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Sexual transmission of hepatitis C virus: cohort study (1981-9) among European homosexual men

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Abstract

Objective—To determine the prevalence, incidence, and persistence of positivity for antibodies to hepatitis C virus (anti-HCV) and the potential for sexual transmission of the virus.

Design—A cohort analysis covering 1981-9 comparing estimated cumulative incidences of and seroconversion rates for anti-HCV with those of hepatitis B core antibody (anti-HBc) and antibodies to the human immunodeficiency virus (anti-HIV).

Setting—Copenhagen and Aarhus, Denmark.

Subjects—259 Male members of a Danish homosexual organisation.

Main outcome measures—Correlations of prevalence and incidence with a wide range of sexual lifestyle variables.

Results—Only four (1.6%) subjects were positive for anti-HCV in 1981. The estimated cumulative incidence of positivity for anti-HCV was 4.1% in 1984 (seroconversion rate during 1981-4 (2.5%)) and remained at 4.1% in 1989 (seroconversion rate nil during 1984-9). In contrast, positivity for anti-HBc rose from 44.0% in 1981 to 52.7% in 1984 (seroconversion rate 15.5%) and 58.8% in 1989 (seroconversion rate 12.9%), and that for anti-HIV rose from 8.8% to 24.0% (seroconversion rate 16.7%) and 30.1% (seroconversion rate 8.0%) respectively. Three anti-HCV positive patients seroconverted three to five years later. None of the anti-HCV positive subjects had had a transfusion and only one gave a past history of intravenous drug use. Variables in sexual lifestyle correlated with the presence of anti-HBc but not with that of anti-HCV.

Conclusions—In contrast with hepatitis B virus and HIV, sexual transmission of hepatitis C virus seems to be a rare event. Furthermore, antibodies to the virus may become undetectable after several years.

Introduction

Although the classification and early descriptions of clinical non-A non-B hepatitis were derived primarily from cases associated with transfusion, this mode of transmission has recently been estimated to account for only 5-10% of patients with the disease in the developed world.¹ In a substantial proportion of cases no obvious route or source of transmission is found. In this respect, therefore, the importance of sexual transmission has been an open question. A possibility for better understanding has emerged with the molecular cloning of an agent designated hepatitis C virus, which seems responsible for most cases of parenteral non-A non-B

hepatitis.^{2,3} To date frequent transmission of hepatitis C virus by exposure to blood has been described in drug addicts and patients with haemophilia⁴⁻⁸ whereas little has been reported on the frequency of sexual transmission of the virus. We have studied the prevalence and persistence of antibodies to hepatitis C virus among homosexual men and analysed their possible association with a range of lifestyle factors to see if there is evidence for homosexual spread of hepatitis C virus. Comparison was made with two other viral agents known to be frequently transmitted sexually—namely, hepatitis B virus⁹ and HIV.¹⁰

Subjects and methods

We studied a cohort of Danish homosexual men who had been followed up since 1981.^{10,11} Briefly, 259 subjects were initially enrolled from volunteers belonging to a national organisation of homosexual men. At enrolment their average age was 32.0 years, their average duration of homosexual activity 12.2 years, and their average number of partners 24.9 a year. Cross sectional analyses were performed on all subjects comparing antibody state with lifestyle and demographic variables. In addition, longitudinal studies were done on subjects who subsequent to the 1981 visit were also seen in 1984 or 1989, or in both years. Compared with the original 1981 cohort members of this subset were slightly more experienced sexually (1984, 13.3 years of homosexual activity; 1989, 14.0 years) but otherwise were similar.

A log linear model was used to compute the non-parametric maximum likelihood estimate of the survival curves (1—estimated cumulative antibody incidence) from interval censored data, as detailed elsewhere.¹² We also calculated the seroconversion rates between years of testing using the same methodology. Associations between serological markers and variables in lifestyle were analysed by Spearman rank order correlations and linear regressions.

Serum samples were kept frozen at -70°C until assay and had not previously been thawed. All serum samples were tested for antibodies to hepatitis C virus (anti-HCV) by an enzyme linked immunosorbent assay (ELISA; Ortho Diagnostic Systems). Samples that were non-reactive to hepatitis C virus in the initial run were considered to be anti-HCV negative. Samples that were reactive to hepatitis C virus were retested and considered to be positive if reactive in both tests. Exposure to hepatitis B was determined by an assay for antibodies to hepatitis B core antigen (anti-HBc; CORZYME, Abbott Laboratories). This marker does not recognise patients immunised by vaccination.

