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WORKSHOP ON HEPATITIS C VIRUS

The six papers that follow are based on a workshop held in the College in 1993 but updated to 1995. They are a record of specialists talking to the specially interested, and general readers may find them difficult in places. But the effort of reading them is worthwhile as the viruses responsible for hepatitis are not only important clinically but present fascinating problems in biology. Older readers will remember that their textbooks in the 1930s contained a section on catarrhal jaundice which was distinguished from obstructive and haemolytic jaundice. The cause of the catarrh was unknown. The single diagnostic label was soon replaced by two, infectious hepatitis and serum jaundice, the latter being a common condition in patients being treated for syphilis with intravenous injections. When means were discovered for isolating and identifying viruses, these conditions were found to be due to separate viruses, hepatitis A and B (HAV and HBV). A third distinct virus with an affinity for the liver was yellow fever virus. Other identified viruses are hepatitis C virus (HCV), hepatitis D (HDV) and hepatitis E virus (HEV).

Yellow fever virus is spread by an arthropod vector from a pool of infection which still persists in some jungle primates. HAV and HEV infection is spread from case to case by the faecal-oral route. Infection by HBV is transmitted via intimate (usually sexual) contact or parenteral injection through a contaminated needle or transfusion fluid. HCV is rarely transmitted by sexual contact, occasionally by needle stick injury but usually by infusion fluid.

There is extreme variation in the clinical manifestations of infection with hepatic viruses. A self limiting attack of fever with jaundice is the common presentation with yellow fever and with HAV and HEV infections, but is often absent with HBV and HCV infection. A fulminating, usually fatal, hepatitis is common in yellow fever, very rare with HAV, HCV and HEV, a well known tragedy with HBV infection. A persistent inflammatory response, with or without the continuing presence of virus, leading to cirrhosis and carcinoma is the main clinical feature of HCV infection and common in HBV infection. It is rare, if it ever occurs, in yellow fever or in HAV infection. Hepatitis D virus is strongly related to intravenous drug use but has similar epidemiological and clinical features to HBV with which it is often associated in time. In the immunocompromised patient, as with AIDS, the liver may be affected by other viruses, in particular cytomegalovirus, herpes simplex virus, measles virus in adults and Coxsackie virus B, all of which may give rise to hepatitis in occasional individuals.

Do these marked variations in the clinical responses to infection arise from differences in the strains of infecting virus or in the nature of the immune response of individual patients? An understanding of these questions would help both in prevention of the infections and in the treatment of patients.

The Editors

EPIDEMIOLOGY OF HEPATITIS C

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Historical perspective

In the 1960s, in Washington in the USA, a recipient of a blood transfusion had a 1 in 3 chance of developing post-transfusion hepatitis. In 1970 two things changed. Firstly, testing for hepatitis B became available, which reduced post-transfusion hepatitis by about 50%. Secondly, the blood donor service moved to an all-volunteer programme with a further significant reduction in hepatitis amongst recipients. In the 1980s, donors with raised ALT levels were excluded, but a rump of post-transfusion hepatitis cases remained. When testing for hepatitis C became available it became clear that 95% of non-A, non-B hepatitis was due to hepatitis C.

In 1982, the Centre for Disease Control, Atlanta, set up a 'Sentinel Counties Study', looking into the risk factors for non-A, non-B hepatitis in sporadically occurring cases in the community.[1] It soon became apparent that transfusion only accounted for 3% of such cases and in approximately 50% no risk factors could be identified. In the first year of this study, 13% of cases were associated with intravenous drug abuse, but by 1988 this figure had risen to over 40%. When second generation assays for HCV antibody became available, retrospective testing confirmed that HCV was responsible for 100% of cases acquired through intravenous drug abuse. In 1988, no source of infection could be identified for approximately one third of cases, and HCV was only identified in 52% of these. It should be noted that when testing for anti-HCV in patients with acute non-A, non-B Hepatitis, sufficient time must be allowed to elapse for seroconversion to take place. For example in one study[2] only 10 of 20 (50%) patients who developed non-A, non-B hepatitis following blood transfusion and were tested within 6 weeks of the onset of illness, were found to be anti-HCV positive, compared to 19 of 25 (76%) who were tested 6 months after the onset of illness.

