

Risk Factors in Chronic Hepatitis B Infection: A Case-control Study

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Background and Aims: In order to evaluate some possible risk factors for the spread of hepatitis B infection, a case-control study was undertaken.

Methods: The study population consisted of subjects who came to Karaj Hepatitis Center. All subjects who met the inclusion criteria were considered as having chronic hepatitis and comprised our case group. Risk factors were evaluated using a questionnaire. Backward conditional logistic regression analysis was used.

Results: The case group consisted of 500 chronic subjects, and 434 subjects with negative tests for hepatitis B, hepatitis C and HIV comprised the control group. Age, male sex, marital status (being married), history of contact with hepatitis, extramarital sexual activity, IV-drug use, major surgery, experimental dentist visit and some jobs (police, barber, and driver) were found to be independent risk factors of being chronically infected with hepatitis B virus (odds ratio: 0.9, 2.3, 2.1, 8.9, 6.5, 5.4, 1.6, 1.8 and 2.3, respectively).

Conclusions: It seems to be of great importance to pay more attention to certain jobs, life styles and cultural matters in Iran that predispose people to a number of risk factors so as to implement measures to control HBV spread. Despite existence of a long list of risk factors, different epidemiological studies with alternative methodologies accompanied by meta-analysis of risk factors in each separate area seems to be helpful in providing information about transmission routes and surveillance of hepatitis B infection.

Keywords: Hepatitis B, Iran, Risk Factor, Transmission

Introduction

Hepatitis B virus (HBV) infection is the major cause of mortality and morbidity worldwide^(1,2). Hepatitis B carrier rate varies widely from 0.01% to 20% through the world⁽³⁾. Annually up to 1 million of this population die due to the consequences of this infection such as cirrhosis and hepatocellular carcinoma (HCC)⁽⁴⁾.

Despite the existence of a safe and effective vaccine, HBV continues to be a substantial and devastating health problem whose new cases are still being reported throughout the world⁽⁴⁾.

Given the capability of HBV elimination, it seems to be one of the health priorities to find the routes of its transmission in order to know the risk factors responsible for its spread and to find the target population on whom we should have put a great emphasis⁽⁵⁾. It is necessary to find the important transmission routes of hepatitis for prevention of this disease in every country,

specifically in endemic regions. Considering Iran an area of intermediate endemicity for HBV infection in the Middle East⁽⁶⁾, the importance of programs for controlling risk factors becomes clearer, especially when many patients who are infected with hepatitis are asymptomatic⁽⁷⁾.

In an attempt to identify the risk factors for acquisition of HBV infection, we have conducted a case-control study on subjects referred to Karaj Hepatitis Center from the general hospital infection clinic (Shahid Beheshti hospital) in which subjects with chronic hepatitis B were compared with control healthy subjects.

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Methods

A case-control study was carried out on subjects who came to Karaj Hepatitis Center suspected for chronic hepatitis B infection from February 2001 to December 2003. Subjects were referred from infectious disease clinic in Shahid Beheshti hospital (situated in Karaj) near the Karaj Hepatitis Center. Karaj is a city in Iran, located in Tehran province with 1.2 million inhabitants and situated 20 km west of Tehran, at the foot of Alborz Mountains. All subjects who met the following inclusion criteria were considered as having chronic hepatitis: 1. documented and confirmed HBsAg positivity for more than 6 months 2. an inactive chronic carrier state (without any acute symptoms) 3. transaminases (alanine transaminase and aspartate transaminase) values lower than 7 times normal for exclusion of acute hepatitis infection. Subjects who had chronic hepatitis B surface antigen (HBsAg) test comprised the case group although they were examined to have negative hepatitis C antibody tests (by ELISA test) and HIV test. Subjects who had tested negative for hepatitis B, hepatitis C and HIV comprised our control group. HBsAg was determined using commercially available ELISA kits (Heapanostika HBsAg Uniform 2 Microelisa System, Organon Teknika, Holland). Positive samples were also rechecked by ELISA method. For HCV infection, anti-HCV antibody was detected using a third-generation ELISA kit (ETI HCV K-3, DiaSorin, Spain). Positive results of anti-HCV Ab were confirmed with the recombinant immunoblot assay; RIBA-3 Chiron, New Jersey, USA). The serum samples were tested for anti-HIV antibody using ELISA kits (Genscreen HIV, Biso Rad, France). No special measures were taken to match the two groups for age or sex. All subjects who gave written informed consent were then referred for a structured confidential interview to encompass the risk factors evaluated in this study. Those refusing to answer the questions were excluded from the study. The definitions of all risk factors are in appendix I. If exposure with risk factor was after the time of HBV infection diagnosis or the subject had a negative test at least 6-8 weeks after exposure, the subjects were considered as not having that risk factor. The questioners were general practitioners, blinded to the HBsAg test results of the subjects before and during the interview, who worked in the study setting. All subjects were also evaluated for any signs and symptoms related to liver diseases. The study protocol conforms to the ethical guidelines of the declaration of Helsinki (1975) as reflected in a priori approval by the institution's ethical review

