Lack of evidence for the heterosexual transmission of hepatitis C

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Summary
The importance of sexual transmission in the epidemiology of hepatitis C virus (HCV) infection is still controversial. To assess the risk of heterosexual HCV transmission, we examined eighty patients with chronic HCV-associated liver disease and their spouses in a cross-sectional clinical and serological cohort study. Serum samples from index patients and their spouses were assayed for HCV antibodies and HCV RNA. In the couples positive for both, further HCV genotyping was done. A questionnaire addressing points such as additional risk factors for HCV infection, sexual behaviour or duration of partnership was completed by all couples. HCV antibodies were detected in four (5%) spouses, of whom three (4%) were also positive for HCV-RNA. HCV genotyping revealed concordance (genotype 1) in two couples, indicating a risk of interspousal HCV transmission of 2.5%. Spouses of patients with HCV viraemia and chronic liver disease have a low risk for acquiring HCV. Even long-term spouses seem not to be at increased risk. We therefore suggest that the risk of HCV transmission between monogamous sex partners does not depend on the duration of sexual exposure.

Introduction
The use of advanced gene technology made possible the characterization of hepatitis C virus (HCV) by Choo and coworkers in 1989. Soon HCV was identified as the major cause of non-A, non-B hepatitis worldwide.1–4 Epidemiological studies showed that its most efficient route of transmission is parenteral, by transfusion of blood or blood products, by intravenous drug abuse, occupational needle-stick injuries, haemodialysis and organ transplantation. Parenteral transmission is well established, and accounts for the high rates of HCV among haemophiliacs and intravenous (i.v.) drug users. In about 30–40% of HCV cases, the routes of transmission remain unknown.5,6 Sexual transmission or other close human contact could play a role in these sporadic or community-acquired infections.

Many studies have addressed this question and achieved somewhat conflicting results. The high prevalence of HCV found in prostitutes,7 male homosexuals,8–10 sex partners of patients infected with both HCV and human immunodeficiency virus11 and patients attending sexually-transmitted-disease clinics,9,12,13 suggests that sexual transmission may occur. Other studies, however, having investigated monogamous sex partners of HCV-infected transfusion recipients and of patients with acute or chronic hepatitis C, reveal infrequent or no sexual HCV transmission.14–20,25,26

Results from Asian countries indicate that interspousal transmission becomes more important with longer duration of partnership.21–23 Similar data from Western countries are rare.24–26 To evaluate the prevalence of interspousal transmission of HCV for Central Europe, we investigated the heterosexual partners of 80 referred patients with HCV viraemia and chronic liver disease in a cross-sectional study, and compared the HCV genotype among the infected couples.

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Methods

From January to September 1998, spouses of 80 patients with chronic HCV-associated liver disease were screened for HCV infection at our Division of Gastroenterology at the University of Innsbruck. Chronic HCV-associated liver disease was defined as elevated liver enzymes for at least 6 months and a positive reaction in a second-generation anti-HCV assay. A total of 80 patients were enrolled: 43 men (54%) and 37 women (46%) with a mean age of 47.1 years (range 24–83). Forty-six (57.5%) had chronic persistent hepatitis, six (7%) chronic active hepatitis, 24 (30%) cirrhosis, and four (5%) hepatocellular carcinoma. The diagnoses were confirmed by liver biopsy in 54 patients (68%). In the majority of cases the aetiology and duration of HCV infection were unknown; in 38 (48%), parenteral exposure was considered to be the source of infection.

The couples completed a questionnaire addressing the occurrence of premarital non-A, non-B hepatitis or other liver diseases, history and timing of blood transfusion or injuries by needle stick, use of illicit intravenous drugs, tattoos and piercings, duration of their present marriage, sexual activity, such as weekly frequency of intercourse, various sexual practices, the use of condoms, extramarital relationships, sharing of personal hygiene implements such as toothbrush or razor, and at least weekly alcohol intake and nicotine consumption.

