disease associations. Other viruses which may cause acute hepatitis but do not result in chronic liver disease in the immunocompetent hosts include EBV, HSV, CMV and adenovirus.

Hepatitis A virus (HAV)

The hepatitis A virus (HAV) is the most widespread of all the hepatitis viruses. It is usually transmitted in food or water contaminated with infected faecal material. Infection with HAV usually follows an acute asymptomatic or mildly symptomatic course. As a result of changing epidemiology, decreasing endemicity and reduced acquired immunity to hepatitis A infection, the clinical pattern of acute hepatitis A is changing, with a transition from asymptomatic childhood infections to an increased incidence of symptomatic disease in the 18- to 40-year-old age group. This is because the age at which hepatitis A infection is acquired is the major determinant of disease severity.

A second factor that may lead to an increase in the severity of acute viral hepatitis A is the presence of concomitant infections or disease. Existing chronic hepatitis B infection has been reported to increase the risk of developing acute liver failure following hepatitis A infection. It is not clear whether it is the presence of hepatitis B itself or the degree of liver damage associated with chronic hepatitis B that determines the final outcome of superimposed hepatitis A. Nevertheless, those with well-compensated liver disease appear to tolerate hepatitis A quite well, whereas those with limited hepatic reserve will probably develop a more severe disease when infected with hepatitis A as well. Alcoholics, promiscuous homosexual men and injection drug users all appear to be at increased risk of severe disease as a result of hepatitis A, and it has been speculated that this occurs as a result of underlying chronic liver disease.

Until recently, the options for HAV prevention were limited to advice on hygiene and/or passive immunization with HAV immunoglobulins, which provide protection for around 3 months. With the availability of inactivated hepatitis A vaccine protection for up to 10 years is now possible with only a single dose, followed by a booster at 6 months. Thus, the high-risk groups can now be protected effectively, and this is likely to markedly reduce associated morbidity and mortality.

Hepatitis B virus (HBV)

Currently approximately 350 million people - or 5% of the world's population - are chronic carriers of the hepatitis B virus. Nearly 25% of all carriers will develop serious liver diseases such as chronic hepatitis, cirrhosis and primary hepatocellular carcinoma. According to WHO estimates, hepatitis B infection causes more than one million deaths every year from HBV-associated cirrhosis and primary liver cancer.

Ever since hepatitis B vaccines became commercially available in 1982, more than 80 countries, including Malaysia, have introduced it into their national immunization programmes. Since most HBV infection occurs during childhood, the vaccine is 80-95% effective in preventing the carrier state. Thus, in any
country vaccination will essentially eliminate horizontal transmission in immunised cohorts. In fact, a recent study in Taiwan has already shown evidence of a reduction in liver cancer among those immunised in childhood.

While the disease can be prevented by vaccination, effective antiviral therapy is needed for existing carriers to reduce the morbidity from the sequelae of this disease. Interferon therapy has so far remain the mainstay of treatment of hepatitis B, even though it is effective in fewer than half of the patients, is expensive, and is not without side effects. The recommended regimen is either 5 million unit daily or 10 million units thrice weekly, given subcutaneously for 4 months. On the other hand HC Thomas et al and the International Hepatitis Trial Group had shown that 2.5 MIU.m\(^{-2}\) of interferon-alpha 2a, given 3 times weekly by intramuscular injection for 24 weeks was adequate in clearing HBeAg and HBV DNA, even after follow-up for 12 months after treatment was discontinued. A more recent study was even able to associate treatment of interferon-alpha with improved clinical outcome on follow-up for around 4 years.

Other antiviral therapies for chronic hepatitis B have been attempted and several have shown remarkable success. Inosine pranobex (Isoprinosine), a compound with antiviral and immunomodulatory activity, has been reported to induce seroconversion in 43% of HBeAg-positive patients. Thymosin alpha 1 is a synthetic immune stimulant that is known to enhance suppressor T-cell activity and in vitro B-cell synthesis of IgG. Small controlled trials have shown that HBV DNA become negative in some patients with chronic hepatitis B. New oral nucleoside analogues with potent activity against HBV and low toxicity in man have been discovered and are currently being used before and after liver transplantation to prevent HBV reinfection. They include lamivudine and famciclovir. Unfortunately with lamivudine HBV resistance due to mutations has already been reported.

