

Hepatitis C transmission

Since 1989, when M. Houghton managed to clone the agent responsible for hepatitis C, which was followed by the development of immunological techniques for anti-C-virus (anti-HCV) antibody detection (1), multiple prevalence studies were reported in blood donors, the general population, groups at risk for HCV infection, and patients with liver disease that allowed the distribution of HCV per countries to be mapped.

Early studies in donors underestimated viral prevalence due to this being a biased group, and showed a variable distribution from below 1% in Northern Europe to 1.2% in Spain (2), 1.5% in Japan and North America, and above 6% in Africa (15% in Egypt). Studies in the general population showed prevalences 2 or 3 times higher *versus* donor in the area. This prevalence was 2% in Spain according to Sacristán (3), and 3.2% in Italy according to the Dyonisos Project. The prevalence of anti-HCV increased with age, and ranged from 0.1% in subjects younger than 15 years to 8% in individuals older than 55. High prevalences were also found in specific areas, where they were attributed to medical practices such as “suidama” (a Japanese folk-medicine remedy involving the application of a sucker on the skin). In contrast, no anti-HCV were detected in isolated communities with no links to traditional medicine, including the Peruvian jungle, while these same populations had a high prevalence of B-virus markers. Such differential penetrance for B virus and C virus would also be in support of differential transmission routes.

The higher prevalence of HCV among older patients, with nearly 0% in subjects younger than 15 years and very high prevalences in those older than 60, suggests scarce vertical transmission, and that some past factor must be responsible for high anti-HCV prevalence.

The real rate of new HCV infection cases is difficult to ascertain, as this condition is usually asymptomatic; however, a serious decrease in the incidence of HCV has been reported in the United States from 1989 –with 180,000 cases per year– to 1995, when 28,000 cases were estimated. This important incidence reduction may be due to a number of factors, including the introduction of anti-HCV testing in blood banks, the fear of human immunodeficiency virus among drug abusers (and the resulting fear of sharing syringes in this group), and the introduction of disposable medical implements in many countries, which has allegedly resulted in the primary transmission route –the parenteral route– being currently under control.

The relevant discrepancy between the high prevalence and low incidence of HCV, together with the scarcity of symptoms found in acute infection, determines

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that most cases diagnosed today, in countries having adopted the above measures, represent patients presumably infected before 1990, albeit obscure spots remain in the understanding of transmission routes.

C virus is responsible for post-transfusion hepatitis, which allowed the characterization of this condition even before this agent had been isolated and could be diagnosed (non-A non-B hepatitis) (4). The introduction of the first anti-HCV test in Spain decreased the risk for post-transfusion hepatitis from 10% to 1%. The introduction of C virus RNA testing in blood banks to detect donors in a window period has currently cancelled transfusion-related risks.

Hemophiliacs and patients with thalassemia or hypogammaglobulinemia represented groups with a high prevalence of anti-HCV due to replacement therapies using blood products. The general population has also been affected by contaminated gamma-globulin batches, and some crops have been detected.

Patients with chronic renal failure undergoing hemodialysis are another group with a high prevalence (around 20%) of anti-HCV, but variations are wide according to HCV prevalence in various regions and countries, ranging from 1.7% in Ireland to 55% in Japan. A study performed in 1993 found a 17% prevalence (20.1% in transfused vs. 11.1% in non-transfused patients) (5). Factors involved in transmission included transfusions and length of time in hemodialysis. Transfusions are no longer a risk factor, and cases detected may be associated with monitoring devices or nosocomial etiology through a yet unknown mechanism.

Parenteral drug abusers represent a high-risk group for HCV infection; prevalences as high as 90% have been found, with this being the first most common cause of infection in young adults. Infection is usually acquired through shared syringes within 6 months of addiction onset. The number of new cases in this group is decreasing in the United States and Western Europe, possibly as a result of public health programs and the fear of HIV, but substance abuse is currently in other countries (Russia and Eastern Europe), where illicit drugs were more recently introduced, the most common cause of acute infection.