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Testing for HIV antibody (anti-HIV) was performed by an indirect second generation ELISA with western blot for confirmation.

Results

HEPATITIS C VIRUS

Of the 259 subjects in the original cohort, 250 (96.5%) had serum remaining for hepatitis tests. In 1981 four (1.6%) of these men were positive for anti-HCV. Three others seroconverted between 1981 and 1984 and one between 1981 and 1989 (table I). Using a log linear model we found the cumulative (since 1981) incidence of positivity for anti-HCV to be 4.1% in 1984 and also 4.1% in 1989 (table II). This analysis included anti-HCV positive subjects who later seroreverted.

Two of the three men who seroconverted to hepatitis C virus between 1981 and 1984 also seroconverted to HIV during that period. By 1989 these two subjects were profoundly immunosuppressed (CD4 to CD8 ratios 0.20 and 0.04) and one had lost antibody to hepatitis C virus. The third seroconverter was anti-HIV negative throughout, yet had also lost reactivity to hepatitis C virus by 1989.

None of the subjects on whom information was available had ever received a transfusion, and only one had ever used drugs intravenously (table I). Neither age, duration of homosexual activity, type of sexual activity, treatment for venereal disease, nor HIV state was significantly correlated with being anti-HCV positive (figure). The few anti-HCV positive subjects, however, tended to have more partners than seronegative subjects.

HEPATITIS B VIRUS AND HIV

Table II summarises the data on hepatitis and HIV. Anti-HBc was found in an estimated 44.0% of the men in 1981, 52.7% in 1984, and 58.8% in 1989. In 1981 being positive for anti-HBc was correlated with numbers of sexual partners a year ($p < 0.0001$), older age ($p < 0.0001$), years of homosexual activity ($p < 0.0001$), number of previous treatments for gonorrhoea and syphilis ($p < 0.0001$), and also being seropositive to HIV ($p < 0.2$) or seroconverting later ($p < 0.03$) (figure). In logistic regression analyses the strongest single variable was number of partners (in all models $p < 0.0001$). In a model with the number of

Correlates of positivity for anti-HBc (□) and anti-HCV (■) with age, years of homosexual activity, and numbers of sexual partners a year among cohort of Danish homosexual men (1981 data)

TABLE I—Presentation of subjects positive for hepatitis C marker

Case No	Year of birth	Serological results in 1981, 1984, and 1989*			Blood transfusion ever†	Intravenous drug use ever†	Clinical hepatitis (year)
		Anti-HCV	Anti-HBc	HBsAg			
1	1939	+++	+++	---	No	No	?
2	1956	+++	---	---	No	No	No
3	1952	---	---	NN-	No	No	1977‡
4§	1959	+NN	-NN	NNN	?	No	No
5	1958	---	+++	---	No	No	1977
6	1944	---	+++	---	No	Yes	No
7	1949	---	---	N++	No	No	1984
8	1930	-N+	+N+	-N-	No	No	No

*N=Not tested. HBsAg=Hepatitis B surface antigen.

†Up to time of first positive test result for anti-HCV.

‡Diagnosed as non-A non-B hepatitis.

§Subject left Denmark in 1981 and was subsequently lost to follow up.

||Data not available.

TABLE II—Estimated seroconversion rates and cumulative incidence of positivity for antibodies to hepatitis C virus, hepatitis B virus, and HIV in a cohort of homosexual men during 1981-9 (analyses include subjects who later seroreverted)

Year of testing*	Anti-HCV		Anti-HBc		Anti-HIV	
	Cumulative % positivity	Seroconversion rate (%) (95% confidence interval)	Cumulative % positivity	Seroconversion rate (%) (95% confidence interval)	Cumulative % positivity	Seroconversion rate (%) (95% confidence interval)
1981	1.6	2.5 (0 to 5.0)	44.0	15.5 (7.4 to 22.9)	8.8	16.7 (10.8 to 22.2)
1984	4.1	0	52.7	12.9 (3.2 to 21.5)	24.0	8.0 (2.7 to 13.0)
1989	4.1		58.8		30.1	

*250 Subjects tested in 1981; 122 tested in 1981 and 1984; 112 tested in 1981 and 1989; 73 tested in all three years.

partners held constant, years of homosexual activity but not age was also significant ($p=0.0002$). Number of episodes of venereal disease remained significantly associated even after adjustment for the number of partners. Two subjects were initially anti-HBc positive but seroreverted between 1984 and 1989. Both were anti-HIV positive and had abnormal CD4 to CD8 ratios (0.04 and 0.17) with low CD4 values in 1989.