Serum samples from study patients and their spouses were collected and assayed for anti-HCV with a second-generation assay (Abbott Laboratories). Serum HCV RNA was detected by reverse-transcription nested polymerase chain reaction (PCR) with primers deduced from the 5'-noncoding region (Amplicor, Roche Diagnostic Systems). HCV genotypes in spouses and corresponding patients were determined by a PCR typing assay (Inno-Lipa HCV 2, Innogenetics).

Frequencies between groups were compared using the $\chi^2$ test and Fisher’s exact test. A $p$ value of $<0.05$ was considered significant.

Results

Forty-three (54%) of the 80 spouses were female, 37 (46%) were male. Their mean age was 44.6 years (range 24–81). All had a sexual relationship with the study patient. The couples were divided into six groups according to the duration of partnership: 0–5 years ($n=8$); 6–10 years ($n=17$); 11–20 years ($n=17$); 21–30 years ($n=14$); 31–40 years ($n=14$); and >40 years ($n=10$). The mean length of sexual relationship was 21.4 years; 75 couples (94%) remained sexually active, and five (6%) did not. The average rate of sexual intercourse was 1.6 times per week, estimated for the whole period of partnership. All but three couples (96%) conducted unprotected sexual intercourse (without condom), 33 (41%) reported practicing oral sex, and four (5%) anal intercourse. Nicotine consumption was recorded in 33 cases (41%), former i.v. drug abuse in nine (11%) and the mean intake of alcohol per week was about 70 g. Five partners (6%) had received blood transfusions, seven (9%) had tattoos and/or piercings, and one woman reported having suffered several needle-stick injuries in her occupation as a nurse.

Of the 80 spouses negative for hepatitis B surface antigen, four (5%) were positive for anti-HCV antibodies, of whom three (4%) were positive for HCV RNA as well. The characteristics of these study patients and their spouses are summarized in the table. One female partner tested positive for HCV antibodies but negative for HCV RNA several times; she was a former i.v. drug user, had normal levels of liver enzymes, and had no clinical or biochemical evidence of liver disease. All other spouses positive for anti-HCV had no history of premarital hepatitis or extramarital relationship. All were sexually active with the study patient, and denied using condoms or sharing personal hygiene implements.

Of the three spouses positive for HCV antibodies and HCV RNA, one suffered from cirrhosis, one from chronic persistent hepatitis and the last, although not biopsied, was considered to be an healthy HCV carrier. Their HCV genotypes were analysed and compared with those of the study patients. In two couples (2.5%) the genotypes were concordant (genotype 1b, the predominant type in Western Europe) and in one discordant. In the latter case, the partner, a nurse who had suffered several needle-stick injuries, was infected with genotype 2b, while her partner, a former i.v. drug user, was infected with genotype 3. Analysis of the questionnaires completed by the two couples with concordant HCV genotypes showed that one case involved an additional risk factor for HCV infection, namely a blood transfusion in 1996 that tested negative for anti-HCV. The other case showed no additional risk factors. A male spouse reported having had bloody sexual intercourse with his wife several times over many years. He had suffered from phimosis, which was later treated by circumcision.

There was no statistical difference in sex distribution, mean age, mean peak serum ALT level, stage of liver disease, duration of marriage, sexual behaviour, amount of alcohol and nicotine consumption or risk factors for acquiring HCV infection between study patients with anti-HCV-positive and anti-HCV-negative spouses.
Discussion

Our study finds no convincing evidence for the heterosexual transmission of hepatitis C. The HCV seroprevalence in spouses of patients with chronic HCV infection and viremia is 5%. Sexual transmission, however, appears possible in only 2.5%, due to the results of HCV genotyping. The real risk of interspousal transmission may even be half that (1.25%) when excluding spouses with concordant but additional independent risk factors for HCV infection.

