HEPATITIS

Higher clearance of hepatitis C virus infection in females compared with males

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Background and aims: According to the literature, 14–46% of subjects clear hepatitis C virus (HCV) from blood after infection. Controversy exists about sex differences in HCV clearance rates.
Patients and methods: We compared HCV clearance in males and females using data from a large population based study on HCV infection in Egypt. Definitions used in the paper were: cleared HCV infection (positive HCV antibody and negative HCV RNA test results) and chronic HCV infection (positive HCV antibody and positive HCV RNA test results). The study sample included 4720 village residents aged 18–65 years recruited through home based visits (n = 2425) or voluntary screening (n = 2295).
Results: Overall, HCV antibody prevalence was 910/4720 (19.3% (95% confidence interval 18.2–20.4)). Of those with HCV antibodies (n = 910), 61.5% had chronic HCV infection. Compared with males, females were more likely to have cleared the virus (44.6% *v* 33.7%, respectively; p = 0.001). Control for age, schistosomiasis history, iatrogenic exposures, and sexual exposure to HCV did not alter the positive association between female sex and viral clearance.
Conclusion: This study provides strong evidence in favour of a higher HCV clearance rate in females compared with males.

Progression of hepatitis C virus (HCV) infection is known to be worse in males than in females.[1–2] Independent of alcohol intake, males have a twofold greater progression rate to fibrosis compared with females.[3] Less is known about sex differences in HCV clearance rates, defined in cross sectional surveys as the proportion of non-viraemic subjects among those with HCV antibodies. Viral clearance rates vary from 14% to 46% according to the literature.[1] Two studies showing the highest clearance rates (45%) were of Irish and German women who received HCV contaminated Rh immune globulin in late pregnancy or early post partum.[4–5] Based on the results of these two studies, it is commonly believed that women clear HCV well, and most likely better than males. However, the studies had no male comparison group, included women who were pregnant or in early post partum when infected with HCV (unknown influence on HCV clearance rate), and women who were young when infected with HCV (known factor of higher clearance rate[6 7]).

Moreover, three of the largest population based studies, NHANES in the USA, the Trent Study in the UK, and Dionysos in Italy, gave controversial results. In the NHANES study, a sex difference in HCV clearance was seen only in the subgroup of non-Hispanic Blacks while no sex difference was observed in the other groups (non-Hispanic Whites and Mexican Americans).[8] In the Trent and Dionysos studies, no sex difference in HCV clearance was seen.[9–11] We took the opportunity of using data from a large population based study of HCV infection in a village in Egypt to compare viral clearance rates between males and females.

SUBJECTS AND METHODS

Participants were inhabitants of the village Zawyat Razin, a 90 minute drive north west of Cairo in Menofia Governorate (Nile Delta). All residents older than five years of age and living in one sector of the village (25% of the village population, estimated at approximately 20 000) were invited to participate in the study.[12] Invitations took place during home visits, which were repeated outside of working hours when adult residents were not found at the initial visit. In addition, all village residents over 18 years of age and living outside of the study sector who were willing to be tested for HCV antibodies were invited to participate through a voluntary screening programme. After informed consent was obtained (from the head of household for children less than 18 years of age), participants were given a questionnaire on sociodemographic characteristics, clinical history, and risk factors for HCV infection. Participants were asked to provide blood and stool samples. Stool samples were examined at a local laboratory for *S mansoni* eggs using the Kato test. Blood samples were transported the same day for centrifugation and freezing of serum (−80°C) at the National Hepatology and Tropical Medicine Reference Institute in Cairo.

Sera were tested for HCV antibodies using Innotest HCV Ab IV (Innogenetics, Ghent, Belgium) (lower 95% confidence limit of specificity was reported as 98.1% during evaluation of hepatitis C assays by the Blood Safety and Clinical Technology of the World Health Organisation).[13] Samples positive for HCV antibodies were tested again using Abbott HCV EIA 3.0 (Abbott Laboratories, Diagnostics Division, Illinois, USA), and those testing positive by the two serological tests were considered positive for HCV antibodies.[14] Samples with discordant results (n = 35) were considered to be negative. All HCV antibody positive samples were tested for HCV-RNA using a one step reverse transcriptase-polymerase chain reaction in house assay, using 5′UTR primers with modifications,[15] and for serum alanine aminotransferase (ALT). Genotyping was performed by sequencing the NS5B and E1 regions of 135 HCV-RNA positive sera included in a substudy of intrafamilial transmission of HCV. Participants with positive HCV-RNA and elevated ALT were invited to attend the study clinic at Ismail Sallam Hospital for an eligibility screening for treatment with pegylated interferon and ribavirin. The study

Abbreviations: HCV, hepatitis C virus; ALT, alanine aminotransferase; OR, odds ratio; HIV, human immunodeficiency virus