Hepatitis C virus (HCV)

Since the discovery of the HCV genome in 1989, it has been recognised that hepatitis C accounts for 60-90% of what was formally known as NANB hepatitis. Like hepatitis B, chronic hepatitis C is often silent. In fact 50% may even show normal or minimally elevated ALAT. Even so, these patients can have significant histological evidence of hepatitis in the presence of normal ALAT levels. Of those who are acutely infected, one study showed that 50% will develop cirrhosis, and life-threatening complications will occur in 15% in the subsequent 4 years, but that study did not address the risk to progression in the individual. Factors that influence the natural history include mode of acquisition, viral load, viral genotype, and concomitant alcohol use. Epidemiologic evidence have already implicated hepatitis C as a possible cause in the development of some cases of hepatocellular carcinoma.

In the use of interferon alpha for chronic hepatitis C, large placebo controlled trials indicate that 50% will have normal ALAT after 6 months of interferon alpha 3 MU three times a week. After treatment for 6 months, half of the initial responders will promptly relapse. Since relapses still occur (although at a lower rate) after higher doses and patients have more side effects, giving a second course of treatment with a different interferon may be useful in some patients. Unfortunately, this will require the need for HCV RNA testing facilities. Others have even suggested that categorising patients as 'good' or 'poor' responders according to the known host and viral determinants of response to interferon may be a third option since long term response rates to treatment have been disappointing. Several workers have suggested that those with types 2 and 3 infection are more likely to have a sustained response to treatment than those with type 1 and possibly type 4. Long term responses are also higher in patients with lower circulating levels of virus. Therefore, patients in the good response group could be offered interferon alpha for one year, whereas those in the poor response group may require combination antiviral therapy with ribavirin.

Recently, a study from Japan actually claimed that interferon alpha improved liver function in chronic active hepatitis C with cirrhosis, and its use was associated with a decreased incidence of hepatocellular carcinoma.
**Hepatitis D virus (HDV)**

The hepatitis D or delta virus (HDV) is a unique RNA virus that infects only persons simultaneously infected by the hepatitis B virus. Three genotypes of HDV have been cloned and sequenced. Like the satellite RNA viruses of higher plants, HDV depends on a second virus, HBV to become infectious and activated to produce disease.

Infection with HDV can lead to either an acute or chronic hepatitis - both forms are severe. Acute delta hepatitis is often fulminant. Chronic delta hepatitis frequently results in cirrhosis, hepatocellular failure, and death. In Taiwan it was found that when compared with genotype I, genotype II was less frequently associated with fulminant hepatitis at the acute stage, and it showed an unfavourable long-term clinical outcome at the chronic stage in that genotype II was dominant in cirrhosis and hepatocellular carcinoma.

Early studies have shown that interferon is the drug of choice for chronic type D hepatitis and that high doses ranging from 5-10 MU will be required, and administered for a prolonged and possibly indefinite period due to the high frequency of relapse of the disease on discontinuation of therapy.

**Hepatitis E virus (HEV)**

Hepatitis E, previously known as enterically transmitted non-A, non-B (ET-NANB) hepatitis is due to a non-enveloped, ssRNA virus. It is found predominantly in the warm countries of Asia, Africa, the Mediterranean, and Central America where it occurs in the form of epidemics or sporadic cases.

In uncomplicated cases hepatitis E lasts 12-15 days, and complete recovery usually takes place within one month. Hepatitis E infection does not appear to progress to a chronic state although it can aggravate the course of chronic hepatitis B and result in increased mortality. It carries a higher rate of fulminant disease during epidemic and sporadic episodes, when compared with hepatitis A and hepatitis B. Fulminant disease occurs predominantly in pregnant women, especially in the third trimester, with case fatality rates ranging from 10-40%. Death is usually due to encephalopathy, hemorrhagic diathesis, or renal failure.

