

QUICK UPDATE

HEPATITIS C AND E

THE HEPATITIS C VIRUS : A BLOOD BORNE NON A NON B VIRUS

Hepatitis C, caused by the Hepatitis C virus (HCV), is the term proposed for the parenterally transmitted, principally blood borne form of what was previously called "Non A Non B Hepatitis" (NANBH). The epidemic, enterically transmitted form of NANBH which is associated with the Hepatitis E virus, HEV, is now referred to as Hepatitis E.

Research work into HCV has benefitted from developments in molecular biology. The use of starting material derived from infected chimpanzees together with recombinant DNA techniques allowed the identification of an immunoreactive clone that encoded the dominant viral epitopes. From this, a fusion protein, C-100, was constructed and expressed in yeast. This was used to develop assays that were subsequently shown to be sensitive and specific for the blood borne, transfusion associated form of NANBH or Hepatitis C.^{1,2}

Subsequent studies have also allowed the characterisation and cloning of the HCV genome even though the virus has not yet been isolated, purified or even visualised.

The virus has been shown to be small, 50–60 nm in diameter, with a viral genome consisting of a single stranded, linear positive-sense RNA of approximately 10,000 nucleotides. The agent was sensitive to lipid solvents and thus probably possesses a lipid rich envelope. Nucleotide sequence analyses of the genome organisation indicate that HCV is most closely related to the Flavi and Pestiviruses but with sufficient structural differences to make it distinct and different. The virus induces characteristic electronmicroscopic tubular ultrastructures in the liver cells of experimentally infected chimpanzees.

Preliminary seroprevalence studies using assays based on C-100 show that between 0.2 – 2.2% of healthy blood donors³ have detectable anti-HCV compared with 1.8% in a similar study involving samples collected from the National Blood Transfusion Service and the University Hospital, Kuala Lumpur.⁴

HCV transmission via blood and blood product use has been clearly demonstrated.⁵ The importance of sexual transmission is as yet unclear. Early studies document a low prevalence of anti-HCV in homosexuals. The results of more recent studies indicate that sexual transmission, both homosexual and heterosexual, probably does occur but most of the authors conclude that this is probably not an efficient mode.^{6,7,8}

Several studies addressing the issue of transmission from infected mothers to their newborns suggest that this either does not occur or if it does, is probably not important.^{9,10}

A strong relationship has been demonstrated between HCV infection, alcoholism and advanced liver disease especially of cirrhosis and this has been shown to occur independently of age, sex, duration and intensity of drinking and of presence or absence of Hepatitis B markers.¹¹

Dual infections of HBV and HCV are not rare and appear to be associated with progression to more serious liver disease. Prevalence of anti-HCV appears to increase with the severity of the liver disease whilst chronically infected Hepatitis B carriers who are not HCV infected appear to remain asymptomatic and well.¹²

Hepatitis C infections appear to progress to chronicity more frequently than following Hepatitis B infections and in Japan, more deaths occur from HCV associated hepatocellular carcinoma than HBV associated ones.¹³

The first generation assays for anti-HCV, though useful have a limited sensitivity and specificity. There also appears to be a long seronegative window period during which the patient is already infected, may even be ill, liver enzymes are elevated but anti-HCV remains undetectable by the current tests. Alter and co-workers report that anti-HCV was not detected in patients with post transfusion hepatitis until almost 6 months after transfusion and 4 months after the onset of hepatitis.¹⁴

The limitations of the current tests, coupled with the very long seronegative period and the current very high cost of the test make implementation of anti-HCV screening for donated blood units currently unattractive. As the tests improve, become cheaper and research can establish a definite need for routine screening, the time will come when this can be included in the battery of tests to be run before any unit of blood is used. This should then make the blood supplies even safer.

HEPATITIS E VIRUS : AN ENTERICALLY TRANSMITTED NANBV

An enterically transmitted form of NANBH, tending to occur in epidemics and transmitted mainly by ingestion of contaminated water and food, was recognised in 1955–56. This form, now called Hepatitis E, is often associated with poor socio-economic settings, involving mainly developing world populations in areas with poor sanitation, inadequate water supplies and poor standards of hygiene.¹⁴

The disease closely resembles Hepatitis A but in all cases, serological markers of Hepatitis A were consistently negative. Hepatitis E tends to occur more frequently in young to middle aged adults and causes a mortality of up to 20% in pregnant women infected in the later months of pregnancy. HEV infections tend to resolve spontaneously, probably do not progress to chronicity. A chronic HEV carrier state has not been reported.