Table 1 Sociodemographic characteristics of the study population (Zawyat Razin, 2002)

	Males (n = 2326)	Females (n = 2394)	p Value*	Total (n = 4720)
Age groups (y)				
18–29 (%)	1047 (45.0)	1104 (46.1)		2151 (45.6)
30–39 (%)	570 (24.5)	552 (23.1)		1122 (23.8)
40–49 (%)	348 (15.0)	392 (16.4)	> 0.05	740 (15.7)
⩾ 50 (%)	361 (15.5)	346 (14.5)		707 (15.0)
Lifetime residents (%)	2172 (93.4)	2204 (92.1)	> 0.05	4376 (92.7)
Education level				
No education (%)	877 (37.7)	1748 (73.0)		2625 (55.6)
Able to read and write (%)	702 (30.2)	281 (11.7)	< 0.001	853 (18.1)
Higher education (%)	747 (32.1)	365 (15.2)		1242 (26.3)
History of schistosomiasis treatment				
No (%)	1181 (51.0)	1823 (76.3)		3004 (63.8)
Tablets only (%)	536 (23.1)	215 (9.0)		751 (16.0)
Injections ± tablets (%)	356 (15.4)	74 (3.1)	< 0.001	430 (9.1)
Does not remember (%)	245 (10.6)	276 (11.6)		521 (11.1)
Missing	8	6		14
Type of recruitment				
Village cohort	1137 (48.9)	1288 (53.8)	0.001	2425 (51.4)
Voluntary screening	1189 (51.1)	1106 (46.1)		2295 (48.6)

*Comparing males with females.

protocol was approved by the Egyptian Ministry of Health and Population Institutional Review Board and a local ethics committee set up for hepatitis studies in Egypt.

The analysis focused on adults aged 18–65 years as pretreatment screening was offered exclusively to this age group. Definitions used to categorise participants were: cleared HCV infection (positive HCV antibody and negative HCV RNA) and chronic HCV infection (positive HCV antibody and positive HCV RNA). Means and proportions were compared across study groups using the Mann-Whitney and χ^2 tests, respectively. The main outcome of interest was clearance of HCV infection among those with HCV antibodies. Factors associated with HCV clearance were studied in univariate and multivariate analyses (logistic regression). Factors introduced into the multivariate models were age (in five year categories), sociodemographic variables (sex, type of recruitment, and duration of residence), and risk factors for HCV transmission identified in a previous study[12] in the adult cohort population (past treatment for schistosomiasis, categorised as intravenous, oral or unknown using dummy variables; injections and intravenous infusions; blood transfusion; abscess drainage; endoscopy; dental gum treatment; instrumental delivery, and caesarean section). A subgroup analysis restricted to married couples was carried out to study the effect of marriage with a chronically infected partner (a proxy for sexual exposure to HCV) on the risk of being HCV infected and also clearing the virus. Data were analysed using Stata statistical software (Stata 8.0; Stata Corporation, College Station, Texas, USA).

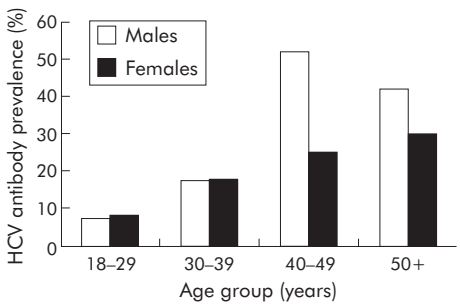

Figure 1 Hepatitis C virus antibody prevalence (%) by age and sex.

RESULTS

From May to November 2002, 820 houses, containing 1178 families, 5813 inhabitants, and 5130 inhabitants over five years of age, were visited. Of the 5130 eligible individuals, 4054 (79.0%) were present at the time of the survey and agreed to participate in the cohort study. Of these, 2426 were aged 18–65 years, of whom 2425 had complete HCV serology data. Of those who came to the voluntary screening programme, 2298 were between 18 and 65 years of age, of whom 2295 had complete HCV serology data. Overall, 4720 adults (2425 from the cohort study and 2295 from the voluntary screening programme) were enrolled in the study.

As shown in table 1, half of the study population was male, and 30.7% were 40 years or older. In this latter age group, 336/1444 (23.3%) remembered having received intravenous treatment for schistosomiasis. This proportion was only 74/1118 (6.6%) among those aged 30–39 years, and 20/2144 (0.9%) among those aged 18–29 years (14 missing values). History of intravenous schistosomiasis treatment was also more common in males compared with females (15.4% *v* 3.1%; p<0.001), with even more pronounced differences when the analysis was restricted to those 40 years of age and above (40.2% *v* 7.1%; p<0.001). *S mansoni* eggs were found in 58/2404 (2.4%) of the participants who provided stool samples for a Kato test.