Geography

HCV is a worldwide problem. In the Far East there is a significant problem with hepatitis B virus infection, high rates of vertical transmission and a strong association with hepatocellular carcinoma. In most countries where there are significant rates of HBV infection, HCV is also prevalent, although usually less so. It is not known why the seroprevalence rates for HCV and HBV differ. In the majority of countries in the Far East, most hepatocellular carcinoma cases are associated with HBV infection. This is not the case in Japan where a greater proportion of cases of hepatocellular carcinoma are associated with HCV infection. Even within Japan, prevalence rates vary according to locality. In one town of 1,500 inhabitants, tested for HCV in 1990, 12·2% were found to be HCV seropositive, a much higher rate than that for blood donors (1·2% across the whole of Japan).[3] However, when this town was subdivided into areas, there was even greater fluctuation in seroprevalence rates between areas, which ranged from 5·1% to 48·6% in the most densely infected area. The reasons for this are unclear, but might possibly relate to reuse of needles used for mass vaccination.

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In the Middle East high rates of HCV infection occur in Egypt, with 4% of Egyptian blood donors being anti-HCV positive.[4] In rural communities, the figure is much higher. In Kuwait 1·2% of blood donors are HCV positive.[5] In South American countries, blood donors tend to show seroprevalence rates of 0·6 to 0·9%, although the rate in Brazil is higher at 2·7%[6] and in rural Peru the seroprevalence rate is 0.[7] Little is known about the epidemiology of HCV in Sub-Saharan Africa, but in the Republic of South Africa seroprevalence rates are similar to those found in South America with a 0·9% seroprevalence rate amongst blood donors. An identical rate has been obtained for blood donors in Zimbabwe, and it is of interest that the seroprevalence rates for HIV and HBV seem to be higher than this, the first indication that sexual transmission may be less important for HCV than it is for HIV or HBV.

United Kingdom

It should be appreciated that the data from the Blood Transfusion Service do not accurately reflect the overall population prevalence of HCV, as blood donors in the UK are a highly selected group of individuals. The Service tries very hard to exclude donors who have a risk of parenteral exposure to viruses. Initial screening for HCV was carried out on 10,633 blood donors from Glasgow, Newcastle and North London using a first generation test and 0·65% of donors were found to be HCV seropositive.[8] However, when a confirmatory test was used, the vast majority of these tests were found to be false positives and the seropositive rate was readjusted to 0·047%. When all these specimens were tested by PCR, a few more positives were discovered, giving an overall prevalence rate of 0·06%. Since the adoption of routine screening of blood donations for HCV infection, the seroprevalence rate amongst blood donors has steadily fallen as seropositive donors are excluded from the pool. Any cases which turn up now should either represent seroconversion amongst regular blood donors or the introduction of a new donor to the transfusion service. Again because of the degree of selection, these data do not give a true reflection of the rate of infection amongst the general population. Nonetheless some information has been obtained. In the two years since testing began in our Service we have identified approximately 300 seropositive donors. We have also tried to extrapolate from this rate of donor seropositivity the number of transfusion recipients who have been infected in the past by these donors. In a small study in South East Scotland looking at the first 20 HCV seropositive donors to be identified, we found that over 70 potentially infectious units of blood had been donated by these individuals. However, many of the recipients of these units of blood died of their primary disease, some were untraceable and there remained fewer than 10 live patients who were available, could be tested, and were at risk of developing liver disease. We would therefore estimate that in Scotland there may be 150 infected recipients of blood transfusions. Translated to the UK population, a reasonable estimate is that there are 3,000 HCV seropositive recipients of blood transfusion alive and at risk of developing chronic liver disease.[9] This has implications for identification and management of such individuals.

