Sexual transmission of hepatitis C virus infection

Review

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Background: Hepatitis C virus (HCV) is the cause of almost all cases of parenterally transmitted non-A, non-B viral hepatitis (NANBH). HCV is an RNA virus, unrelated to the hepatitis viruses A, B, D, or E; it was first identified in 1989. Although most infections become chronic, and it may lead to chronic liver disease, most patients with HCV infection are asymptomatic. The predominant modes of transmission are by blood, blood products, or other parenteral exposure, particularly injecting drug use. More contentious is the role of sexual transmission, although evidence for this was provided by studies of NANBH.

Objective: This review considers the evidence for sexual transmission, and the types of studies used to estimate the rate of transmission and the factors that may influence it.

Method: A Medline search using the keywords hepatitis C, sex, transmission, and prevalence in MeSH and free text. References in papers were searched, and some unpublished data identified. References were further selected to illustrate different methodologies.

Findings: Evidence for sexual transmission is provided by several types of study including prevalence studies in groups at risk of other STDs, investigation of cases identified from surveillance reports, and cross sectional and longitudinal partner studies. Many studies are limited by their small size, the sensitivity and specificity of early assays, lack of controls, or the difficulty of excluding other routes of transmission. One prospective cohort study reported an incidence of 12 per 1000 person years in the sexual partners of HCV infected patients. 1–3% of partners of HCV infected patients are found to be infected in cross sectional studies. Co-infection with HIV, duration of the relationship, or chronic liver disease may be independent cofactors increasing the risk of transmission. A meta-analysis of selected studies may be informative, and further larger prospective studies are required. There is a small but definite risk of sexual transmission of hepatitis C.

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Introduction

Hepatitis C virus (HCV) is an RNA virus most closely related to the flaviviruses.[1] It is structurally unrelated to other hepatitis viruses, except hepatitis G[2] which is of uncertain pathogenicity.[3][4] Although acute infection with HCV is usually asymptomatic, about 80% of patients develop chronic infection.[5] Most chronic carriers are also asymptomatic but infection may lead to chronic liver disease including cirrhosis, hepatocellular carcinoma, and liver failure.[6] Serological screening for HCV infection is by detection of HCV antibodies. First generation assays lacked sensitivity and specificity, but current tests detect antibodies in almost all patients with chronic or resolved infection.[7] Immunoblot and other supplementary tests exist to confirm antibody reactivity. Seroconversion may be delayed some weeks after patients present with acute hepatitis C; seroconversion more than 3 months after the date of infection is very uncommon. HCV viraemia is detected by reverse transcription polymerase chain reaction (RT-PCR) or signal amplification (branched DNA) assays; chronic infection is usually defined as persistence of viraemia for more than 6 months.

Since its identification in 1989, HCV has been shown to be the agent responsible for over 90% of cases of what was previously denoted as parenterally transmitted non-A, non-B hepatitis (NANBH).[8] Epidemiological studies of NANBH indicated that the agent was efficiently transmitted by blood or blood products.[9] Most cases of HCV infection so far identified in the United Kingdom have been associated with a history of injecting drug use, blood transfusion, or treatment with blood products.[10] New infections related to blood or blood product exposure have been rare since the introduction of donor screening for HCV antibodies.[11] Screening of new donors continues to identify HCV infected individuals, about half of whom have a history of injecting drug use; in some cases there is no apparent history of parenteral exposure.[12]

For those found to be infected, and their partners, there is a need to know what the risks of transmission are, including sexual transmission. What is the probability that a sexual partner will be found to have HCV infection? What advice should be given regarding the use of condoms? Published advice is conflicting—for example, some recommending use of condoms and others not,[13–16] while some advise only using condoms, or abstaining from intercourse, during menstruation or in the presence of genital lesions.[17]

This review discusses some of the evidence for, and against, sexual transmission; the types of study involved; future research needs; and the advice offered to patients at the authors' centre, pending the availability of definitive studies.

Review methodology

A Medline search of the literature was performed using the keywords hepatitis C, sex, transmission, and prevalence in MeSH and free text. References in papers identified were also searched, and some unpublished data obtained. The search was further focused on publications representative of the different methods used to examine sexual transmission; the list of publications referred to in this overview is not exhaustive of all those that may contain relevant information. No attempt was made to combine data from different studies.

Methods used to study sexual transmission

The routes of HCV transmission have been inferred from prevalence studies and case reports, including cases of post-transfusion hepatitis and infections occurring in the sexual partners of known HCV infected individuals.[18 19] Such reports indicate that sexual partners may be infected but do not prove that transmission occurred by the sexual route. Detection of HCV RNA in semen in some,[20 21] although not all, studies[22] provides evidence for the biological plausibility of sexual transmission. In assessing the evidence for particular routes of transmission provided by prevalence studies in groups with particular behavioural risks, it is important to know the prevalence in a control group. In most cases the appropriate controls would be a sample of the general population in that region. General population prevalence estimates are rarely available and the prevalence in blood donors, the population most extensively studied worldwide, is often used. Blood donors are not, however, an unselected sample of the general population. For example, individuals with a history of parenteral exposure are specifically discouraged from donating.