board. The results were analyzed using SPSS® for Windows release 11.5 (SPSS, Chicago, IL, USA). Logistic regression was used as described. Univariate analysis was performed for using the crude model and all possible risk factors were evaluated by calculating odds ratios. All risk factors with significant odds ratios ($P < 0.05$) or those with borderline significance ($P < 0.2$) were chosen for further evaluation. Logistic regression was used to analyze independent risk factors of HBV infection. Several models were built using a conditional backward method. Risk factors changing the Chi-square value of the model significantly were preserved and thus the final model was built.

Results

During a period from February 2001 to December 2003, 632 subjects who had chronic hepatitis B were identified in our center. All the subjects were then referred to be checked for hepatitis C and HIV, and seventeen subjects with positive results for hepatitis C were excluded among who six cases had thalassemia and two cases had hemophilia and one case had a history of hemodialysis.

Of the remaining 615 HBV positive subjects, 115 subjects either refused to answer the questions or failed to attend the following sessions and were excluded from the study; leaving 500 subjects for the case group.

During the same period, a number of subjects with negative tests for hepatitis B, hepatitis C and HIV who had come to the infectious disease clinic were requested by authors to enter the study as control group using simple random sampling. Among the 720 subjects requested, only 434 subjects came to our study. They were also rechecked for the aforementioned tests, which were negative in all subjects in the control group.

Both case and control groups were matched for age (p value > 0.05). Mean age of our total subjects, cases and controls was 37.6 ± 15.1 , 37.5 ± 12.9 and 37.6 ± 17.3 , respectively. The case group showed male predominance and control group showed the female predominance.

The descriptive characteristics of subjects along with their corresponding odds ratio are summarized in table 1. Being male, being married, age, alcohol consumption, smoking, transfusion history, STD history, jail history, history of contact with hepatitis, having extramarital sexual relationship, history of IV drug use (IDU), history of Non-IV drug use (Non-IDU), Hejamat (phlebotomy) and high risk jobs (police, driver, and barber) were found as risk factors

Table 1. Baseline characteristics of study subjects and correspondent odds ratio for each factor.

Risk factor	HBsAg-positive (n=500)	HBsAg-negative (n=434)	Odds Ratio (95% CI*)	P value
Sex (male), n(%)	338(67.6%)	210(48.4%)	2.2(1.7-2.9)	<0.001
Contact history within family, n (%)	99(19.8%)	13 (3%)	6.9 (4.4-14.4)	<0.001
Transfusion history, n (%)	30(6%)	12(2.8%)	2.2 (1.1-4.4)	0.017
Tattooing, n (%)	44(8.8%)	28(6.5%)	1.4 (0.85-2.29)	0.180
Endoscopy, n(%)	36(7.2%)	43(9.9%)	0.71 (0.44-1.12)	0.138
STD, n (%)	11(2.2%)	2(0.5%)	4.8 (1.06-21.09)	0.024
Phlebotomy (Hejamat) [¥] , n(%)	34(6.8%)	17(3.9%)	1.79 (0.98-3.25)	0.053
Dialysis and renal transplantation, n (%)	1(0.2%)	0	N.R.	N.R.
Jail [£] , n (%)	14(2.8%)	2(0.5%)	6.2 (1.4-27.5)	0.006
Extramarital sex, n (%)	25(5%)	3(0.7%)	7.56 (2.56-25.22)	<0.001
Alcohol, n (%)	25(5%)	8(1.8%)	2.8 (1.2-6.2)	0.009
Smoking, n (%)	94(18.8%)	52(12%)	1.7 (1.1-2.4)	0.004
IDU, n (%)	21(4.2%)	2(0.5%)	9.4 (2.2-40.6)	<0.001
Non-IDU [€] , n (%)	15(3%)	4(0.9%)	3.3 (1.09-10.09)	0.025
Malaria history, n (%)	2(0.4%)	0	N.R.	N.R.
Major surgery, n (%)	166(33.2%)	120(27.8%)	1.29 (0.98-1.71)	0.073
Dentist visit, n (%)	348(69.6%)	339(78.1%)	0.64 (0.48-0.86)	0.003
Experimental dentist visit ^{**} , n (%)	87(17.4%)	48(11.1%)	1.6 (1.1-2.4)	0.007
Needle stick, n (%)	7(1.4%)	3(0.7%)	2.04 (0.52-7.92)	0.296
High educational level [†] , n (%)	308(61.6%)	278(64.1%)	0.9 (0.69-1.17)	0.439
High risk job [‡] , n (%)	87(17.4%)	26(6%)	3.3 (2.08-5.23)	<0.001
Marital status (married) n (%)	387(77.4%)	303(69.8%)	1.4 (1.1-1.9)	0.009
War injury n (%)	10(2%)	9(2.1%)	0.95 (0.38-2.37)	0.924

