The Tattooing Paradox

Are Studies of Acute Hepatitis Adequate to Identify Routes of Transmission of Subclinical Hepatitis C Infection?

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Background: The Hepatitis Branch of the Centers for Disease Control and Prevention does not recommend routine regulation and inspection of tattoo parlors because surveillance of hepatitis C virus (HCV)-positive acute hepatitis cases rarely identifies tattooing in the incubation period. However, the majority of seroepidemiological studies agree that tattooing is a strong, independent risk factor for subclinical HCV seropositivity. We postulated that this paradox might be explained if transmission of HCV by tattooing generally caused subclinical HCV seropositivity without the acute hepatitis syndrome.

Methods: We reanalyzed data from a prior seroepidemiological study of 626 consecutive patients who were unaware of their HCV serologic status and whose risk factors were ascertained by interview of an internist. Separate multiple logistic regression models were developed to predict a history of the acute hepatitis syndrome and HCV seropositivity.

Results: A history of injection-drug use was strongly associated with both HCV seropositivity (adjusted odds ratio [AOR], 7.2; 95% confidence interval [CI], 3.1-16.5) and a history of acute hepatitis (AOR, 5.9; 95% CI, 2.5-13.8), whereas having a commercially applied tattoo was strongly associated with HCV seropositivity (AOR, 6.5; 95% CI, 2.9-14.4) but not with a history of acute hepatitis (AOR, 1.2; 95% CI, 0.5-3.3).

Conclusions: Intravenous injection of relatively large quantities of inocula of HCV may be more likely to result in the relatively rare acute HCV hepatitis syndrome, whereas intradermal exposure to small quantities of inocula may cause only subclinical HCV infections. If so, public policy on regulation and inspection of tattoo parlors should be determined by seroepidemiological studies rather than by the Sentinel Counties Study of acute hepatitis cases.

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Before the development of the serologic test for hepatitis C virus (HCV), the study of non-A, non-B hepatitis necessarily centered around a case definition of the acute hepatitis syndrome, which is characterized by the discrete onset of nausea, vomiting, jaundice, highly elevated transaminase levels, and exclusion of other causes of liver disease, including negative results on serologic tests for hepatitis A and B.1 Epidemiological research in the 1980s by the Hepatitis Branch, Centers for Disease Control and Prevention (CDC) and others found non-A, non-B acute hepatitis to be relatively uncommon, its prevalence being only 10% to 15% that of acute hepatitis caused by the hepatitis B virus (HBV).2 They also identified certain risk factors, such as injection-drug use and multiple blood transfusions, to be strongly associated with non-A, non-B acute hepatitis, and others, such as multiple sexual partners, to be equivocally associated.3 Later serologic studies identified HCV as the etiologic agent of most non-A, non-B acute hepatitis cases.

The widespread availability of the HCV serologic test after 1990, however, identified a new, vastly more common clinical presentation for HCV infection, namely, chronic asymptomatic, usually unsuspected HCV seropositivity and viremia with no history of the acute hepatitis syndrome (subclinical HCV infection).1 Subsequently, 3% of whites and Hispanics and 6% of African Americans in the working age groups in the US population were found to be HCV seropositive,2 and approximately 75% of these had chronic HCV viremia on the polymerase chain reaction test.4 In comparison, whereas HBV seropositivity rates were of similar magnitude,3 only 0.3% to 0.4% of the population had chronic viremia indicated by a positive hepatitis B surface antigen test.2 Consequently, the prevalence of chronic viremia with HCV is approximately 10 times that of HBV, making subclinical HCV...
infection by far the most prevalent chronic viral infection in the US population. Often progressing to hepatic cirrhosis and liver cancer after 20 years or more, chronic subclinical HCV infection has become the most common indication for liver transplantation.

Controversy has arisen, however, over the modes of transmission of HCV, particularly over the role of commercial tattooing. In our recent review of the world’s literature, we identified 3 reported clusters of HCV seroconversion associated with individual tattooing parlors and 9 seroepidemiological surveys, all consistently reporting elevated relative risks of commercial tattooing with subclinical HCV seropositivity. The relative risks in 7 of the studies were statistically significant, and in 6 they remained at 4.0 or higher after other risk factors, such as injection-drug use, transfusions, sexual promiscuity, and being a health care worker, were adjusted for. We found 12 studies showing a similar association of tattooing with HBV seroconversion or seropositivity. Despite the consistency of the published evidence, the US Public Health Service does not recognize commercial tattooing as an important risk factor. The evidence cited for this position is that prospective surveillance in 4 county health departments participating in the Sentinel Counties Study of Viral Hepatitis, sponsored by the CDC Hepatitis Branch, has commonly identified injection-drug use, transfusions, and promiscuous sexual activity, but rarely tattooing, in the characteristic incubation period of patients presenting with the acute hepatitis syndrome and a positive HCV serologic test result.

