Review Article

Viral hepatitis-Recent trends and aeromedical implications

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Infective diseases are of critical importance to the Armed Forces. The sudden outbreak of a contagious illness can compromise operational efficiency. Traditionally hepatitis caused by Hepatitis A Virus (HAV) has been considered to be of special importance to the military due to its feco-oral transmission route and predilection for group living under poor hygienic conditions, both these situations are precipitated during war and mass troop movements. The risk of contacting hepatitis B and C also increases exponentially during wartime due to injuries, in helping military or civilian personnel who are injured, due to urgent blood transfusion of unscreened blood and probably due to increased promiscuity[1]. In peace time also hepatitis causes considerable morbidity with consequent loss of man days. Post Hepatitis, after apparent recovery, also merits surveillance.

Viral hepatitis (VH) is a systemic viral infection in which hepatic inflammation and necrosis predominate and cause characteristic clinical, biochemical and pathological features. There have been rapid advances in understanding the etiology, immunopathology and management of VH. Controversy still exists as to the need and duration of convalesence period as also its impact on the rather stressful nature of flying duties. A brief review of the subject with emphasis on epidemiological, preventive and aeromedical aspects is presented here.

The agent

There is now direct evidence of five types of viruses and probably some more will be found in the future. These viruses have been given alphabets to designate them *viz* Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C virus (HCV), Hepatitis D virus (HDV) and Hepatitis E virus (HEV). HCV and HEV were earlier grouped as Non A-non B virus (NANB).

HAV was discovered in 1973 [2]. It is an enterovirus of the Picorna group [3]. It measures approximately 27 nm in diameter and has a single stranded RNA structure. It is inactivated by chlorination at 1.0 PPM residual chlorine at half an hour or by boiling water for one minute and by ultraviolet rays. It can survive acid pH of 3.0 upto 3 hours.

HBV is a DNA virus in the form of small circular partly double stranded particle. It was discovered in 1965 by Blumberg [4] for which he was later awarded the Nobel Prize. Eversince its discovery, this virus has been the subject of intense study and there has been an explosion of knowledge about this virus. It circulates in the blood in three distinct forms (i) 22 nm spherical particles (ii) Rod like shapes with a diameter of 22 nm but variable length measuring upto several hundred nm (iii) 42 nm spherical particle known as Dane particle. The first two forms represent the excess surface antigen whereas Dane particle is the complete virus. HBV is inactivated by autoclaving, dry heat temp of 100°C for 20 minutes or glutaraldelyde 0.1–1.0% at 24°C in 5 minutes.

HDV was recognised by Rizzeto in Italy in 1977 [5]. It is believed to be a defective RNA virus, which needs HBV for its own survival.

Therefore it can only infect an individual who also has pre-existing or concurrent infection with HBV. In most instances it goes unrecognised and the patient is labelled to be suffering from HBV infection. When actively looked for, the prevalence of HDV among HBV infected individuals is reported to be varying from 2% to 6% in different parts of the world.

HCV was earlier known as the parenteral NANB hepatitis virus. The genome of this virus was worked out in 1988 using specialised techniques involving computerised amino acid sequence analysis [7]. It is believed to be an enveloped, positively stranded RNA virus whose size is about 10 kilobases [8].

HEV is the other member of the NANB group. It was known as Enteric NANB (ENANB) before it was named as HEV. It is a 29 nm RNA virus of the family calciviridae. It is only slightly longer than HAV.

Immunopathology

The viruses or components of the virus acting as antigens in the human host lead to very important immune reactions and many of the clinical features are caused by these immune reactions. In the case of HBV, the virus is known to be noncytopathogenic and the clinical spectrum is totally immune-mediated [9], the various immunological changes are summarised in the table.

Besides this humoral immunity, the various components of cell mediated immunity like lymphocytes and macrophages take active part in the pathogenesis of the hepatic lesions as well as the extra hepatic abnormalities.

Epidemiology

The epidemiology of viral hepatitis is known since long. The development of specific laboratory tests in the 1960s, 1970s and finally 1980s have resulted in important revisions of many concepts. Broadly the HAV and HEV form one epidemiological group and HBV, HCV and HDV form the other group.

The mean incubation period for HAV is about 30 days with a range of 15–40 days. HEV also has more or less similar incubation period. Transmission of HAV is only from cases to susceptible humans and there is no reservoir of infection. HAV attacks mostly children, and is uncommon among adults. Converse is true of HEV. HEV occurs in large epidemics. The

Antigen	Antibody	Remarks
HAV	Anti HAV IgM IgG	Acute infection Past infection
Hep B Surface Antigen (HBs Ag)	Anti Hbs	HBs Ag is detected in the serum during early part of illness later the HBSAg is replaced by Anti HBs
Hep B Core Antigen (Hbc Ag)	Anti HBc IgM IgG	Acute infection with HBV In Chronic infection HBc Ag does not circulate in the blood.
Hep B E Antigen (HBe Ag)	Anti HBe	HBe Ag represents active viral replication. Anti HBe represents reduced or no viral replication.
Hep D Antigen (HD Ag)	Anti HD IgM IgG	
Hep C Antigen (HCAg)	Anti HCV	
Hep E Antigen (HE Ag)	Anti HEV	

earlier epidemics which were considered to be due to HAV have now retrospectively been proven to be due to HEV like the large Delhi epidemic of 1955. HEV, constitutes about 44% of sporadic adult cases of acute viral hepatitis, where as HAV contributes about 14% [11].