* ,CI: confidence interval; **, Experimental dentist: they assist dentists for several years without any academic education, and after gaining some experience, they start to practice independently in their offices; ¥, Hejamat: a procedure in traditional medicine of Iran that seems similar to blood letting. £, jail: Having been in jail for at least 3 months for retraining; †, High education level: having education level equal or above bachelors; ‡, High risk job: police, barber, and driver. €, IDU: intravenous drug use. N.R.: Not relevant or not calculable; Ref: reference or comparison category, Odds Ratio assumed to be 1.

in univariate analysis.

Logistic regression analysis showed that only male sex, age, being married, close contact history within family, extramarital sexual activity, undergoing major surgery, history of IDU, experimental dentist visit, Hejamat (phlebotomy) and high risk jobs (police, driver, and barber) are independent risk factors for prediction of hepatitis B infection. Significant level and odds ratio (with 95% CI) of these variables are shown in table 2.

Discussion

Sexual promiscuity (8-14) and IDU (9, 13, 15-17, 19) have repeatedly been found by studies worldwide to be independent risk factors of HBV infection. Other risk factors such as blood transfusion(9,20,22), surgical procedures(9, 10, 23), liver disease in family and contact history with hepatitis(9, 17, 19, 24-27), low educational level(10, 28), dental procedures(9, 10, 12), job(2, 29-32), history of STD(33-35), being in

Table 2. Independent risk factors of hepatitis B virus infection from logistic regression analysis.

Risk factors	Odds Ratio	95.0% CI for Odds Ratio	P value
Sex (male)	2.386	1.761-3.232	.000
Age (years)	.976	.964-988	.000
Marital status(married)	2.109	1.397-3.184	.000
Contact history within family	8.970	4.850-16.592	.000
Hejamat [†] (phlebotomy)	1.864	.955-3.640	.068
Extramarital sex	6.511	1.428-29.688	.016
IDU [‡]	5.478	1.185-25.330	.029
Major surgery	1.600	1.164-2.199	.004
Experimental dentist visit ^{**}	1.802	1.171-2.772	.007
High risk job [¥]	2.399	1.457-3.949	.001

*, CI: confidence interval. †, Hejamat: a procedure in traditional medicine of Iran that is similar to blood letting. ‡, IDU: intravenous drug use. **, Experimental dentist: they assist dentists for several years without any academic education, and after gaining some experience, they to practice independently in their offices. ; ¥, High risk jobs: police, barber and driver. £, Constant number in regression model.

detention centers or jail(36), age(22), endoscopy(37), hemodialysis(37), sex(22, 26, 38), tattooing(10, 38), ear

piercing⁽²⁸⁾, sharing articles^(28, 39) are also identified as risk factors in some studies. A considerable number (up to 30%) of the subjects infected with acute hepatitis B with unknown risk factors have been reported, depicting the complex nature of HBV transmission and warranting the need for meticulous listing and validity checking of the risk factors for HBV spread, as well as implementing screening programs based on these results with the focus on high risk groups⁽⁴⁰⁾.

Different studies have estimated hepatitis B carrier rate varies widely from 0.1% to 20% through the world^(3, 40). In the Middle East, the endemicity is intermediate, with a carrier rate of 2% to 7%^(7, 41, 42). It is estimated that over 35% of Iranians have been exposed to HBV and about 3% are chronic carriers⁽⁴³⁾, ranging from 1.07% in Fars Province⁽⁴⁴⁾ to over 5% in Sistan and Balouchestan⁽⁴⁵⁾. Given that the HBV infection affects people globally, it's vital to know the ways of its spread in each area.