Anti-HCV prevalence studies among healthcare professionals show conflicting results –some find a prevalence similar to that of the general population, some find a prevalence as high as 4.4%. C virus infection risk after accidental puncture with contaminated materials has been estimated as 1% overall, in accordance with the finding of a similar prevalence in both healthcare personnel and the general population. While this risk is low, documented cases of HCV transmission from patients to health providers have been reported.

Psychiatric and handicapped patients have been considered a population at risk for selected infections due to their staying at institutions. Some anti-HCV prevalence studies have shown a prevalence as high as 6.8% in these groups; however, their validity must be questioned since they do not consider age and other parenteral factors in their analyses. Other studies reveal a prevalence similar to that of the general population with no special risk, in contrast to hepatitis B virus, which has shown a higher prevalence in these groups.

Hospital stay has also been analyzed by multiple epidemiological studies as a potential risk factor for HCV infection, and both blood products and puncture with non-disposable materials have been implied as possible transmission factors. Despite the control exerted on the above-mentioned mechanisms, cases of C-virus in-

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fection are still reported after hospital stays –even infection outbreaks following admission to common wards. A study at Hospital Clínico de Barcelona has shown that HCV transmission occurs in hepatology units after a long stay, and 0.27 infections per 100 admissions were detected (6).

Only one half of patients with chronic infection with C virus, or of HCV-positive blood donors, acknowledge a history of potential parenteral transmission (transfusion, parenteral substance abuse, etc.). Even in acute hepatitis C a parenteral risk factor is evident in only 2/3 of cases (7), and this is why hepatitis C acquisition routes other than the parenteral one have been investigated that might explain the high HCV prevalence.

This is the so-called sporadic or community-acquired hepatitis C, cases of which may result from intrafamilial, sexual, or vertical transmission.

Sexual transmission is a risk factor in some studies showing a high anti-HCV prevalence in the sexual partners of anti-HCV-positive patients. However, other authors find a low prevalence ranging from 0 to 2.7%. Two clear facts stand out among discrepant results: a higher anti-HCV prevalence in the partners of patients with anti-HIV antibodies, and also in series including the partners of patients with sexually transmitted diseases (with possible mucosal ulcerations), whereas series including stable heterosexual partners show a lower prevalence (8).

Most studies show that prevalence increases with age, with very low figures at 20-40 years of age (highest sexual activity) and very high values over 60 years of age, which does not represent a sexually transmitted pattern; this leads to consider factors other than sexual activity (live under same conditions in same environment) for transmission between partners.

Establishing whether the high anti-HCV prevalence seen in subjects within groups with high-risk behaviors (sexual promiscuity, intravenous drug use, etc.) is due to sexual transmission is challenging, and such subjects have a higher prevalence (up to 27%) when compared to those in groups with no high-risk behaviors (lower than 7%). In an STD clinic Thomas found an HCV prevalence of 7% in males and 4% in females among the sexual partners of 309 patients, and risk factors included the presence of HIV or sexually transmitted diseases, and having had more than 24 sexual partners (9).

No anti-HCV positivity was found among the husbands (stable partners) of 94 women who were infected with HCV through anti-D immunoglobulin use in Germany after living together for 10-15 years.

Prevalence studies in groups at risk for sexually transmitted infections, including prostitutes (prevalence between 3.3 and 8%) and male homosexuals (between 1.4 and 5%) also do not support a sexual transmission route for HCV. Individual cases of sexually-acquired acute hepatitis C have also been reported. A consistency in genotype and nucleotide sequences between the index case and his or her partner has been of great value in contagion studies, even if such studies do not document a sexual entry point.

Regarding non-sexual intrafamilial transmission, multiple studies have been performed in few patients and with conflicting results; most of them reveal prevalences similar to those in the general population (1.3-2%), and some show higher prevalences (4.9%). In 1976 we studied 1,451 relatives of 535 anti-HCV-positive patients (index cases). These relatives had a mean age of 31.8 years, and

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included 394 stable sexual partners, 157 parents, 658 children, 139 siblings, and 103 other.