The Hepatitis E virus, HEV, responsible for this form of NANBH has not yet been visualised but experimental infection of pigs, chimpanzees, marmosets and cynomolgus monkeys have provided adequate amounts of virus like particles in faecal samples for study.

HEV has been shown to be small and spherical, 27–38 nm in size. It has a single stranded RNA genome and appears to share characteristics with the Picornaviruses (which include enterovirus 72/ Hepatitis A virus) and the Caliciviruses. Isolates collected from epidemics in many tropical and subtropical developing world countries suggest the existence of only 1 serotype. This will make the development of assays and vaccines easier.

AND YET ANOTHER BLOOD BORNE NANB VIRUS?

Yet another virus transmitted by blood and blood product use has been reported by Yoshizawa¹⁵ and by Bradley.¹⁶ This is believed to be a much smaller, non enveloped or naked virus of 25–30 nm which does not induce the formation of tubular ultrastructures in infected chimpanzee liver cells. No antibodies related to this virus has yet been identified. Its role and importance is not yet established but is believed to be secondary to that of HCV in causing NANBH in transfused patients. It is not yet known just how many other viruses are associated with the parenteral and enterically transmitted forms of NANBH.

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HUMAN IMMUNODEFICIENCY VIRUS 2 (HIV 2)

The immunodeficiency viruses infecting a variety of mammals including man, simians and felines are classified as Lentiviruses in the family of Retroviruses. Infection with these viruses are characterised by a long and variable incubation period, chronic viraemia in the presence of circulating antibodies, progressive immune system dysfunction, followed by a whole spectrum of opportunistic infections, unusual malignancies and culminating in the Acquired Immune Deficiency Syndrome (AIDS).

There are at least 2 distinct human immunodeficiency viruses causing AIDS, HIV-1 and HIV-2. A third virus may also exist as its isolation and characterisation was reported by Belgian scientists in 1988 but little else is known about HIV-3 beyond the early reports.

HIV 1 has been the cause of most of the worldwide cases of AIDS but in 1985, a seroprevalence survey of Senegalese prostitutes in Dakar identified sera which reacted more strongly with a related non human primate retrovirus, the Simian Immunodeficiency Virus (SIV) than with HIV-1.¹

In 1986, Clavel et al² reported the isolation of this new virus, now called HIV-2, from patients with AIDS-like illnesses in Guinea-Bissau and Cape Verde in West Africa. This virus gave atypical patterns when tested against HIV-1 sera. It resembles HIV-1 in structure and morphology, in its tropism for cells with CD4+ receptors, in vitro cytopathic effects and in the organisation of its genome. The viruses differ significantly in their nucleotide sequences. The gag and pol genes appear to be more conserved, with a 56% and 66% nucleotide sequence homology.³

Though HIV-2 does cross react with SIV, there are sufficient genomic differences between the 2 viruses to regard them as distinct from each other.

HIV-2 is endemic in several West African countries but has spread to several European countries with close West African connections. These include France, Portugal, West Germany, Sweden and Norway. Sporadic cases have also been reported from the United Kingdom and USA. It is currently much less important in causing the worldwide pandemic of AIDS than HIV-1. The very rapid spread of HIV-1 suggests that unless preventive measures are rapidly and aggressively applied, HIV-2 may soon spread and be a problem in many other countries.

HIV-1 and HIV-2 dual infections are reported to occur frequently in the West African countries.⁴ The clinical features of disease caused by HIV-2 are similar but not identical to that of HIV-1⁵ but the pathogenic potential is yet to be established as its recently discovered and follow up periods of infected persons is as yet very short.

Though HIV-1 and HIV-2 may differ by as much as 35% overall, sera containing antibodies to HIV-1 and HIV-2 tend to cross react to some degree. Enzyme immunoassays designed to pick up anti-HIV-1 can in fact also detect anti-HIV-2. The commercially available indirect enzyme immunoassays are reported to detect between 70-95% of sera reactive for anti-HIV-2 whilst the competitive assays either do not do this or do so much less efficiently.

HIV-2 infection has been studied on a small scale at both the Institute of Medical Research and at the University of Malaya using specific anti-HIV-2 tests and indirect assays that should pick up a significant proportion of reactives if anti-HIV-2 is present. No sample reactive to HIV-2 has been found. All sera reactive for anti-HIV were confirmed as HIV-1.⁶

The rate of mutation of the HIVs has been reported to be many million times that demonstrated for typical human DNAs. It is very likely that in the future many more HIV strains and perhaps other HIVs will make their appearance.

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V.J.L. HOW

Department of Medical Microbiology Faculty of Medicine, University of Malaya.