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Original Article

Intrafamilial spread of hepatitis B virus in Guilan Province-North of Iran

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Abstract: The aim of the present study was to determine the intrafamilial spread of HBV in the family members of patients with Hepatitis B in Guilan Province, North of Iran. In a descriptive-comparative study, 156 patients with Hepatitis B, 415 family members of the index cases and 599 age and gender matched people as a control group were enrolled. Blood samples were taken from the participants and were checked for HBs Ag, HBC Ab, HBs Ab, and HBV DNA. Totally 44 (10.6%) of family members and only 1 (0.2%) of control group were HBs Ag positive (P=0.0001, OR=70.92). The overall prevalence in members of the original family was 5.3% (1.2% of the mothers, 2.2% of the brothers, 1.9% of the sisters), in sexual partners it was 1.4%, in offsprings it was 2.4% and in other households it was 1.4%. The mean age of HBs Ag positive family members was 35.3 ± 12.9 years old. Among them 27 (61.4%) were female. Only 8 (18.2%) of all HBsAg-positive reported previous HBV vaccination but just one person had the vaccine titer checked. The present survey indicates that there is a significant difference in the prevalence of Hepatitis B in the general population and family members of Hepatitis B patients and this is an evidence for horizontal transmission of HBV in household contacts.

Keywords: Hepatitis B virus, familial

Introduction

Hepatitis B Virus (HBV) infection as a serious global health problem has infected 2 billion people worldwide. While 350 million people suffer from chronic HBV infection worldwide, 75% of all of them are Asians [1, 2]. One of the major causes of acute and chronic liver disease is HBV infection [3, 4]. Hepatitis B infection is considered the 10th leading cause of death worldwide [5, 6] through chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) which result in up to 1.2 million deaths per year. HCC accounts for 320 000 deaths per year [7].

The HBV infection has a prevalence of 0.1% to 20% in different parts of the world [6]. The World Health Organization (WHO) divides the world into zones of low, intermediate and high endemicity for HBV infection [6, 8-10]. Overall, 45% of the world population lives in high prevalence regions (hepatitis B surface antigen positivity rates > 8%), resulting in the massive global burden associated with the infection [11]. Middle East countries including Iran show an intermediate prevalence of hepatitis B [12]. Farzadegan et al reported the prevalence of hepatitis B surface antigen (HBsAg) in Iran 2.5%-7.2% [13]. In the 1980s the prevalence of HBV infection was reported 3% in the Iranian population [14].

Hepatitis B virus (HBV) may be transmitted through parenteral, sexual and perinatal contacts as well as child-to-child or household personal contacts [1, 15]. Amini et al. in a study in Hamadan of Iran [16] reported low prevalence of HBV infection in unmarried men and women (18.26%) and high prevalence of it in widows and divorcees (51.59%) and suggested that the primary mode of acquisition of HBV infection in children and young adults is horizontal transmission. Also, HBsAg-carrier mothers can trans-

mit the infection to babies before or soon after birth. The impact of Socio-economic and demographic variables on the prevalence of HBV infection is greater than blood or medical care dependent variables in this population [12].

Although after the introduce of the vaccination program the rate of new infection is to some extent reduced [1], he effects of past infection will remain, leading to serious risk of developing chronic liver disease, fatal cirrhosis and hepatocellular carcinoma. It is known by several surveys that family members of HBV-infected persons are at an increased risk of infection [4, 17]. Quite often, several members of the same household are infected with HBV infection, but while in the studies it was shown that spouses were frequently anti-HBs positive, siblings or the parents were often hepatitis B surface antigen (HBsAg) positive. Therefore it is suggested that HBV in such cases may be transmitted through intra-familial contact and the higher rate of carriers among siblings is associated to the early infancy infection [18]. In addition, horizontal transmission through close family contact is also important in early life [4, 19].

It has been suggested that household members can transmit HBV possibly through direct or indirect personal oral, mucosal or percutaneous contacts. Seroconversion in 1 year old children strongly suggests the importance of intrafamilial transmission [20].