In the absence of prior parenteral exposure, the percentage of anti-HCV was 4.5% (65/1451). Prevalences were 7.6% (30/394) for sexual partners and 3.3% (35/1057) for non-sexual contacts. The highest prevalence was found among parents (9.5%), which was associated with their older mean age. Prevalence increased with age from 0.76% in subjects younger than 20 years to 18.6% in those older than 59. These data suggested that sexual transmission may occur, but should be interpreted with caution since no difference in prevalence between sexual and non-sexual contacts could be found after age adjustment. Increased prevalence with age leads to consider that non-disposable medical implements, commonly used in Spain up to 30 years ago, and to which older people was exposed, may be the factor accounting for the high prevalence in subjects older than 59 years (10). A genotyping study showed genotypical inconsistency between index cases and contacts in half of sexual partners (11).

Early studies on vertical transmission during the early 90s showed highly conflicting results –both studies rejecting vertical transmission, and studies suggesting a high risk were reported. HIV coinfection is an important factor, as is a high C viral load in vertical transmission. Otho et al. (12) showed lack of infection when mothers were HCV-RNA-negative; however, transmission occurred in 36% of cases for viral loads above a million copies per ml. Whether transmission occurs within the uterus or after exposure to blood in the birth canal could not be identified, but the latter possibility has more supporters; however, no differences in transmission according to type of delivery (vaginal/cesarean section) have been found.

Breast feeding seems to play no role in vertical transmission; while some studies have detected the presence of HVC-RNA in breast milk, such presence could not be related to mother-child transmission. Given their magnitude, it is clear that intrafamilial, sexual, and vertical transmission cannot explain the high number of hepatitis C cases with unknown etiology that we care for. Possibly, the use of disposable medical materials, and the common use of gammaglobulins in previous times may be factors involved in the high HCV prevalence of many countries.

It is a well known fact that preventive measures have already been adopted regarding parenteral risks (transfusion safety, disposable implements). We are currently witnessing a decrease in new cases, and in most such cases a history of medical procedures or hospital stay is present –these are circumstances where extreme hygienic caution should be exerted, and where every effort at identifying infection sources should be made.

Recommendations to prevent transmission through potential non-parenteral routes, according to the European Association for the Study of the Liver (EASL) consensus meeting held in Paris during February 1999 (13), suggested no need for condom use in stable heterosexual couples, a scarce risk for vertical transmission, and no contraindication of breast feeding.

Parenteral transmission routes, including transfusions and blood products, are fully under control and have a zero risk since the introduction of nucleic acid measurements in donations. Single-use medical devices are now commonplace. However, we still identify new cases of acute hepatitis C with an unknown acquisition route on occasion, as well as in parenteral drug abusers and victims of nosocomial

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transmission (3). It is along the lines of inapparent nosocomial transmission that we should investigate further to fully understand and counteract such yet unknown mechanisms. Possibly, by strict adherence to basic staff cleanliness a relevant number of hepatitis C cases could be prevented in the hospital setting. Genotype concordance and nucleotide sequence studies comparing index cases to contacts are nowadays valuable tools in contagion research.

The study published in the present issue, which studies the prevalence of C virus in various populations at risk for infection in the city of Maracaibo (14), shows a very low prevalence in drug abusers, albeit abusers through the oral or nasal route (little efficient for C virus) are referred to (59%), with only 15 parenteral drug addicts included. It is reported that half of them had tattoos, which may constitute another risk factor. Anyway, the suggested viral penetrance in the area is very low.

No HCV-positive case was found among sex workers, 90% of which had no substance abuse, which is consistent with a lack of C virus transmission through the sexual route. No cases were found among subjects in dialysis programs too, as opposed to reports from most areas worldwide.

This lower penetrance of C virus is corroborated by other HCV prevalence information to which I had access in Venezuelan blood banks, which quote 0.3% for the last few years. Lizarzabal also found a 0.3% prevalence in a population of 1,658 people undergoing vaccination in 2002, but found no cases among 620 healthcare professionals (15). In subjects at risk, including polytransfused subjects, patients undergoing dialysis, or individuals with a history of surgical procedures, prevalence ranges from 10 to 22% (16) .

All these data reflect a lower prevalence of C virus in this area when compared to Europe, the US, or Japan.

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