The incubation period of Hepatitis B has a wide range of 28–180 days, with a mean of 70–80 days. The inoculum size is probably inversely related to the incubation period as shown in some experimental studies [12]. The incubation period of HAV seems to over lap that of HBV. For HCV the incubation period appears to be about 15–160 days with a mean of about 27–50 days.

Infective materials and period of infectivity: HAV and HBV have faeco-oral transmission. HAV is demonstrated in the liver, bile and faeces. HAV is demonstrated in faeces from late incubation period to early symptomatic phase. Peak viral shedding occurs around the time of onset of symptoms. The virus is excreted in the stools of patients for a brief period mostly in the preicteric phase. This point is very important and makes prevention difficult. By the time the patient is diagnosed to be having viral hepatitis, he has already been excreting virus particles. In fact once the jaundice has appeared, stools of most of the patients become non-infectious as virus shedding declines and in 90% patients it completely stops by 2nd-3rd week of illness [10]. In HBV infection viraemia occurs in the incubation period and in the symptomatic phase. In one study on volunteers, Hepatitis B was transmitted with blood taken 87 days prior to onset of symptoms. HBs Ag may be found in serum sometimes as early as one week but usually 1–2 months after exposure. Viraemia may persist in 5–10% beyond convalescence and these cases become the chronic carriers. HBV is present in most secretions and excretions. The only other important route of transmission is sexual contact. Precise information is not available about other forms of hepatitis, but it is felt that infective materials and periods of infectivity for HCV and HDV resembles that of HBV and HEV resembles HAV in this regard.

Modes of transmission

Feco-oral transmission is the major route of spread for HAV and HEV. Blood borne spread is likely, but less important, because there are no chronic carriers of HAV. For HBV, blood borne spread is the most important followed by venereal spread. The other important mode of spread is the vertical transmission from the mother to the child during birth or early post-partum. The mode of transmission for HCV and HDV is considered to be similar to that of HBV.

HAV and HEV occur as epidemics due to water or food borne spread. Most of the epidemics initially considered to be due to HAV including the great Delhi epidemic of 1955 have now been proven to be due to HEV [14]. Fecal contamination of cooked food by food handlers and flies is also important in the spread of HAV and HEV. Blood sucking insects like bed-bugs and mosquitoes have been shown to be HBsAg positive, but there is no conclusive evidence that these insects can transmit any of the hepatitis virus. Blood transfusion, hemodialysis, syringes and needles, tattooing and vaccinations, illicit self injection in drug abusers and barber's razors and other instruments are other modes of transmission responsible for the spread of HBV, HCV and HDV.

Prognosis and outcome

Recovery is the rule after typical Hepatitis A. There is no evidence that HAV leads to a chronic carrier state or to chronic hepatitis. On the contrary 5–10% cases of HBV and almost 50% of HCV go on to develop chronic conditions [15]. Persistence of viral markers or evidence of hepato cellular inflammation/necrosis for more than 6 months is generally taken as the criterion of chronicity. A signifi-

cant problem with HBV and HCV is that the disease is frequently asymptomatic, both initially as well as for a long time thereafter, and the patient may present directly with cirrhosis or with liver cancer [16]. There are certain special circumstances which increase the chances of chronicity in cases of hepatitis B. These include extremes of age and other states like patients on steroids, hemodialysis and post renal transplant patients.

Fulminant hepatitis is a life threatening variant of viral hepatitis which can be caused by any of the viruses, although HBV and HEV are the predominant causes. Pregnant females in the 3rd trimester are particularly prone to develop fulminant hepatitis and mortality reaches upto 80% despite adequate treatment [17]. The survival rates are best in HAV and poorest in NANB associated diseases [18].

Prevention

Although vaccines for HAV and HBV have been developed they are not yet readily available. Therefore we have to mainly depend on other means and ways of prevention. Feco-oral transmission of HAV and HEV is eminently preventable by improving hygiene and sanitation, health education of food handlers, good antifly measures and ensuring safe drinking water supply. Adequate washing of all vegetables and fruits which are to be eaten without cooking, safe storage of food after cooking are elementary things which should be impressed upon all. Health education of general population and food handlers is particularly important. Passive immunity for HAV is also available as type specific neutralising antibody popularly known as IgG. It is given in a dose of 0.01 to 0.08 mg/kg as pre or post exposure prophylaxis.