It is not rare to have several members of same household with infected with HBV [5, 17, 21]. However, the precise mechanism of the intrafamilial spread of HBV is not determined [5, 8, 15]. Several papers about intrafamilial transmission of HBV from different geographic areas have been published since [5, 9, 15, 22, 23], but few studies have been carried out so far about this issue in Iran. The present study aimed to investigate the intrafamilial transmission of HBV among family members of HBV-infected persons and to identify the family members with the highest risk of infection among and risk factors of the intrafamilial transmission in Guilan Province-North of Iran.

Materials and methods

Study design and sampling

This is a descriptive-comparative study which was carried out in an 18-month period during 2011-2012 in Guilan Province-North of Iran. The study subjects were 415 family members of 156 patients who were positive with Hepatitis B for more than 6 months and considered as index case. HBV infected patients were referred from private offices of gastroenterologists, or were those whose names were registered in data bank of Gastrointestinal and Liver Diseases Research Center (GLDRC) of Guilan University of Medical Sciences. The family members of index cases including 17 mothers, 13 fathers, 26 brothers, 37 sisters, 76 sons, 93 daughters, 79 wives, 27 husbands and 47 other households who were older than 15 years old were included in the study. The meaning of other households is the grandfathers, grandmothers, uncles, aunts and other people who live in the same house with them.

Also 599 attendants of non gastrointestinal patients who referred to Razi Hospital outpatient clinic (age and gender matched) were included in the survey as the control group. Sampling of control group was done in a systematic random sampling method. The first number was selected randomly and after each 7-people interval the next one was selected and entered the study. People who had history of Hepatitis B, other liver diseases and hepatitis B in their family were excluded.

The participants who didn't have consent to enroll in the study and didn't continue their cooperation were excluded from the survey.

Questioners and laboratory tests

Questioners including demographic data, marital state, the kind of family relationship, occupation, history of vaccination, and risk factors of HBV were developed. Then after taking consent of the participants, 5 ml blood samples were taken from them and sent to the laboratory. HBs Ag was checked by Diapro-Italy Kits. If it was positive the sample was considered infected and the negative ones were assessed for HBC Ab by ELISA method and the use of Diapro Kits. The negative samples for HBC Ab were considered uninfected and if HBC Ab was positive, HBs Ab was checked and the positive samples showed that the subject had encountered the virus and had immunity against it. If HBs Ab was negative, HBV DNA was assessed by PCR method by Qiagen-Germany Kits.

The questioners were filled by two trained physicians and the laboratory results were recorded in the questioners too.

Table 1. Comparison of demographic variables in the study groups

Demographic variables		Study groups	
		Family members of the index cases (415)	Control group (599)
Age	Year (mean ± SD)	34.5 ± 13.5	33.6 ± 10.6
Gender	Female	251 (60.5)	363 (61)
	Male	164 (39.5)	236 (39)
Marital state	Single	126 (30.4)	2.6 (36.1)
	Married	289 (60.6)	383 (63.9)
Education	Illiterate	25 (6.4)	97 (15.8)
	Diploma or under diploma	307 (72.3)	346 (58.6)
	University degree	83 (21.3)	156 (25.6)
High risk jobs	Doctor	3 (0.7)	7 (1.2)
	Nurse	0 (0.0)	27 (4.5)
	Health care worker	6 (1.4)	10 (1.7)
	Laboratory worker	2 (0.5)	1 (0.2)
	Barber	0 (0.0)	8 (1.3)
Living place	Urban	413 (99.4)	579 (96.7)
	Rural	2 (0.6)	20 (3.3)
Vaccination history	Yes	217 (52.3)	145 (24.2)
	No	198 (47.7)	454 (75.8)
Vaccine titer after vaccination	Not checked	194 (89.4)	583 (76.8)
	Adequate	20 (9.2)	14 (20.3)
	Inadequate	3 (1.4)	2 (2.9)

Data analysis

The variables were included age, gender, vaccination history, risk factors of hepatitis B, hepatitis B infection, the time of diagnosis, and the kind of family relationship. Data were analyzed in SPSS version18 by the use of descriptive statistics (mean, standard deviation) and comparison means (Chi Square and Exact Fisher tests). $P < 0.05$ was considered significant.

Results

Three groups enrolled in the survey including 156 index cases with Hepatitis B, 415 family members of the index cases, and 599 people without history of Hepatitis B or other liver diseases in control group.