Risk factors in the United Kingdom

Having identified our seropositive cohort of blood donors, we looked for possible risk factors, and found that in 40% of cases seropositivity was related to previous

intravenous drug use.[10] This was somewhat alarming to us, as we go to great lengths to exclude such individuals from the blood donor panel. We discovered that many cases were related to drug use up to 20 or 30 years previously, the inference being that the donors themselves thought this to be irrelevant. Other parenteral exposures e.g. blood transfusion, tattooing, ear piercing probably accounted for a number of cases. We also found 8 cases where the only discernible risk factor was sexual intercourse with an intravenous drug user, implying a possible role for sexual transmission of infection. As with other studies we were left with about a third of our cohort for whom we could identify no risk factors. It is possible that some of these may reflect undisclosed intravenous use of drugs in the past.

The risk of acquiring HCV through blood transfusion in relative terms appears to be small. In one study from North London, only one of 387 transfused patients was shown to seroconvert for HCV post-transfusion.[11] However in haemophiliacs, who may be exposed to multiple donors in a lifetime, the situation is quite different, with seropositive rates approaching 100% in some groups exposed to non-heat-treated Factor VIII.[12] Haemodialysis patients may also be at risk of HCV infection, with seroprevalence rates around the world that are usually up to 10%,[13] but have reached 50% in some studies from the Far East.[14]

Sexual transmission

Early work disclosed that sexual transmission of HCV from intravenous drug users to a sexual partner was much lower that might have been expected, and much lower than the transmission rate for HIV. A study from Glasgow has shown that the seroprevalence amongst male intravenous drug users is 85%, but amongst their female sexual partners the rate is only 8%. Amongst homosexual men tested in Glasgow, there have been no cases of HCV infection, except where there was a history of intravenous drug use, when 6/17 were seropositive, (E. A. C. Follett, personal communication). A study of prostitutes in the USA has shown that the seroprevalence for HCV amongst drug using women is 68%, but amongst non-drug using women is only 12%. It is now becoming clear that HCV seropositivity is one of the best markers available for identifying current or previous intravenous drug misuse, with much higher seroprevalence rates than for HIV or HBV. The reverse situation applied in a cohort of homosexual men from Barcelona, where the seroprevalence rates for anti-HIV, anti-HBc and anti-HCV were 84%, 81% and 16% respectively.[15] Table 1 shows the changes over time in the seroprevalence of these three viruses in a cohort of Danish homosexual men, and it does show that the seroprevalence of HCV rises slightly during the follow-up period, although less so than for HBV and HIV.[16] Turning to the female sexual partners of men with haemophilia, a study by Eyster published in 1991 showed only 5/194 female partners of HCV seropositive haemophiliac men to be infected. Moreover HCV transmission appeared to be affected by HIV infection in the index case.[17] In a study from Glasgow on sexual partners of HCV seropositive blood donors, only 3/60 were found to be HCV infected, of whom 2 had previously undergone blood transfusion. One indeterminate result was also obtained in a sexual partner with a history of previous intravenous drug use. More recent studies have indicated higher rates of transmission with infection more likely the longer a sexual relationship continues.[18–20] Vertical transmission,

is a very important issue especially in parts of the world where HCV is more prevalent. There are difficulties in interpreting the results of serological tests of HCV in this setting, and PCR has proved essential in clarifying the transmission risk. The first important study was from Thaler in California, and rather worryingly all 8 neonates born to HCV seropositive mothers were found by PCR to be HCV infected,[21] but further studies from New York and Sweden showed transmission rates of 0/24 and 3/21 respectively, suggesting a small risk of vertical transmission.[22,23] In Edinburgh, of 58 babies born to HCV seropositive mothers, only 4 have been found to be infected with HCV.[24] In addition, the rate of transmission is not increased by concomitant infection with the human immunodeficiency virus.

TABLE 1

Changes over time in seroprevalence of hepatitis B and hepatitis C viruses in a cohort of Danish male homosexuals.

Year of testing	*Anti-HCV cumulative % positivity*	*Anti-HBV cumulative % positivity*	*Anti-HIV cumulative % positivity*
1981	1·6	44·0	8·8
1984	4·1	52·7	24·0
1989	4·1	58·8	30·1

Melbye *et al.* 1990.