HCV antibody prevalence was 910/4720 (19.3% (95% confidence interval (CI) 18.2–20.4)), and did not differ between the home based and voluntary screening recruitment procedures (448/2425 = 18.5% and 462/2295 = 20.1%, respectively; p>0.05). Figure 1 shows the age and sex distribution of HCV antibody prevalence for the total adult population tested (n = 4720). Among males, HCV antibody prevalence tripled between the age groups 30–39 and 40–49 years before declining while the increase in HCV prevalence among females was more gradual until the 50–59 year age group. HCV antibody prevalence was higher among those treated for schistosomiasis by intravenous injections compared with others (244/430 = 56.7% *v* 664/4276 = 15.5%, respectively; p<0.001), and this difference remained when analysis was restricted to those aged 40 years and older (216/336 = 64.3% *v* 324/1108 = 29.2%, respectively; p<0.001).

There was no difference between the two study groups (that is, village cohort and voluntary screening recruitment) in the proportion of chronic HCV infections among those with positive HCV antibodies. Overall, 560/910 (61.5% (95%

Table 2 Hepatitis C virus (HCV) clearance rate by sex (Zawyat Razin, 2002)

	Males	Females	p Value
Positive HCV antibodies (% of total population)	511/2326 (22.0)	399/2394 (16.7)	<0.001
Cleared HCV infection (% of those with antibodies)	172/511 (33.7)	178/399 (44.6)	0.001

CI 58.3–64.7)) of those with HCV antibodies had chronic infection at the time of the survey (table 2). Among patients with chronic infections, almost all of those genotyped were genotype 4 (133/135 = 98.5%). Women were more likely to have cleared the virus compared with men (44.6% *v* 33.7%, respectively; p = 0.001). There was no difference in clearance rate by age groups. The odds ratio (OR) of the association between female sex and HCV clearance (OR 1.59 (95% CI 1.21–2.08)) remained unaltered after controlling for age, schistosomiasis treatment history, and other iatrogenic exposures associated with HCV antibodies (see subjects and methods for the list of iatrogenic exposures; adjusted OR 1.77 (95% CI 1.27–2.46)).

A subanalysis among participants whose spouse's HCV infection status was known (n = 2164) was carried out to study the effect of sexual exposure to HCV on the risk of becoming infected and clearing the virus. The prevalence of HCV antibodies was 116/303 (38.3%) among those whose spouse had chronic HCV infection, 66/196 (33.7%) among those whose spouse had HCV antibodies only, and 317/1665 (19.0%) among those whose spouse had no HCV antibody (p<0.001). Control for age, sex, and iatrogenic exposures to HCV did not alter the association between having HCV antibody and a spouse with chronic HCV infection (unadjusted and adjusted ORs were 2.64 and 2.53, respectively). Duration of marriage with a chronically infected spouse was also associated with an increased risk of having HCV antibodies (adjusted OR for an increase of 10 years of marriage was 1.40 (95% CI 1.23–1.59)). Among participants with HCV antibodies whose spouse's HCV infection status was known (n = 482), the same association between female sex and HCV clearance was found (univariate OR 1.73 (95%CI 1.18–2.53)), and the association remained after controlling for age, iatrogenic exposure, and HCV infection status of the spouse (adjusted OR 2.17), or duration of marriage with a chronically infected spouse (adjusted OR 2.12). There was no interaction between spouse HCV infection status and sex in any of the models tested.

DISCUSSION

HCV antibody prevalence in this study was extremely high, reaching 50% and 30% in older age groups for males and females, respectively. Such values are typical of those found in other rural areas of Egypt. The origin of the epidemic has been attributed to mass campaigns for intravenous schistosomiasis treatment in rural areas in the 1960s–70s.[16] Treatment consisted of several (up to 16) intravenous injections of tartar emetic administered in weekly doses to infected individuals living in schistosomiasis endemic areas, and particularly children and young adults. HCV transmission most likely occurred because of insufficient sterilisation of injection equipment between patients. In this study, past history of intravenous treatment for schistosomiasis was found in 23.3% of those aged 40 years and older, and HCV antibody prevalence in this group was particularly high (64.3%). Following this initial founding event, the HCV epidemic has spread into the community via iatrogenic factors, particularly injections.[12]