Statutory case notifications of hepatitis C substantially underestimate the number of cases in the population because of the high proportion of asymptomatic infections.[23] Such reports usually provide very limited information about the route of transmission. However, surveillance reports of acute NANBH have been used as the basis for population based studies with more detailed information being obtained to supplement the routinely collected data.[24] Such studies can estimate the attributable risk for different modes of transmission in the population, but do not provide a direct estimate of the rate of HCV transmission.

The study design best suited to estimate the rate, and determinants, of sexual transmission would be a prospective cohort study of discordant couples where HCV infected index cases and their uninfected partners are recruited and the incidence of infection in the partners is determined by repeated testing over time. However, even this design has limitations; by excluding those cases where the partner is already infected the remaining population is likely to comprise those couples in whom transmission is less likely to occur.

Most studies of sexual transmission are of cross sectional design, measuring the prevalence in the sexual contacts of patients with HCV infection. Where control groups have been included, they have usually been other family or household contacts of the index case, or blood donors from the same region. The results from such studies have been conflicting and some may not be generalisable. Interpretation of the data is often limited by the lack of an appropriate control group. Early studies were also limited by the lower sensitivity and specificity of first generation HCV antibody assays. Comparison of HCV gene sequences between concordant couples has been used as evidence that transmission has occurred, but has not always supported transmission, and cannot confirm the route of transmission.[25] Given the apparent low rate of transmission, some studies may not have been large enough to detect any cases of infection in the partners. The direction of transmission may also be uncertain, particularly in studies where other possible risk factors, such as injecting drug use, have not been excluded or controlled for. One approach to analysing data where a contact may have more than one possible route of exposure is to define a hierarchy of risks. For example, if the risks, in descending order, are considered to be injecting drug use, blood transfusion, sexual transmission, and family contact then transmission is attributed to the first characteristic in the list possessed by each case.[24]

Prevalence studies

General population prevalence estimates are difficult to obtain. Prevalence varies between countries and between ethnic groups within one country.[26–30] In the United States, the prevalence among those tested in a national population survey (NHANES-III) was 1.4%.[31] There is no equivalent general population prevalence estimate for the United Kingdom.

The prevalence in United Kingdom blood donors is 0.01% to 0.09%,[10 12 32–34] and has fallen since screening of donors was introduced, and HCV infected donors have been withdrawn from donor panels. In London, HCV viraemia was detected in 0.7% of 305 patients tested in a study in general practice (primary care) surgeries,[35] and in 1% of 1000 antenatal clinic attenders (NS Brink, personal communication); in the West Midlands, the antenatal clinic prevalence was 0.18%.[26] The prevalence among blood donors in Israel,[27] Mexico,[28] and Brazil[29] ranged from 0.44% to 2.9%. In Egypt, the general population prevalence is high,[36] and the prevalence in blood donors has been reported as 26.6%.[37] Prevalence increases with age[38 39] either because of a continuing risk of exposure, or a cohort effect with declining risk in more recent times.

Studies of injecting drug users have found a consistently high prevalence of infection (38%–98%[40–44]). Patients with clotting disorders who received blood products before the introduction of effective viral inactivation procedures, also have a high prevalence of HCV infection (76%–98%[45–47]). Among sexually

transmitted disease (STD) clinic attenders the prevalence is much lower than in injecting drug users, but is higher than general population estimates or blood donors. At the STD clinic at the Middlesex Hospital, London, testing of unlinked anonymised syphilis serology samples revealed a prevalence of 2.2% (95% CI 0.5–4.0) in homosexual men and 0.4% (0–0.8) in heterosexuals.[48] A subsequent study in which injecting drug users were excluded showed no significant difference between the sexual orientation groups; the overall prevalence was 1.5% (Gilson, unpublished data). Other, uncontrolled, studies in homosexual men have revealed a prevalence of 1.4% in Denmark,[42] 4.6% in the United States,[49] and 6.9% in Italy[50]; in the latter two studies prevalence was related to the number of sexual partners in the past year or lifetime. In Japan, the prevalence in female prostitutes (6.2%) was similar to female STD clinic attenders (6.1%) but higher than blood donors (1.5%).[51]

Surveillance studies

As referred to above, the groups identified as most at risk are those with a history of parenteral exposure, including injecting drug users and patients with clotting disorders. It has been more difficult to document transmission by other, less efficient routes. In the United States, the Centers for Disease Control conducted an intensive surveillance programme of acute NANBH in four sentinel counties. Using first generation antibody assays, 68% cases had detectable HCV antibodies at 6 months. A history of sexual exposure was associated with 6% cases.[24] In 40% there was no identifiable risk exposure, although indirect evidence suggested many of these may also have been acquired sexually.