Discussion

The profile of an association between hepatitis B and a wide range of sexual lifestyle variables indicates that hepatitis B is a sexually transmitted disease among homosexual men. We have analysed these variables in detail in order to contrast the findings with reactivity to hepatitis C virus. Had hepatitis C been readily transmitted sexually we should expect to have seen a characteristic epidemiological profile. We found no direct evidence of sexual transmission of hepatitis C. Nevertheless, although few of our cohort of homosexual men were positive for anti-HCV, the proportion was considerably higher than that among male blood donors (0.3%) of the same age in Denmark (Wantzin *et al*, unpublished data). Yet none of our anti-HCV positive subjects had ever received a transfusion and only one gave a history of intravenous drug use. The absence of parenteral exposure favours the possibility of sexual transmission, although at a much lower rate than in the case of hepatitis B virus or HIV. Rates of seroconversion detected to hepatitis C virus were six to 13 times lower than those recorded to hepatitis B virus and HIV.

One caveat arose from the longitudinal data: the hepatitis C marker was not consistently present among all initially reactive or seroconverting subjects. Loss of anti-HCV has also been described in three patients with resolving non-A non-B hepatitis in a prospective study of transfusion recipients.¹³ We have reported declines in reactivity to hepatitis B virus, sometimes to undetectable levels, with progressive immunodeficiency¹⁴ and also observed the phenomenon with anti-HBc in this study. Not all subjects who lost reactivity to hepatitis C virus in this study were infected with HIV and had abnormal immunity, however, which argues for a different explanation for the phenomenon of seroreversion to hepatitis C virus.

Our observation that seroreversion to hepatitis C virus may be fairly common suggests that the cumulative incidence of seropositivity for the period 1981-9 may have been slightly higher than the 4.1% recorded in this study. Alter *et al*, however, found the mean duration of anti-HCV positivity among subjects

who later seroreverted to be 4.1 years (range 7 months to 11 years).¹³ Hence the number of anti-HCV positive subjects missed in our series was probably small.

The persistence of reactivity in some subjects may indicate that some of these men were chronic carriers of hepatitis C. Although a test for hepatitis C virus in the blood is not available, we note that the highest figures for the prevalence of circulating anti-HCV are reportedly found among patients with chronic non-A non-B hepatitis and that among these patients seroreversion is unlikely to occur.¹³ The high prevalence of anti-HCV in patients with haemophilia and intravenous drug users^{4-6,8} may be explained by these people being chronic carriers or recurrently exposed to hepatitis C virus.

We conclude that hepatitis C virus is not readily spread by homosexual activity, although sexual transmission may occur occasionally. Anti-HCV positive subjects may lose their antibodies and it remains to be seen whether those people are less infectious than persistently seropositive subjects.

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Diarrhoea due to cryptosporidium infection in thalassaemia major

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Cryptosporidium has been increasingly recognised as a cause of diarrhoea in both immunocompetent and immunocompromised patients with the advent of adequate staining techniques. It is a coccidian parasite, which seems to be a single species able to infect a range of animal hosts.¹ In immunocompetent adults it ranks third in the non-viral causes of gastrointestinal symptoms after salmonella and campylobacter,¹ and in patients with AIDS it is the commonest cause of diarrhoea.

The severity of infection with cryptosporidium varies, and immunocompetent patients may be asymptomatic.² Usually there is an attack of watery, non-bloody diarrhoea with abdominal pain, vomiting, and fever. Temperatures of up to 38.3°C have been reported.² The illness is self limiting, and symptoms may be short lived or persist for many weeks. In immunocompromised subjects the illness is prolonged and debilitating and may be fatal.¹

Case report

A 22 year old woman with β thalassaemia major had been dependent on transfusions since birth and received desferrioxamine for iron overload. She had had a splenectomy at the age of 7, and a test for HIV in March 1989 had yielded negative results. In June she presented to casualty with a 24 hour history of watery diarrhoea, colicky abdominal pain, vomiting, dizzi-

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