LEADING ARTICLE

HEPATITIS A UPDATED

I Yap

SINGAPORE MED J 1995; Vol 36: 23-24

Hepatitis A is a relatively old disease that has been well-documented since the 17th century, especially during warfare. A viral aetiology was postulated in 1908[1] and this was not proven until 1944, when the hypothesis that the disease could be transmitted by bacteria-free faecal filtrate was demonstrated[2]. The aetiological agent of hepatitis A was discovered in 1973[3] and the concurrent demonstration of specific antibody to hepatitis A antigen in sera of convalescent hepatitis A patients brought an important breakthrough in the field of viral hepatitis A.

Hepatitis A virus (HAV) is a pathogenic, hepatotropic picornavirus transmitted by the faecal-oral route, either from person to person or through contaminated food or water. Viral replication probably occurs in the jejunum prior to transmission via the portal vein to the liver. HAV is then shed in bile and hence to faeces. Man is probably the only natural host. HAV usually causes a minor or unnoticed illness in children and young adults, and on a worldwide scale fewer than 5% of cases are recognised clinically[4,5]. In recent epidemics in rural China, about one third of those shown serologically to have had acute HAV were never symptomatic and only 20% had overt clinical hepatitis[6]. The mean incubation of hepatitis A is approximately 30 days with a range of 15-50 days and may be dose dependent. Nearly all adult patients with clinically apparent diseases have complete recovery by 6 months. Relapses and prolonged cholestasis are unusual manifestations of hepatitis A and recovery is the rule and chronic hepatitis is not seen. Although hepatitis A is usually a self-limiting infection, its severity and fatality increase with age[7]. Fulminant hepatitis A is rare and is also age-dependent. In infants and children (up to 14 years of age), the case-fatality rate is 0.1% while in adolescents and young adults (age 15-39), it increases to 0.4%, and among patients 40 years or older, it is 1.1%[8]. However hepatitis A during pregnancy is not associated with increased severity of the hepatitis, increased maternal mortality, foetal losses or identifiable chromosomal abnormalities[9].

The diagnosis of hepatitis A required the detection of immunoglobulin M antibody to HAV (IgM anti-HAV). IgM anti-HAV levels peaked during acute or early convalescent phase and disappeared by 3 to 4 months after the onset of illness. IgG anti-HAV reaches peak levels during convalescent phase and remains detectable for decades. Serum alanine and aspartate aminotransferase levels usually rise rapidly during the prodromal period, reaching peak levels that are often well about 500 iu/l. High levels are found in patients with severe hepatitis but are not necessarily a bad prognostic sign. Subsequently aminotransferase levels decrease by about 75% per week for a few weeks. Serum bilirubin concentrations reach peak level later and decline less rapidly. The period of jaundice, if present, tends to be brief, persisting for less than two weeks in about 85% of cases.

Epidemiologic patterns of hepatitis A infection vary in different parts of the world although the difference are linked more to socio-economic conditions than to geographic regions. In countries with poor hygiene and sanitation, subclinical childhood infection is common and most children are immune by the age of 10 years. As standards of hygiene improve, infection is delayed until adolescence or early adult life when they are usually associated with clinical illness. In developed countries with high standards of hygiene or sanitation, infection is uncommon in the young and is usually acquired during travel to endemic areas[10-12]. Recent local studies have shown progression of the pattern of age-related hepatitis A virus exposure towards that seen in developed countries[13,14]. The frequency of HAV infections has also declined in many developing countries and these changes have been attributed to improved standards of public health. However, decreased asymptomatic childhood HAV infections have paradoxically increased the proportion of susceptible adults and creating the potential for large-scale epidemics such as the recent hepatitis A epidemic that occurred in Shanghai which involved more than 300,000 cases[15].

Treatment of HAV infection has been mainly supportive. Bed rest and high calorie nutritional supplementation have not been proven to have value in controlled trial. Corticosteroids may be of value in expediting recovery from late cholestasis[16] but a trial of methyl-prednisolone in acute infection showed a higher mortality in treated patients than those who received placebo[17].

Improving standards of hygiene and sanitation by proper sewage disposal and clean water supplies are traditional ways in reducing HAV infection. This is a relatively slow process and takes two or more decades to accomplish and eventually although the number of infections is falling, the shift of infection to older age group will increase the number of clinical infections. Human immunoglobulin has been used in developed countries as prophylaxis both before and after exposure. However, it may become less effective with the declining prevalence of immunity to hepatitis A and it is costly and gives only short-lived protection (3 to 6 months). The development of the hepatitis A vaccine offers a better alternative to passive immunisation for high risk groups. An inactivated hepatitis A vaccine (Havrix, SmithKline Beecham Biologicals) licensed in December 1991 showed a sero-conversion rate of 95.7% one month after the first dose and 99.8% after the second dose[18]. The antibody titers obtained after two doses of the vaccine were 25 times higher than those observed following administration of immunoglobulin, which is known to protect against the disease. Another inactivated hepatitis A vaccine has been shown to be highly protective in an endemic setting in United States after a single dose[19]. The vaccines being tested are likely to protect against all strains of HAV. The duration of protection of hepatitis A vaccine is unknown but it seems likely that the vaccine can induce long periods of protection against clinical disease after a course of three doses. Use of

Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

I Yap, MBBS, M Med (Int Med), FAMS
Associate Professor

hepatitis A vaccine will depend on the epidemiological circumstances of the country concerned, the cost of the vaccine and the duration of protection that the vaccine affords. The relatively high cost of the inactivated HAV vaccine will probably preclude its widespread use on a population basis for a number of years. It is recommended for travellers to endemic areas, army personnel, people working with children, male homosexuals, intravenous drug abusers and food handlers whose lifestyle or occupation place them at increased risk of infection. Live attenuated vaccine has been developed and undergoing clinical trial. On theoretical grounds, a live attenuated vaccine would be more potent, cheaper and would induce an even longer duration of protection, but this remains to be established. So far inactivated or live attenuated vaccine has been given by injection; the oral route would be preferable but results have been disappointing. Points of concern include excretion and transmission of the virus, reversion to virulence and the possibility of persistence of the virus in the liver. Combinations with other vaccines such as hepatitis B vaccine, diphtheria-petussis-tetanus or haemophilus influenzae type b should be developed to make routine use of hepatitis A vaccine more practical and cost effective. The price of vaccine must be lowered so that universal infant and/or adolescent immunisation becomes cost-effective throughout the world.

References

1. McDonald S. Acute yellow atrophy of the liver. Edinburgh Med J 1908; 1: 83.
2. MacCallum FO, Bradley WH. Transmission of infective hepatitis to human volunteers. Lancet 1944; ii: 228.
3. Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: detection by immune electron microscopy of a virus-like antigen associated with acute illness. Science 1973; 182: 1026-8.
4. Gust ID, Feinstone SM. Hepatitis A. Boca Raton, Florida: CRC Press. 1988: 163-91.
5. Lemon SM. Type A viral hepatitis. New developments in an old disease. N Engl J Med 1985; 313: 1059-67.
6. Yang NY, Yu PH, Mao ZX, Chen NL, Chai SA, Mao JS. Inapparent infection of hepatitis A virus. Am J Epidemiol 1988; 127: 599-604.
7. Forbes A, William R. Increasing age – an important prognostic factor in hepatitis A virus infection. J R Coll Physician Lond 1988; 22: 237-9.
8. Centers for Disease Control. Hepatitis Surveillance Report. Morbidity Mortality Weekly Report. 1990; 53: 23.
9. Koff RS. Clinical manifestations and diagnosis of hepatitis A infection. Vaccine 1992; 10: S15-S17.
10. Gust ID, Feinstone SM. Hepatitis A. In: Proper H, Schaffner F. eds. Progress in liver diseases, Vol 9. New York: Grune & Stratton 1989: 371-8.
11. Forbes A, Williams R. Changing epidemiology and clinical aspects of hepatitis A. Med Bull 1990; 46: 303-18.
12. Szmuness W, Dienstag JL, Purcell RH, Stevens CE, Wong DC, Ikram H, et al. The prevalence of antibody to hepatitis antigen in various parts of the world: a pilot study. Am J Epidemol 1977; 106: 392-8.
13. Yap I, Guan R. Hepatitis A sero-epidemiology in Singapore: a changing pattern. Transaction of the Royal Soc Tropical Med Hygiene 1993; 97: 22-3.
14. Fock KM, Tay HH, Phua KB, Guan R, Chia SC, Chong R, et al. Seroprevalence of antibodies against hepatitis A in Singapore: The NFDD experience. Singapore Med J 1994; 35: 30-1.
15. Halliday ML, Kang LY, Zhou TK, Hu MD, Pan QC, Fu TY, et al. An epidemic of hepatitis A attributable to the ingestion of raw clams in Shanghai, China. J Infect Dis 1991; 164: 852-9.
16. Gordon SC, Reddy KR, Shiff L, Shiff ER. Prolonged intrahepatic cholestasis secondary to acute hepatitis A. Ann Intern Med 1984; 101: 635-7.
17. Gregory PB, Knauer CM, Kempson RL, Miller R. Steroid therapy in severe viral hepatitis A: a double blind, randomized trial of methyl-prednisolone versus placebo. N Engl J Med 1976; 294: 681-7.
18. Andre FE, D'Hondt E, Delem A, Safary A. Clinical assessment of the safety and efficacy of an inactivated hepatitis A vaccine: rationale and summary of findings. Vaccine 1992; 10: S160-S169.
19. Werzberger A, Mensch B, Kuter B, Brown I, Lewis J, Sitrin R, et al. A controlled trial of formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med 1992; 327: 453-7.