Prospective partner studies

There are no prospective observational cohort studies published that have been specifically designed to determine the rate of transmission to sexual partners. In a study of the sexual partners of 46 women who acquired HCV infection from contaminated anti-D immunoglobulin, none of their partners were found to be infected 10–15 years later.[52] In a randomised controlled trial, in which immune serum globulin was shown to reduce the rate of sexual transmission of HCV,[53] the placebo control group represented a prospectively followed cohort of HCV infected patients and their sexual partners. The partners were seronegative for HCV infection at entry, and none had a history of parenteral exposure. During follow up six of the 449 partners became infected, an incidence of 12 per 1000 person years. Analysis of HCV genome sequence homology between infected partners strongly suggested transmission had occurred from the index case in four of the cases, and less certainly in a further two. In the absence of other risks, sexual contact was considered the most likely route of transmission. HCV transmission occurred only in partners of HCV infected individuals with active liver disease, although the numbers were too small to draw definite conclusions from this.

Cross sectional partner studies

Some studies have found little or no evidence for sexual transmission. Everhart *et al* [54] found none of the heterosexual partners of 42 index cases to be seropositive for HCV antibodies, but used only the less sensitive first generation antibody test. Brettler *et al* [55] also concluded that the risk of sexual transmission was low, finding a prevalence of 2.7% (3/106) in the female partners of HCV infected haemophiliacs; at least one of the infected partners had a possible parenteral risk. Other studies which have found similar low rates of transmission have been in groups where the risk to the index case was multiple blood transfusions or blood products (including anti-D immunoglobulin); estimates have ranged from 0% to 2.9%.[15 56–60] In some cases, there may have been a longstanding awareness of the risk of transmission, such as in the partners of haemophiliacs who may therefore have used barrier contraception, which would have reduced or eliminated the risk of transmission.

In the studies where transmission between partners has been observed, the small number involved, and the difficulty of excluding other routes of transmission limit the further examination of factors determining the rate of infection. In a study of STD clinic attenders, Thomas *et al* [61] found women were 3.7 times more likely to be infected with HCV if their partner was infected. No such relation was found in men. However, whether it can be concluded that there is a greater risk of male to female transmission is uncertain because the overall prevalence of HCV infection was higher in males than females (7% versus 4%) and the direction of transmission remains uncertain; other sources of infection may have been implicated in some of the male cases.

Co-infection with HIV may increase the rate of transmission.[57 62 63] Eyster *et al* [57] found that HCV transmission only occurred when the male index case was also HIV infected. In Spain, Lissen *et al* [64] studied the regular partners of 147 HCV infected patients (98 of whom were also HIV infected). The prevalence of HCV antibody was 9.2% in the partners of HIV infected index cases and 4.1% in the partners of HIV uninfected index cases. Similarly, Gabrielli *et al* [63] found a prevalence of 9.5% (8/84) among the non-drug using sexual partners of HCV infected injecting drug users; partners were excluded from the study if they had a history of previous parenteral exposure, hepatitis, or STDs. Antibody reactivity was confirmed by immunoblot. None of the partners of HIV uninfected index cases were HCV positive (0/30), but HCV prevalence was 13% (6/47) in the partners of HIV co-infected index cases, and 29% (2/7) if both the index and the partner were HIV infected. Although HIV infection appears to increase transmission, it is not clear by how much. Most studies do not detail the HIV status of those

investigated[39 54 56 58 65–71] or exclude HIV infected individuals.[15 52 72–75] Other studies have found no association with HIV infection.[55 59–61]

A number of studies, particularly those from Asia and the Far East, have compared the risks to sexual partners with those to other family or household contacts, and with controls. In Japan, Oshita *et al* [39] found that 12% (26/219) of contacts of HCV infected patients were infected, compared with 2% (6/298) of controls. Within the group of contacts, the prevalence ranged from 24% (18/75) in spouses to 5.6% (8/144) in children and other household contacts. The proportion of spouses infected increased with age; 11.5% (3/26) for those aged up to 50 compared with 31% (15/49) in those aged over 50. In volunteer blood donors screened in the same region, the overall prevalence was 1.5% and also increased with age, from 0.2% in those aged less than 20 rising to 4.6% in those aged 50–64 years. Therefore, the age related increase in prevalence may not be attributable, or only in part, to the cumulative risk associated with long term sexual contact.