In two studies conducted in Italy and also in Canada (Montreal), it has been shown that intravenous drug use was independently associated with hepatitis B^(9, 13, 19). In another study performed in Brazil, hepatitis B was detected in 55.6% among IDUs, confirming literature finding which indicates high levels in these specific groups⁽²¹⁾. In Ireland, the most important predictor of being positive for hepatitis B was a history of IDU⁽¹⁸⁾. IDU was also the single most important independent factor for hepatitis B in Denmark⁽¹⁵⁾; however, IDU was not a risk factor in Yemen⁽⁴⁴⁾. Our study strongly corroborates this as an important way of HBV spread. It is not uncommon in Iran to share the syringes for IDU, which justifies IDU as an independent risk factor. Although non-IDU can not be theoretically assumed as an independent risk factor, its close association with IDU explains drug abusers' life style that predisposes them to risk factors to which general population are not as exposed. It should be remembered that indulgence in one risky behavior is sometimes associated with other risky behaviors, so there are core groups who share such behaviors. It's of importance to note that non-IDUs were excluded from the model because of the close association between IDU and non-IDU.

In Iran, there are some special characteristics regarding sexual activity. 1) Although HBV may be transmitted by both heterosexual and homosexual contact, it is almost always transmitted by heterosexual contact in Iran. 2) Virginity is strongly appraised and premarital sex, if any, is usually only with the intended marriage partners for women. 3) Sexual activity starts at an older age compared to that of western countries. 4) The role of sexual

contact with female prostitutes by men should not be underestimated. 5) The culture of our country condemns extramarital sexual activity and allows men to have more than one partner legally at the same time, but not women, highlighting men's role in the spread of infection. It is said that sexual contact plays a major role in transmission of HBV in different parts of the world independent of HBV endemicity⁽²⁹⁾. In Latin America, there is an increase in seroprevalence in all countries at or after adolescence, suggesting that sexual activity is a major route of transmission⁽¹⁰⁾. There are some factors indicating sexual promiscuity. It is not the sexual activity per se that is the risk factor, but the number of partners⁽²⁹⁾. It was shown in the USA that having more than 10 lifetime sexual partners was a significant risk factor for HBV infection⁽⁴⁷⁾. In Mexico, one of the main risk factors was unsafe sexual practices⁽¹²⁾. The time of the first sexual experience varies considerably from culture to culture with the tendency to happen earlier in regions with low endemicity than in those with high endemicity. The number of STDs a person has had before is a useful surrogate measure of sexual promiscuity⁽²⁹⁾. In northeast region of Iran, it has been shown that the prevalence of HBV in attendees to the laboratories for STDs test was high, exceeding the national estimates⁽³³⁾. In another study conducted in Iran, HBV prevalence in STD clinic attendees was high, exceeding the national estimate, which indicates that STD clinic population may be considered a high risk group, that these risk groups should be screened for HBV and that counseling and contact tracing seems to be of great importance⁽³⁵⁾. In accordance with what has been said, STD clinics are one of the places we can implement our HBV control strategies. In our study, extramarital sexual relationship was an independent factor for HBsAg positivity and STD history was found as a risk factor in univariate analysis. Our study revealed that marriage augments the risk of HBV acquisition. Considering the beginning of sexual relationship after being married, especially in Iran and according to what has been said before, this seems to be an acceptable result.

The risk of transmission of HBV is known to be high in people who are in contact with chronically infected subjects^(17, 24, 25). In Amazon, the high prevalence among siblings clarifies the importance of personal contact in the transmission of this virus⁽²⁴⁾. The most important risk factor for HBV infection was contact with an infected person in Romania⁽⁴⁸⁾ and in Thailand⁽⁴⁹⁾. In Greece, one of the major independent risk factors was interfamilial exposure⁽²⁶⁾. In Thailand, the reports revealed that

history of jaundice in husbands was an important risk factor among pregnant women⁽³⁸⁾. In Italy, being the household of a chronic HBsAg carrier was independently associated with hepatitis B⁽⁹⁾. In France, among military recruits, mention of a family history of hepatitis B was a significant predictor of infection⁽²⁷⁾. In an area of Naples, household contact was an independent risk factor⁽¹⁸⁾. In Korea, it has been shown that HBV has strong familial clustering⁽⁵⁰⁾. Our study also strongly revealed that contact with HBV-infected person is an independent risk factor for its spread.