During the last few years, some shifts in the epidemiological patterns of HCV transmission have been observed. In the past, transfusion of blood and blood products was the classical source of infection, but it is believed that currently, high-risk drug and sexual exposures accounts for most HCV transmissions. The source of infection is unknown in 30–40% of all HCV infections. Sexual and intrafamilial transmission have been discussed as possible routes of transmission. So far, discordant results have been reported, and the importance of sexual HCV transmission remains unclear. The controversy of previous reports is probably due to the small sample size of many studies investigating heterogeneous groups at varying risk, to the various means of testing, especially the lack of genotyping, and to geographic differences. The reported risk for heterosexual transmission is estimated at between 0% and 27%.14–18,21–28 The highest rates were reported in studies conducted in the Far East or Southeast Asia,21,22 citing a risk of between 17% and 27% for heterosexual transmission, and emphasizing older age and longer duration of marriage as the most evident risk factors. In Southeast Asia, however, the prevalence of HCV is much higher, and common external sources, such as dentistry, acupuncture or medical injections, may interfere with interspousal transmission of concordant genotypes.

In Western societies, there is little evidence to show that sexual transmission of HCV is of epidemiological importance. The few studies27,28 reporting high rates of 11% to 14% were performed with small sample sizes (n=21) and unreliable screening methods (first-generation ELISA). In contrast, there are many reports documenting a low or absent risk of sexual transmission.14–20,25,26 Some of the discrepancies in the literature among reported seroprevalence rates for groups with sexual risk factors may also be due to missing or inadequate information about additional parenteral exposure. Particularly in studies investigating the sexual risk of prostitutes, homosexual men and STD clients, accurate histories of former i.v. drug abuse may not be available.

Our study does not find an increased risk for couples for acquiring HCV. This finding is all the more significant with a view to the high percentage of long-lasting sexual partnerships (the median sexual relationship was 21.4 years) and to the high frequency of unprotected sexual intercourse. Evaluation of the questionnaires and statistical analysis revealed no risk factors for HCV transmission in the everyday life of couples. Neither sex, stage of liver disease, duration of marriage, sexual behavior nor condom use had an influence on the risk of interspousal transmission. Further special risk factors like phimosis or other conditions causing bleeding during intercourse, seem to be needed to cause sexual transmission. An example of this is couple 2 (Table 1) with concordant HCV genotype 1b, absent additional risk factors for HCV infection, but bleeding during intercourse.

The sample size of our trial is small, and studies on larger samples are needed to be able to draw

<table>
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<th>Table 1 Characteristics of the four index patients and their spouses where both were positive for anti-HCV antibodies</th>
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<td><strong>Partner 1</strong></td>
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<td><strong>Sex</strong></td>
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<td><strong>Anti-HCV</strong></td>
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<td><strong>HCV RNA</strong></td>
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<td><strong>HCV genotype (partner)</strong></td>
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<td><strong>Additional risk factors for HCV infection</strong></td>
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<td><strong>Duration of marriage (yrs)</strong></td>
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<td><strong>Frequency of sexual intercourse (per week)</strong></td>
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<td><strong>Use of condoms</strong></td>
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<td><strong>Anal/oral intercourse</strong></td>
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<td><strong>Bleeding during sex</strong></td>
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<td><strong>Liver disease (spouse)</strong></td>
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<td><strong>Liver disease (index partner)</strong></td>
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CPH, chronic persistent hepatitis; Cl, liver cirrhosis; TF, blood transfusion; NS, needle-stick injury; iv, i.v. drug abuse; NA, not applicable.
more conclusions. However, the findings are significant and confirmed by recent results from Italy\textsuperscript{25,26} where similar HCV seroprevalences (7.3\%) were found in larger sex partner studies, and sexual transmission did not seem to play a role in the intrafamilial spread of HCV infection. The risk of heterosexual HCV transmission calculated in this study is 2.5\%. In the USA, the United States Public Health Service estimates that the risk of sexual transmission is approximately 5\%, well below the risk of sexual transmission of hepatitis B or human immunodeficiency virus.\textsuperscript{29}

In conclusion, the heterosexual transmission of HCV is possible but infrequent in monogamous sex partners of patients with HCV viraemia and chronic liver disease. The risk of sexual transmission does not seem to correlate with intensity and duration of sexual exposure.

References


