

Surgical Procedures as a Major Risk Factor for Chronic Hepatitis C Virus Infection in Italy: Evidence from a Case-Control Study

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ABSTRACT

Objectives: The study was carried out to evaluate the risk factors associated with chronic hepatitis C virus (HCV) infection.

Methods: This case-control study used multiple logistic regression analysis to determine risk factors associated with HCV infection. Study participants were followed at 10 liver or gastroenterologic units and included 294 subjects with chronic HCV infection and 295 age and sex matched anti-HCV-negative controls.

Results: The use of glass syringes and surgical procedures was reported by as many as 77.6% and 73.8% of cases, respectively; blood transfusion was recorded in nearly a quarter of cases; 10.2% of cases, but none of the controls, reported past or current intravenous drug use. Multiple logistic regression analysis showed that blood transfusion, being the sexual partner of an intravenous drug user, and surgery all were independent predictors of the likelihood of HCV infection.

Conclusions: These findings indicate that, besides the well-known sources of infection, such as blood transfusion and intravenous drug use, surgical procedures may play an important role in the spread of HCV infection in Italy. Given that a large proportion of the general population undergoes surgery, a rational and relatively inexpensive policy for the prevention of HCV infection must focus on implementing efficient procedures for the sterilization of instruments and the use of disposable materials in surgical units.

Key Words: HCV, intravenous drug use, prevention, risk, surgery, transfusion

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Hepatitis C virus (HCV) infection is the main cause of chronic liver disease and hepatocellular carcinoma in Italy.^{1–4} The reasons for the wide spread of the infection largely are unknown. In general, a classic parenteral exposure, such as blood transfusion or drug addiction, may be recognized in only a minority of cases.^{1,2} Other modes of transmission, such as sexual or inapparent parenteral routes, have been examined in different studies, but the results to date have been inconclusive; vertical transmission plays a small role in immunocompetent mothers.^{5–7}

These results contrast with those obtained in the United States, where a definite risk may be identified in 50 to 60% of cases of chronic HCV infection.⁸ Recently, a case-control study performed in northern Italy showed that, besides blood transfusion and drug addiction, previous use of nondisposable needles, hospitalization before 1970, and previous tuberculosis all were independent predictors of HCV positivity.⁹ These findings indicate that, during the past few decades in Italy, the risk of acquiring HCV infection has been multifaceted.

This multicenter case-control study evaluates the risk factors associated to chronic HCV infection in patients from various areas in Italy.

STUDY POPULATION AND METHODS

Ten Italian centers for liver diseases and gastroenterology participated in the study. Cases were consecutive inpatients or outpatients referred to the hospital because of anti-HCV antibodies in serum. Controls were consecutive anti-HCV-negative subjects observed in the same center, and were age and sex matched with cases. Controls were subjects suffering from gallstones, inflammatory bowel diseases, gastric or duodenal ulcer, gastric cancer, cancer of the colon, or diverticulosis. Excluded from both cases and controls were hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus (HIV)-positive patients, hemophiliacs, and thalassemics. To ensure that both the cases and the controls were exposed to the same selection biases, if any, the authors

checked that they lived in the same area, were referred to the hospital through the same channels (generally, request by the general practitioner), and were seen in the same unit. They were interviewed using a standard questionnaire on their admission to the hospital about their sociodemographic characteristics and potential risk factors. Only major surgery (i.e., abdominal and chest surgery, orthopedic and otolaryngeal surgery, etc.) was considered as a potential risk factor. Control patients were rejected only if they did not fit the predetermined criteria. The study period was January to December 1995.

The presence of anti-HCV antibodies was checked in all patients by second generation enzyme-linked immunosorbent assay (ELISA) (Ortho Diagnostics, Raritan, NJ) and confirmed by recombinant immunoblot assay (RIBA); ELISA determined HBsAg and anti-HIV positivity.

The crude odds ratios (OR), which are estimates of the relative risk linking anti-HCV seropositivity to potential risk factors, were estimated by univariate analysis. To identify the variables independently associated to HCV infection, the adjusted OR were estimated by multiple logistic regression analysis.^{10,11}

RESULTS

Two hundred and ninety-four cases and 295 controls were recruited. Of the cases, 30 (10.2%) had normal alanine aminotransferase (ALT) levels, 212 (72.1%) had biopsy-proven chronic hepatitis, 47 (16.0%) had liver cirrhosis, and 3 (1.0%) had hepatocellular carcinoma. The main sociodemographic characteristics of the cases and controls are reported in Table 1. The groups were matched for age and sex; moreover, no differences were observed for place of birth, educational level, or number of subjects in the household.