Other studies have also examined the effect of the duration of the relationship with the index case. In Italy, Pipan *et al*[72] found 16% (10/61) of long term partners were HCV infected. The mean duration of the relationship was over 29 years; the distribution of other risk factors for the acquisition of HCV infection was no different between the infected and uninfected groups. Akahane *et al* [76] studied the spouses of HCV infected patients with various stages of liver disease, and found a prevalence of 27%. Infection was related to age and the duration of the relationship—0% for those relationships of 10 years or less rising to 32% in those of 30 years or more. Logistic regression analysis showed an adjusted odds ratio of 1.5 for each decade of marriage (CI 1.05–2.2). In the spouses with detectable viraemia, 89% of the genotypes matched those of the respective index case. Similar rates of infection in spouses have been reported from Taiwan.[68 69]

The rate of transmission may be related to the stage of HCV disease or the severity of liver disease, possibly as an indirect measure of the duration of infection and therefore of exposure. Alternatively, the stage of disease may be related to the level of viraemia, and hence infectivity. Buscarini *et al* [71] found HCV infection in 15% (16/109) of household contacts of patients with HCV related chronic liver disease (including spouses and other family members), but no infection in household contacts of 30 asymptomatic HCV infected blood donors. In both the Japanese[39 76] and the Taiwanese[68 69] studies, the index partners had chronic liver disease. Honda *et al* [65] suggested that transmission was related to the stage of liver disease in the index case and not to the length of the relationship. This study found similar rates of infection in spouses and other household members, but lacked information on other risks for infection in the contacts. This leaves greater uncertainty about who was infected first. Many studies do not report on the stage of liver disease in the index cases.

Conclusion

There is considerable variation in the prevalence of HCV infection in different parts of the world, which may be largely attributable to the differing exposure to risks for parenteral transmission. The prevalence in the United Kingdom is low, but as in other countries, we lack precise estimates of the general population prevalence. Because of the high rate of persistent carriage following infection, a substantial burden of chronic infection remains among those individuals exposed in the past. Those with persistent HCV viraemia remain potentially infectious, but as the majority are asymptomatic or have only mild, non-specific symptoms, they may have not been diagnosed and may be unaware of their risk to others. An increasing number of asymptomatic individuals will be identified as HCV carriers. With attempts to limit the further spread of infection by parenteral exposure, the epidemiology of HCV infection may change. The relative contribution of non-parenteral routes of transmission may increase, except where the continuing increase in injecting drug use more than compensates for the reduction—for example, as a result of blood donor screening.

There is limited information available to advise patients about their infectivity. There is, however, no serological marker analogous to hepatitis B virus e antigen status that can be used to distinguish high and low infectivity carriers. Results from studies of materno-fetal transmission suggest that transmission is extremely unlikely to occur, if ever, from mothers who do not have detectable viraemia by PCR.[77] There is some evidence that quantitative measures of viraemia may correlate with infectivity, but studies have been complicated by the effect of HIV co-infection. Results from a variety of different types of study confirm that sexual transmission does occur, at a low rate.

The cross sectional studies suggest that the probability of the sexual partner of an HCV infected patient being found to be infected is of the order of 0–3% in northern Europe or North America. Rates in other regions, such as southern Europe and the Far East, are higher and reflect the higher background prevalence in these countries. The predominant genotypes found in Japan and Taiwan are different from Europe; whether infectivity is related to genotype is not known. Other factors that have been suggested which may affect the rate of transmission include the stage of disease and HIV status, as well as the duration of the period of exposure. Other routes of transmission and environmental factors are likely to be important in explaining the different prevalence rates and apparent rates of transmission in different regions.

Given the limited evidence on which to base advice for patients it is not unexpected that differences exist between guidelines for patient management and in the practice in different centres. In our own centre, patients are advised that anyone with HCV antibodies is potentially at risk of transmitting HCV infection; however, the rate of sexual transmission is very low and for some there may be no risk at all. For those

without detectable HCV RNA, it appears to be highly unlikely that they are at any risk of sexual transmission. For the majority of HCV positive patients, who do have detectable viraemia, we cannot at present distinguish between those at risk of transmission and those who are not. While those in long term relationships who have not transmitted have clearly demonstrated low infectivity, we cannot yet say that they could not transmit in the future. Condom use is advised for all those who are at risk of transmission. The particular problems of those who wish to conceive are discussed; unprotected intercourse only during mid cycle is one strategy for limiting the risk of exposure which has been advocated for couples at risk of transmitting HIV infection.

More quantitative data are needed to be able to advise patients adequately on the risks of sexual transmission. Precise estimates of the rate of transmission will require further, appropriately designed prospective cohort studies. A meta-analysis of the data from some of the many small studies may be feasible, where the methodologies are similar. Such studies should also improve our understanding of the determinants of transmission. More data are essential to model the future epidemiology of hepatitis C and to develop appropriate prevention strategies and clinical practice guidelines. They would also assist in predicting the future need for treatment, and provide a framework for assessing the benefit of a vaccine, should one become available.

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