To attempt to resolve the paradox, we reanalyzed data from a previously reported seroepidemiological survey. We postulated that injection-drug use, which would be expected to transfer relatively large quantities of virus directly into the bloodstream, would be more likely to cause HCV infections presenting as acute symptomatic hepatitis; whereas tattooing, which commonly transfers small quantities only into the skin, would be more likely to cause subclinical HCV infection but not the acute hepatitis syndrome.

### METHODS

In 1991 and 1992, a total of 626 consecutive patients who visited a referral clinic for spinal disorders in Dallas, Tex, were enrolled in a seroepidemiological study of HCV infection approved by our university’s institutional review board. The methods and results of the study were recently published. After giving written informed consent, each patient was evaluated by an internal medicine specialist (R.P.F.) at the end of a regular medical history and physical examination. All risk factors for blood-borne viral infection and a history of acute symptomatic hepatitis were ascertained by the internist using interview techniques designed to maximize completeness of disclosure. At the end of each interview, a blood specimen was obtained for HCV testing by the first- and second-generation enzyme-linked immunosorbent assays, and positive results were confirmed by the second-generation recombinant immunoblot assay. At the time of the interviews, neither the patients nor the physician were aware of the patients’ HCV serologic status. The independent associations of risk factors with a history of acute hepatitis and with anti-HCV serologic status were measured by the adjusted odds ratio and its 95% confidence interval in a multiple logistic regression model controlling for other risk factors for blood-borne viral infection. The analysis was performed with the Logistic Procedure of SAS for Windows statistical software (version 8.02; SAS Institute Inc, Cary, NC).

### RESULTS

Of the 626 consecutive patients, 43 were seropositive for anti-HCV antibodies. When standardized to the age, sex, race, and occupation distributions of the US civilian population, the HCV seroprevalence rate was 2.8%. Forty-eight patients (8%) gave a history of having had acute hepatitis sometime in the past. Forty subjects (6%) gave a history of injection-drug use, and 52 (8%) had a tattoo applied in a commercial tattoo parlor.

After a history of transfusion, having worked in a hospital, number of sexual partners in peak sexual year, and alcohol consumption in multiple logistic regression models were adjusted for, having a history of injection-drug use was strongly associated with both HCV seropositivity and a history of acute hepatitis (Table). In the same multiple logistic regression models, having a commercially applied tattoo was strongly associated with HCV seropositivity but not with a history of acute hepatitis.

### COMMENT

Our findings suggest that, whereas injection-drug use commonly causes both occult anti-HCV seropositivity and the acute hepatitis syndrome, tattooing may commonly cause occult anti-HCV seropositivity, while rarely causing the acute hepatitis syndrome. This difference may be because injection-drug use transfers relatively large amounts of virus directly into the bloodstream, while tattooing transfers relatively small quantities of innocula only into the skin. If this finding is generally true, it would resolve the tattooing paradox and suggest that the prospective surveillance of acute hepatitis cases in the CDC’s Sentinel Counties Study might be systematically overlooking important modes of transmission for subclinical HCV infection, including tattooing, that do not commonly cause the acute hepatitis syndrome.
This finding also emphasizes the difference between the 2 presentations of hepatitis C infection. Chronic subclinical HCV seropositivity is a prodigious public health problem that threatens to overwhelm our health care system in future decades as the currently asymptomatic infected population ages toward the development of progressive hepatic cirrhosis and liver cancer. Despite the well-known methodological limitations of seroepidemiological studies, this form of research is practically the only way to identify modes of transmission of asymptomatic subclinical infections and should be weighted heavily in defining the modes of transmission to be addressed by public health control measures. On the other hand, acute symptomatic hepatitis caused by HCV is a relatively rare phenomenon. It is primarily of clinical interest to practicing physicians who diagnose and treat it acutely. The diagnosis of acute HCV hepatitis is often ambiguous owing to the difficulty of attributing an acute jaundice-transaminase syndrome to a positive HCV test result in view of the high background prevalence of undetected HCV seropositivity in the working-age population. To the extent that risk factors of the 2 conditions differ, the findings of seroepidemiological surveys of the far more common subclinical HCV infections, not those of acute hepatitis cases, should serve as the basis for defining the risk factors to be addressed by public health control measures.