This large community based study gave us a unique opportunity to assess the HCV clearance rate among 910 subjects with HCV antibodies. Spontaneous HCV clearance typically occurs within the first six months after acute infection[11] and is characterised by the disappearance of HCV viraemia and persistence of HCV antibodies. HCV clearance may also occur after treatment, reaching 40–80% depending on the HCV genotype when patients are treated with the best available option (combined pegylated interferon and ribavirin).[17] While the HCV clearance rate is best estimated by prospective follow up of acute HCV infections, the rarity of the latter makes such studies difficult to undertake on a large scale. Alternatively, the HCV clearance rate can be estimated retrospectively in a given population through the proportion of subjects with HCV antibodies and no HCV RNA. Such estimates obtained through cross sectional surveys will suffer from two biases operating in opposite directions: on the one hand, a small proportion of subjects with cleared infection will loose their antibodies with time,[18 19] resulting in an underestimation of the proportion with cleared infection; on the other hand, subjects with chronic infection will have increased mortality compared with those with cleared infection, resulting in overestimation of the proportion with cleared infection. Other factors which make interpretation of HCV serology and RNA data difficult in cross sectional surveys are past treatments for hepatitis C, the possibility of HCV reinfection, and the negative effect of human immunodeficiency virus (HIV) coinfection on HCV clearance.[20 21] However, HCV reinfection and coinfection with HIV are rare except among intravenous drug users. In this study population of rural Egypt, effective treatment for hepatitis C has not been available in the past, intravenous drug use is not practised, and HIV infection is extremely rare,[22] minimising the potential biases associated with estimation of the viral clearance rate. The overall estimate of spontaneous viral clearance obtained in the village population (38.5%) was in the upper range of those (14%–46%) reported by Seeff in his review paper.[1] It is worth mentioning that almost all (98.5%) samples were of genotype 4, the predominant genotype in Egypt.[23]

The difference in HCV clearance rate by sex is still an unresolved issue. A prospective study comparing the HCV clearance rate between males and females after acute HCV infection would require 376 subjects of each sex to have 80% power to detect an absolute 10% difference (40% *v* 30%) in clearance rate under the usual assumptions (alpha = 0.05; two sided tests). Such a study, ideal in its design, is hardly feasible, and one must rely on retrospective studies to compare HCV clearance rates by sex. The estimated HCV clearance rate in females in this study was 44.6%, almost identical to that of women infected with HCV contaminated anti-D immune globulin in Ireland (44.6%)[4] and East Germany (45.5%).[5] It was higher compared with that of males (44.6% *v* 33.7%; p = 0.001). One possible confounding variable is age at infection, a known factor for a higher HCV clearance rate,[6 7] if females in this study had been infected at a younger age compared with males. While age at infection was not known for the study participants, examination of fig 1 suggests a cohort effect in males, with HCV infection of young individuals (aged 10–20 years) during the schistosomiasis treatment campaigns in the 1960–70s, and a more gradual acquisition of HCV infection in females throughout

their lifetime. Indeed, schistosomiasis treatment campaigns, the founding event of the HCV epidemic in rural Egypt,[16] targeted children at school, where boys were overrepresented compared with girls. As a result, the proportion of males with past exposure to intravenous schistosomiasis treatment was higher compared with that of females (40.2% *v* 7.1% among 40 year olds and older; $p<0.001$). For females, past intravenous schistosomiasis treatment was not a major cause of infection, and other means, including obstetric procedures, were involved.[12] In this scenario, mean age at infection in males was lower than that of females.

A second potential confounding factor might be coinfection with *S mansoni*, which has recently been associated with lower HCV clearance following acute HCV infection.[24] However, controlling for past treatment for schistosomiasis (oral and intravenous) resulted in an increase, rather than a decrease, in the observed association between female sex and HCV clearance. A third potential confounding variable could be coinfection with hepatitis B virus, known to facilitate HCV clearance,[25] and more commonly found among males throughout the world.[26] In such cases it would decrease the observed difference between males and females by increasing the male HCV clearance rate.

A fourth potential confounding variable could be alcohol use, known to be negatively associated with HCV clearance,[25] and more common among males. However, alcohol use is extremely limited in this Muslim community, and thus unlikely to be a confounder.

A fifth confounding factor could be route of transmission, if different for males and females, and associated with different HCV clearance rates. To our knowledge, there is no published evidence for differential clearance rates according to route of transmission. However, as detailed data on past iatrogenic exposures were available in this study, we looked at the effect of iatrogenic exposure on the association between sex and HCV clearance, and did not find any. Moreover, neither HCV infection status of the spouse nor duration of marriage with a chronically HCV infected spouse, both used as a proxy for sexual exposure to HCV, altered the OR of the association between female sex and HCV clearance.

Finally, faster progression to disease and HCV related mortality in males compared with females[3] would decrease the observed sex difference in HCV clearance rate, thus providing further support for the association documented in this study.

In conclusion, this study provides strong evidence in favour of a higher HCV clearance rate in females compared with males. A similar phenomenon is seen with hepatitis B virus infection, for which viral clearance from the blood is more common among females than males.[27] Speculation exists around the role of genetic factors or steroid hormones in the sex specific susceptibility to infectious diseases,[28 29] but no model has yet satisfactorily explained these differences. At a time when the treatment indications for acute hepatitis C are discussed,[30] it may be useful to keep in mind the higher chances of spontaneous resolution of infection among females compared with males.

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