The frequencies of risk factors reported by cases and controls and the crude odds ratio linking HCV positivity to the various exposures are shown in Table 2. The use of glass syringes and past surgery were reported by as many as 77.6% and 73.8% of cases, respectively; blood transfusion was reported by nearly a quarter of cases;

Table 1. Sociodemographic Characteristics of Subjects

Parameter	Cases (n = 294)	Controls (n = 295)
Age (y) median (range)	50 (15–78)	50 (14–77)
Male (%)	147 (50.0)	148 (50.2)
Place of birth		
North (%)	130 (44.2)	154 (52.2)
South (%)	164 (55.8)	141 (47.8)
Education		
Primary school (%)	119 (40.5)	106 (35.9)
Junior high school (%)	94 (32.0)	87 (29.5)
High school/university	81 (27.5)	102 (34.6)
Subjects in household		
< 4	245 (83.3)	241 (81.7)
> 4	49 (16.7)	54 (18.3)

Table 2. Frequency of Risk Factors Reported by HCV-Positive Cases and HCV-Negative Controls

Risk Factor	Cases(%)	Controls (%)	OR*	95% CI†
Blood transfusion	26.2	9.0	3.6	2.2–5.8
Surgical procedures	73.8	58.3	2.02	1.42–2.86
Use of glass syringes	77.6	68.3	1.6	1.1–2.3
Sexual partner of drug addict	6.3	1.4	4.8	1.6–14.5
Health care employment	5.4	13.6	0.38	0.20–0.69
Intravenous drug use	10.2	0		

*Crude odds ratios derived from univariate analysis.

†95% confidence intervals.

10.2% of the cases but none of the controls stated past or current intravenous drug use. A positive association was found to link anti-HCV positivity with all the sources of infection considered, except health care employment.

Since none of the controls reported intravenous drug use, odds ratio was not calculated for this association, which would obviously be strong, as 10.2% of cases reported this exposure.

When each risk factor was adjusted for the confounding effects of all the others and for age, sex, and educational level in a multiple logistic regression analysis (Table 3), blood transfusion, being a sexual partner of a drug abuser, and surgical procedures all were noted to be independent predictors of the likelihood of HCV infection. Originating from southern Italy and the use of glass syringes were unassociated factors.

DISCUSSION

The aim of this study was to assess the risk factors associated to HCV infection in chronic anti-HCV-positive subjects, since an overt parenteral exposure is identified in only a limited number of cases.

Since comparability is essential in studies on risk factors, cases and controls were enrolled who lived in the same area, were referred to the hospitals through similar channels, and were matched according to their status as in- or outpatient. This ensured that subjects in both categories were exposed to similar selection bias, if any. Moreover, the broad diagnostic representation of non-hepatic gastrointestinal diseases in control subjects possibly prevented any control selection bias.

Table 3. Risk Factors Associated to HCV Infection

Risk Factors	OR*	95% CI
Region of birth	1.45	0.97–2.17
Transfusion	2.91	1.65–5.14
Surgical procedures	2.18	1.42–3.35
Use of glass syringe	1.23	0.77–1.96
Partner of IV drug user	5.53	1.44–21.3

*Adjusted OR derived from multiple logistic regression; each risk factor was adjusted for the confounding effects of all other listed variables and for age, sex, and educational level of the subjects.

The results of this case-control study emphasize that, besides the well-known sources of infection (e.g., blood transfusion and intravenous drug abuse), surgery and being the sexual partner of a drug addict have played an important role in the spread of HCV infection in Italy. As expected, blood transfusion and intravenous drug use emerged as the main risk factors for chronic HCV infection. In Italy, as in most developed countries, blood donors have been screened for anti-HCV since 1990. The use of the second generation ELISA test in the detection of anti-HCV since 1992 has further increased screening efficacy. As a consequence, the incidence rate of transfusion-associated hepatitis C has dramatically decreased in Italy from 4.4 cases per 1,000,000 inhabitants in 1989 to 0.4 cases in 1993.¹² Thus, the risk of post-transfusion hepatitis C in Italy is now negligible.

Also, being a health care worker is not associated with any increase in the risk of HCV infection in the setting investigated. Indeed, counselling on the protection of health care workers against parenterally transmitted viruses has been ongoing in Italy since the early eighties, because hepatitis B virus infection was highly endemic at that time. Soon after, the spread of HIV infection reinforced the preventive measures and led to a further beneficial effect on HCV infection.

Intravenous drug use was reported by 10.2% of the cases and by none of the controls. Although the risk of HCV infection associated with intravenous drug use is high, few of the HCV infections occurring in Italy can be attributed to intravenous drug use, which is low in the general Italian population.

Surgical procedures proved to be an independent predictor of HCV infection in this study. A possible role of surgery in transmitting non-A, non-B (NANB) hepatitis was shown some years ago by a retrospective analysis of acute hepatitis cases in Italy.¹³ This finding was confirmed by the results of a recent case-control study on subjects with acute NANB hepatitis,¹⁴ which showed that a surgical procedure within 6 months preceding the onset of the disease was strongly associated (OR = 12.0; 95% CI = 4.0-35.0) with acute hepatitis C. Since a large proportion of the general population undergoes surgery, the results underscore the importance of correctly applying the procedures for sterilizing surgical instruments and the use of disposable materials, particularly in those emergency units where the high turnover of patients may further enhance the risk of HCV infection.

In this study, data showed that being a sexual partner of an intravenous drug addict represents an independent risk factor for acquiring HCV infection. In general, the data assessing the sexual risk in the transmission of HCV infection are contradictory.¹⁵⁻¹⁸ A study on community-acquired acute NANB hepatitis showed that patients with no history of parenteral exposure proved to have 11 times as many sexual partners as the controls.⁸ In this study, which

refers to patients exposed to the virus several years earlier, the lifetime number of sexual partners could provide a biased estimate of the true association linking HCV infection to sexual activity. Moreover, it may be expected that some sexual partners of intravenous drug users might have experienced occasional parenteral drug use that they did not admit at the interview.

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