We suggest that commercial tattooing is a good example of an important risk factor for subclinical HCV infection that has been overlooked because of the lack of sensitivity of acute hepatitis surveillance. Risk factors analyzed in published studies have generally explained an average of only 60% of the acute HCV hepatitis cases, suggesting the presence of important unmeasured risk factors. In our recently reported seroepidemiological study and literature review, we found tattooing to be an important risk factor, potentially accounting for 41% of subclinical HCV cases in adults from the northern part of Texas in 1992.7 Besides substantial published evidence demonstrating that tattooing can transmit pyogenic infections, syphilis, leprosy, molluscum contagiosum, verruca vulgaris, and cutaneous tuberculosis, we identified 8 published reports of individual cases or clusters of HBV infections and 3 reports of HCV infection clusters traced to single tattooists.7 Multivariate epidemiological analyses have implicated tattooing as a strong, independent risk factor for HBV seropositivity in 4 controlled seroepidemiological studies and for HCV seropositivity in 6 such studies.7 Only 3 epidemiological studies have been cited in support of the other side of the argument.7 These include 2 small underpowered studies that found elevated, though not statistically significant, relative risks of tattooing for HCV, and 1 large study of blood donors that found a high relative risk for tattooing that did not remain statistically significant in a multivariate analysis. The latter study, however, was subject to strong biases: eg, subjects knew their HCV status before being contacted to participate; only 12% of the HCV recombinant immunoblot assay–positive case patients volunteered to participate; control patients were HCV enzyme immunoassay–positive but recombinant immunoblot assay negative, rather than being clearly HCV negative; and the control patients were more highly educated than the case patients.11 Consequently, on balance, the preponderance of published evidence indicates that tattooing can transmit HBV and HCV infections. The only point of debate is whether it leads to a large enough number of chronic viral infections to justify public health regulation and regular inspection of commercial tattoo parlors.

Over the past decade, fine-art tattooing has grown in popularity in the United States. By 1993, 16% of suburban high school students in Texas already had tattoos, and one third of the remaining teenagers were considering getting one.12 Despite rapid growth in commercial tattooing since then, only one third of the states have laws regulating commercial tattoo parlors,13 but in the absence of regular inspections such tattooing standards appear to have been difficult to monitor and enforce.14,15 To our knowledge, Texas is the only state that licenses all tattooing establishments and carries out regular inspections to ensure proper sterilization and aseptic techniques required to prevent the transmission of viral hepatitis. The effectiveness of the Texas inspection system, implemented in 1993, was suggested by a seroepidemiological survey of approximately 8000 South Texas college students in 2000 and 2001, which showed no association of recent subclinical HCV acquisition with tattooing.16 While restaurants are regularly inspected throughout the United States to prevent the transmission of food-borne gastroenteritis, no such system controls tattooing parlors statewide, except in Texas, and parental exposure practices that can spread chronic hepatitis infections are left to the discretion of tattoo artists.

The reluctance to regulate the tattooing industry has resulted from the US Public Health Service's policy acknowledging that tattooing is a public health threat in other Western countries but contending that it is not an important mode of viral transmission in the United States.1 This policy was originally based on 2 prospective surveillance studies linking risk factors with individual cases of non-A, non-B acute hepatitis, which were published in the 1980s, before the serologic tests for HCV were available.8,9 In more recent years, the policy has been perpetuated by prospectively linking risk factors with individual acute hepatitis cases in CDC's Sentinel Counties Study of Viral Hepatitis.1 Besides counting only cases of the acute hepatitis syndrome, which appear to have different risk factors from the more common subclinical HCV cases, the prospective surveillance approach used in the Sentinel Counties Study has other disadvantages for identifying and attributing risk factors to subclinical HCV infection. First, since the prevalence of chronic HCV seropositivity and viremia in the working-age population is so high, attributing an acute jaundice-transaminase syndrome to a positive HCV test result is uncertain at best. Second, fewer than 40% of acute HCV (non-A, non-B) hepatitis cases are detected by the passive surveillance methods used in the Sentinel Counties Study, and cases are far more likely to be reported from emergency and health departments, favoring injection-drug use and promiscuous sexual behavior, than from physicians' offices.17 Third, for patients reporting 2 or more risk factors during the presumed incubation period, only 1 risk factor is counted, and it is
determined according to a mutually exclusive hierarchy, with transfusion, injection-drug use, men who have sex with men, and occupational blood exposure at the top of the list.10 If any of these common risk factors are present, those lower on the list, including tattooing, are not reported, thus strongly biasing toward favored hypotheses. Fourth, the study collects no control group with which to perform fundamental epidemiological analyses, such as calculating relative risks and performing multivariate risk factor analyses.1,8-10

Despite these substantial disadvantages, the negative findings of the Sentinel Counties Study of the acute hepatitis syndrome have received disproportionate weight over the published seroepidemiological surveys that have repeatedly shown tattooing to be a strong, independent risk factor for subclinical HCV seropositivity.7 Our present findings potentially explain why prospective surveillance of acute hepatitis cases may have overlooked the importance of tattooing. Additional studies, including reanalysis of existing databases, should further examine this relationship to see whether it can be generalized. Meanwhile, in view of the prodigious public health problem presented by ongoing transmission of HCV infection, this finding should stimulate a reevaluation of the policy on the public health importance of tattooing and the need for states to license and regularly inspect commercial tattoo parlors.

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REFERENCES