Household risks of transmission

A study from Spain on 211 non-sexual household contacts of HCV seropositive patients found that 5·7% were infected with HCV.[25] An identical seroprevalence rate was found in a study from Italy on the household contacts of seropositive blood donors.[26] These results are contradicted somewhat by an identical study from Germany which produced a seroprevalence rate of only 0·5% for household contacts.[27] The true picture is unclear and further studies are required. It is important to advise HCV infected patients not to share implements such as toothbrushes and razors, and it is possible that a failure to adhere to this advice may account for some cases of transmission.

Risks to health care workers

Healthcare workers are placed at risk of HCV infection through needlestick injuries. In Japan of 68 healthcare workers suffering needlestick injuries from patients who were HCV RNA positive, 10% seroconverted for HCV.[28] This is a much higher rate of seroconversion than is seen for HIV. Further studies are required.

In summary, the data show that the main route of transmission for HCV is parenteral, with intravenous drug users representing the single biggest risk group. There should no longer be a problem with blood transfusion, and heat-treated blood products should have eliminated the risks to haemophiliacs. Modern screening methods should also significantly reduce the risk through organ donation. In addition to intravenous drug use, the other potential parenteral source of transmission that has not been fully investigated is tattooing. The risk of

sexual and vertical transmission of HCV appears to be small, and therefore gives some hope of being able to control the spread of this infection.

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NATURAL HISTORY OF HEPATITIS C VIRUS INFECTION

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Although HCV has been identified as the causative agent of most cases of parenterally transmitted non-A, non-B hepatitis (NANBH), and diagnostic tests are now freely available, there remains much to be learnt about the natural history of infection with this virus. The natural history of HCV is important because we are all faced with patients with chronic HCV and indeed members of staff who have suffered a needlestick injury, and it is essential to provide them with accurate information about prognosis.

Acute HCV infection

The incubation period of acute infection is about 6–8 weeks, although some patients have been reported to develop an acute hepatitic illness within a few days of transfusion, and it may be that the incubation period can be shortened by a high infecting dose. For most patients the acute illness appears to be completely asymptomatic, with jaundice only developing in about 10% of cases. Diagnosis of acute HCV infection is problematic. In one study of 17 patients with acute HCV infection, all patients had positive serum HCV RNA by PCR within three weeks of the onset of illness, but only 67% of the patients were positive for anti-HCV by RIBA. By 21 weeks this had risen to 86%.[1] In chimpanzees who have been experimentally infected with HCV, RNA can be measured at 4–7 days post-infection, but levels fluctuate considerably and there may be days when HCV RNA is undetectable.[2] In 20–40% of patients with acute HCV infection, transaminases normalise within 4–6 weeks, although in a proportion biphasic elevations of transaminases can make the determination of true convalescence difficult.

Sixty–80% of patients will develop chronic HCV infection.[3,4] As with chronic HBV infection most patients are asymptomatic until late in the disease when they may present with liver failure. Most patients with chronic HCV are detected by screening and will not recollect an acute hepatitic illness. In contrast to HBV, the transaminase levels often fluctuate considerably over time, the reason for which is unclear. Screening for liver disease with transaminase levels may not be adequate, as it is now realised that patients with normal transaminase values who are anti-HCV positive and HCV RNA positive by PCR can nevertheless show chronic hepatitis in a biopsy.[5] There would also seem to be a small group of patients who seem to fit the criteria of a healthy carrier. These patients have both normal transaminase values and normal liver histology.[6]

Initial studies of post-transfusion NANBH had short follow-up periods and it is now realised that these underestimated the risks of liver disease. It is now believed that approximately 20% of patient with HCV infection will ultimately develop cirrhosis, although there is considerable individual variation in the rate of progression to this complication. A recent Italian study looking at 135 patients with post-transfusion NANBH showed that 77% of patients developed chronic hepatitis.[7] Of 65 patients biopsied, 32% had developed cirrhosis by the end of 15

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