The mean age of the index cases group was 46.5 ± 15.1 years old, from them 102 patients (65.4%) were male and 138 (88.5%) were married. The index cases were assessed for risk factors such as the history of surgery, endoscopy, and colonoscopy, dentistry procedures, tattooing, hemodialysis and phlebotomy history. From them 57 index cases (36.5%) had the history of endoscopy, 38 (24.4%) history of surgery, and 106 (67.9%) of them had the history of dentistry procedures. Seven patients (4.5%) reported intravenous drug abuse and 7 (4.5%) of them reported prison history. Phlebotomy (8.3%), tattooing (5.8%), Needle Stick Injury (10.9%), and history of suspicious sexual contact (1.3%) were also reported by the index cases.

Comparison of demographic variables and risk factors of Hepatitis B in family members and control group are shown in **Tables 1** and **2**.

The family members of index cases reported sharing of toothbrushes and toothpastes (1.7%), shaving materials (5.8%), eating materials (41.1%), common dress and towels (24.4%), history of contact with the wounds and wound exudates of the patients (1.2%), and no one reported common use of unsterilized syringe. None of the family members had the interfamily marriages with the index cases.

After statistical analysis using Exact Fisher Test, a significant difference was shown consid-

Table 2. Comparison of risk factors in study groups

History of Risk factors		Family members of the index cases N=415 (%)	Control group N=599 (%)	Statistical estimate
Surgery	Yes	141 (34)	460 (76.8)	P=0.0001
	No	274 (66)	139 (23.2)	OR=1.66
				CI=(1.25-2.2)
Dentistry procedures	Yes	252 (60.7)	399 (66.6)	P=0.076
	No	163 (39.3)	200 (33.4)	OR=0.78
				CI=(0.60-1.02)
Colonoscopy	Yes	13 (3.1)	10 (1.7)	P=0.145
	No	402 (96.9)	589 (98.3)	OR=1.84
				CI=(0.80-4.24)
Endoscopy	Yes	48 (11.6)	44 (7.3)	P=0.025
	No	367 (88.4)	555 (92.7)	OR=1.63
				CI=(1.06-2.51)
Suspicious sexual contact	Yes	0 (0.0)	9 (1.5)	P=0.011
	No	415 (100)	590 (98.5)	OR=1.72
				CI=(1.63-1.82)
Blood transfusion	Yes	30 (7.2)	28 (4.7)	P=0.034
	No	385 (92.8)	571 (95.3)	OR=1.80
				CI=(1.03-3.13)
Tattoo	Yes	20 (4.8)	35 (5.8)	P=0.474
	No	395 (95.2)	564 (94.2)	OR=0.81
				CI=(0.46-1.43)
Needle stick injury	Yes	20 (4.8)	17 (2.8)	P=0.121
	No	395 (95.2)	582 (97.2)	OR=1.67
				CI=(0.86-3.24)
IV-drug use	Yes	3 (0.7)	4 (0.7)	P=0.951
	No	412 (99.3)	595 (99.3)	OR=1.04
				CI=(0.23-4.71)
Hemodialysis	Yes	0 (0.0)	0 (0.0)	-
	No	415 (100)	599 (100)	
Phlebotomy	Yes	9 (2.2)	20 (3.3)	P=0.237
	No	406 (97.8)	579 (96.7)	OR=0.62
				CI=(0.28-0.37)
Total		415 (100)	599 (100)	

ering HBs Ag among family members and control groups (P=0.0001, OR=70.92, CI=[5.6-9.73]); While 44 (10.6%) of family members were HBs Ag positive, only 1 (0.2%) of control group was HBs Ag positive. He was a 32 year old married man who didn't have the history of vaccination and high risk occupation. The overall prevalence in members of the original family was 5.3% (1.2% of the mothers, 2.2% of the brothers, 1.9% of the sisters), in sexual partners it was 1.4%, in offsprings it was 2.4% and in other households it was 1.4%.

The mean age of HBs Ag positive family members was 35.3 ± 12.9 y/o. among them 27 (61.4%) were female and 17 (38.6%) were male. All of the 44 HBs Ag positive family members were urban. Most of them (70.7%) had the education of diploma or under diploma, while 22% had university education and only 3 (7.3%) were illiterate, 17 (38.6%) of them were single while 27 (61.4%) were married. Within HBs Ag positive family members, 8 (18.2%) had the history of vaccination but only one person had the vaccine titer checked who had inadequate titer.