Choosing an occupation can be considered a risk factor for infection with HBV if there is a danger of contact with infected blood⁽²⁹⁾. In addition, it must be mentioned that some jobs have the potential of putting the person at risk of adopting some risky lifestyles. The health care workers (HCWs), barbers, large vehicle drivers, armed forces, sewage workers, detainees and prisoners are special cases mentioned in the literature^(2, 29-32). Workers exposed to sewage should therefore be considered for vaccination against hepatitis B virus⁽³⁰⁾. HCWs are not revealed as high risk groups in the present study. It can be due to sufficient knowledge of our medical personnel groups as well as acceptable knowledge of HBV spread. Small number of subjects in our sample can be an alternative reason, as well. Having considered HCWs, we have found barbers, police officers, and drivers independently at high risk of HBV acquisition.

It has been repeatedly mentioned that male gender poses an important risk factor for HBV infection. In some studies conducted in Greece, Taiwan and Iran, one of the risk factors mentioned for HBV was male sex^(26, 51, 54). In another study conducted in Taiwan, risk factors for HBsAg positivity were male sex, age 50 years, and a family history of hepatocellular carcinoma⁽⁵¹⁾. A study in the USA showed that HBV infection was positively associated with older age, longer duration of injection and heroin use⁽⁵²⁾. Our study revealed that male sex was an independent risk factor for HBV acquisition; moreover, as time passes, the risk of HBV acquisition is decreased.

In two different studies conducted in Italy, blood transfusion and surgical intervention were among the independent risk factors^(9, 23). Our study reveals that surgical intervention increases the risk of hepatitis B. In Brazil, it was shown that blood transfusion is among the predictors of the HBV exposure⁽⁵³⁾. Despite not being found as an independent risk factor, it was in univariate analysis.

Tattooing is among the risk factors mentioned in Mexico⁽¹⁰⁾. It is suggested that tattooing could be a

significant factor to be considered in relation to the transmission of hepatitis B in gypsy communities⁽⁴²⁾. In our study, it was found as a risk factor in univariate analysis.

It has been shown in several studies that dental procedures are the risk factors for HBV acquisition due to lack of sufficient knowledge in clinical infection control^(9, 10, 12). Our study revealed that dental visit is not a risk factor, whereas "experimental" dental visit increases the chance of HBV infection possibly due to not having the knowledge and it was found as an independent risk factor for its transmission.

Since the infection has serious sequelae, there is a continuing need to examine its epidemiology so that we can form some control measures. Hepatitis B is a major public health problem, but it is often neglected because of its largely asymptomatic course with long-term complications. Hepatitis B vaccine is efficacious, safe, and cost-effective, largely available for 15 years, but has been consistently underutilized in high-risk adults despite long-standing recommendations. Instituting routine hepatitis B vaccination for high-risk adults in settings such as prisons and jails, STD clinics, drug treatment centers, and needle exchange programs seems to be necessary. The lifestyle of homeless adolescents places them at high risk for contracting serious illnesses. Targeted programs are needed to immunize this high-risk group in order not to miss them. We need to ensure better training and regulations regarding preventive and safety measures. Prevalence of HBV indicates an urgent need to implement better control of known risk factors. It is particularly essential to know the differences in cultures and varied endemicities which should be surveyed in each district.

To minimize recall bias, the same general practitioner who was blinded to lab results and the same standardized questionnaire were used to ask cases and controls. Since most episodes of hepatitis B are symptom free, cases were likely as controls to recall exposures potentially associated with HBV infection.

When interpreting the results of this study and comparing this study with most of other studies conducted before, it is important to bear in mind that our study population can not be a representative of the general population, but it can convey some knowledge regarding the circulation of HBV. Also, it has not been performed on eligible blood donors who were in good health condition. The growing difficulties in obtaining blood samples from a representative group of patients, as done in classic surveys, make it necessary to look for alternative methodologies which can provide

information determining the presence of transmission routes in a community. Despite the limitations, this methodology may be helpful in epidemiological surveillance of transmission routes known as producing asymptomatic infections in much of the population.

Considering the existence of different studies with alternative methodologies in order to reveal hepatitis risk factors, comparison of these studies may result in either controversial results or long list of risk factors that may not have any clinical importance. We fully recommend a meta-analysis of risk factors in each separate area that seems to be helpful in providing information about transmission routes and surveillance of hepatitis B infection.

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