Risk factors for Hepatitis B infection in military personnel outside situations of actual conflict, consists mainly of sexual contact or IV drug abuse [16]. However drug abuse is not a problem in the Indian Armed Forces. Hepatitis C is also known to be transmitted through sexual promiscuity and IV drug abuse. Avoiding unnecessary injections, infusions and shaving by common razors or by barbers is again very important. Injections should be given with adequately sterilised syringes, preferably disposable syringes. One has to be particularly careful during mass inoculation and vaccination of young recruits, where lapses may occur. Blood transfusion should be given only when really indicated. Blood donors should be healthy volunteers and blood should be screened for HBsAg before transfusion. There is controversy whether routine testing of SGOT/SGPT should be done on donor blood to rule out the possibility of HCV in the donor.

Active immunisation for HBV is available. Universal immunisation with HBV vaccine is desirable but is a costly proposition. Therefore individuals who are at high risk for HBV infection may be protected with HBV vaccine. For post exposure prophylaxis, vaccine is combined with passive protection using Hepatitis B immunoglobulin (19).

Aeromedical aspects

Full clinical and biochemical recovery after HAV and HEV in an asymptomatic individual should not preclude resumption of full flying status. Sherlock has stated that the convalescence period should be double the period of jaundice. This may be a reasonable guideline before permitting full flying status [20].

In HAV and HCV 5–10% and 50% respectively may go on to develop chronic conditions. Peristantly raised biochemical indices would certainly preclude return to flying. Recurrent morbidity, possible disease dissemination, malaise, lethargy and weakness, if associated, will affect the performance of the individual and thus compromise his cockpit effectivity'. Asymptomatic carriers, with no rise in biochemical markers, are however to be considered separately. Such cases are to be throughly assessed

for evidence of ongoing hepatic inflammation and/or necrosis and for evidence of viral replication. If both these features do not exist, then the patient can be observed in restricted flying category for about a year. Subsequently if he maintains status quo, full flying duties may be allowed subject to a yearly surveillance program in a gastro-enterology centre.

References

1. Rizzetto, M. Viral hepatitis in the Military (Introduction). Contemporary treatment series. Pennine Press, Adelphi Communication Ltd, Chesire UK. 1993; 1:3
2. 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
3. Gust ID, Coulepis AG, Feinstone SM et al. Taxonomic classification of hepatitis A virus. Intervirology 1983; 20: 1
4. Blumberg BS, Alter HJ, Visnich S. A new antigen in leukemia sera. JAMA 1965; 191: 541
5. Rizzetto M, Canese MG, Arico S et al. Immunofllourescene detection of new antigen-antibody system (delta/anti delta) associated to hepatitis B virus in liver in serum of HBsAg carriers. Gut 1977; 18: 997
6. Bonino F, Smedile A. Delta agent (Type D) hepatitis. Seminars in Liver Disease. Theieme inc 381 Park Ave South, New York. 1986; 6: 28
7. Choo QL, Kuo G, Weiner AJ et al. Isolation of cDNA clone derived from a blood borne non A, non B viral hepatitis genome. Science 1989; 244: 359
8. Brechot C. Hepatitis C Virus genetic variability: clinical implication. Am J Gastroenterol 1994; 89(5): 41
9. Thomas HC. The hepatitis B virus and the host responses. Jour. Hepatol. 1990; 11 5–83.
10. Coulepis AG, Locarnini SA, Lehmann NL et al. Detection of hepatitis A virus in feaces of patients with naturally acquired hepatitis. J infect Dis 1980; 141: 151
11. Tandon BN, Gandhi BM, Joshi YK et al. Etiological spectrum of viral hepatitis and prevalence of markers of hepatitis A and B virus infection in north India. Bull WHO 1984; 62(1): 67
12. Barker LF, Murray R. Relationship of virus dose to incubation time of clinical hepatitis and time of appearance of hepatitis associated antigen. Am J Med Sci 1972; 63 27
13. Neaf JR et al. Hepatitis due to injection of homologous blood products in human volunteers. J Clin Invest 1944; 23:836
14. Wong DC et al. Epidemic and endemic hepatitis in India. Evidence for a non-A, non-B hepatitis virus etiology. Lancet 1980; 2: 876
15. Dusheiki GM. Diagnosis and treatment of type B and C viral hepatitis. In The contemporary treatment series. Pennine Press Adelphi Communication Ltd. Chesiru UK, 1993; 1: 13
16. Rizzetto M, Schiff ER, Dusheiki GM et al. Chronic hepatitis in the military. Recommendations on prevention, diagnosis and management. In: the contemporary treatment series. Pennine Press, Adephi Communication Ltd., Chesire UK, 1994; 1: 5
17. Berk PD, Popper H. Fulminant hepatic failure. Am J Gastroenterol 1978; 69: 349
18. Mathieson LR. Hepatitis A, B, Non-A, Non-B in fulminant hepatitis. Gut 1980, 21 72
19. Chung WK et al. Prevention of perinatal transmission of hepatitis B virus. A comparison between the efficacy of passive and passive-active immunisation in Korea. J Infect Dis 1985; 151: 280
20. Sherlock S. Virus Hepatitis, Disease of the Liver and Biliary System, 8th Ed 1989; 308. Blackwell Scientific Publications