Commercial assays for serological diagnosis are currently available worldwide. Using these assays and studies with molecular probes, protracted viremia up to 7 weeks with associated fecal shedding was discovered, well after clinical and biochemical recovery. This may account for the frequent reported epidemics and sporadic episodes associated with hepatitis E. Although the study involved a small number of patients, it was also found that hepatitis E commonly causes intrauterine infection as well as substantial perinatal morbidity and mortality.

**Hepatitis F virus (HFV)**

The agent tentatively designated the hepatitis F virus has been described by two groups. The first was reported by Fagan et al in 1992 when a toga virus-like agent was visualised by electron microscopy from liver biopsies of patients with unexplained fulminant viral hepatitis. Further work was subsequently done in excluding hepatitis A, B, C and E by polymerase chain reaction. In 1994 a second group discovered a virus from the feces of a patient with hepatitis and was transmitted to primates. It is not certain if this was the same virus described by Fagan et al. In any case, the findings have not been substantiated, and the role of this virus remains unclear. In fact, the classification of these isolates as a new hepatitis virus was probably premature.

**Hepatitis G virus (HGV)**

Of latest interest are the novel blood-borne viruses that were recently discovered by two independent teams, and designated hepatitis GB virus C (HGBV-C) and hepatitis G virus (HGV). Both actually turned out to be different isolates of the same virus. They are single-stranded RNA viruses, with genomic organization resembling that of the Flaviviridae, and they are distantly related to hepatitis C virus.

Epidemiologically it has been proven that the agent can be transmitted parenterally but no data is
available yet on the sexual or perinatal spread. Such data will only be forthcoming when serological assays become available. Although antibody to E2, an envelope protein of HGV has been detected in some patients, it will be sometime yet before a test kit becomes viable for commercial use. At the moment detection depends on the measurement of HGV RNA by polymerase chain reaction.

As to whether it causes acute liver injury and whether it leads to serious chronic liver disease, the jury is still out. One recent report only managed to show evidence of persistent infection with HGV without progression to chronic disease even in the presence of concomitant hepatitis A, B or C.

References


MCQ

1. Hepatitis A
   A. is only transmitted by the fecal oral route
   B. is usually asymptomatic among the children
   C. can progress to a fulminant course in children as well as in adults
   D. increases the development of acute liver failure in all chronic hepatitis B carriers
   E. can be prevented by giving 2 doses of inactivated hepatitis A vaccine

2. The following are true of hepatitis B:
   A. The causative agent is a partially double-stranded DNA virus
   B. Response to interferon therapy is indicated by the disappearance of both HBV DNA and HBeAg.
   C. Famciclovir alone may be used in the treatment of chronic hepatitis B
   D. Hepatitis B vaccine only contains HBsAg.
   E. Hepatitis B immunization of all age groups will be required to eliminate the horizontal transmission.

3. The following are true of hepatitis C:
   A. Presence of antiHCV antibody indicates previous exposure with recovery.
   B. Chronic active hepatitis C always presents with raised ALAT levels.
   C. Relapse following interferon therapy can be reduced by just increasing the doses.
   D. Patients with HCV genotype 1 and low viremia will still respond poorly to interferon therapy
   E. Combination therapy is available for patients who are resistant to interferon.

4. Hepatitis D
   A. is transmitted parenterally
   B. coinfection occurs in chronic hepatitis B carriers
   C. is associated with hepatocellular carcinoma
   D. genotypes do not influence the response to interferon therapy
   E. can be prevented by giving hepatitis B vaccine

5. The following are true of viral hepatitis:
   A. Cytomegalovirus infection frequently presents with hepatitis in AIDS patients
   B. Fulminant hepatitis E occurs predominantly among the pregnant women
   C. Chronic hepatitis E can occur
   D. Hepatitis G is transmitted parenterally
   E. Persistant hepatitis G is associated with raised ALAT levels