Table 3. Prevalence of HBV positivity in family members according to having the HBV's risk factors

History of the risk factors in family members	Parents and siblings		Offsprings		spouses		other households		*P* Value
	N (93)	HBV+ N (%)	N (169)	HBV+ N (%)	N (106)	HBV+ N (%)	N (47)	HBV+ N (%)	
Surgery	33	10 (30.3)	43	0 (0.0)	47	1 (2.1)	18	2 (11.1)	NS
Dentistry	54	15 (27.8)	95	3 (3.2)	74	2 (2.7)	29	5 (17.2)	
Endoscopy	14	1 (7.1)	14	1 (7.1)	15	0 (0.0)	5	0 (0.0)	
Transfusion	9	1 (11.1)	7	0 (0.0)	12	1 (8.3)	2	0 (0.0)	
Tattoos	6	0 (0.0)	2	0 (0.0)	10	0 (0.0)	2	0 (0.0)	
Phlebotomy	3	2 (66.7)	3	0 (0.0)	3	0 (0.0)	0	0 (0.0)	

HBs Ag was positive in 5 (11.4%) mothers, 8 (18.2%) sisters, 9 (20.5%) brothers, 6 (13.6%) spouses, 6 (13.6%) households, 7 (15.9%) daughters, and 3 (6.8%) sons. The period of common life with the index cases was < 1 years (1.7%), 1-5 years (4.4%), 5-10 years (3.1%) and > 10 years (90.8%). In HBs Ag positive family members sharing of toothbrushes and toothpastes was (2.3%), shaving materials (9.3%), eating materials (37.2%) and common dress and towels (30.2%). Prevalence of HBV positivity in family members according to having the HBV's risk factors is shown in **Table 3** ($p > 0.05$).

It should be mentioned that all the HBs Ag positive offspring had mothers with Hepatitis B, and 3 (50%) of HBs Ag positive spouses were female and the rest half were male. Within the spouses in family member group, only 18 (17.1%) had the history of using barrier and the rest didn't. While 70 (66%) of the spouses had a below 20-year period of married life, 36 (34%) of them had lived more than 20 years with their spouses.

Among 371 HBs Ag negative family members, 61 (16.4%) were HBc Ab positive and of them, 53 (86.9%) had HBs Ab titer above 10 IU/ml and 8 (13.1%) had HBs Ab less than 10 IU/ml. for this group, HBV DNA PCR was checked; it was negative in all of them.

Discussion

Over 2 billion people worldwide are infected with HBV and more than 350 million have chronic infection [1, 5]. The prevalence of hepatitis B surface antigen (HBsAg) in Iran was reported almost 3% in the 1980s with the range of 1.7% (in the Fars Province) to 5% (in Sistan-Balouchestan Province) [1, 14]. Also a prevalence of 4.5% was reported in Gonbad-Kavus [24]. The prevalence of HBsAg and HCV-Ab in blood donors in Guilan province is reported 0.45% and 1.62%, respectively [25].

Hepatitis B infection is often transmitted among household contacts. First papers that addressed intrafamilial transmission of HBV were published in the beginning of HBV research [26]. Several papers from different geographic areas have been published about this topic since [5, 9, 12, 15, 20]. In a study in Bosnia and Herzegovina on 172 family members of 67 hepatitis B surface antigen chronic carriers and 716 individuals in control group, Salik et al. showed that prevalence of hepatitis B surface antigen was higher ($P < 0.001$) among family members of index cases (12.2%) than among controls (3.6%) with relative risk of 3.3 (95% confidence Intervals=1.9–5.8; $P < 0.05$) [5]. In Turkey, Erol et al. in a survey on two 240 family members of 84 HBsAg carriers and 384 control group reported that the prevalence of HBsAg and HBV infection among the family members (29.6% and 43.8%, respectively) was significantly higher than in the control group (9.6%, and 29.7%), $P < 0.001$ [9]. In an Indian survey, Chakravarty et al. reported 140 (19.4%) HBsAg positive individuals in 722 households of HBV-infected patients [17]. The only Iranian study on Intra-familial prevalence of hepatitis B virologic markers in HBsAg positive family members in Nahavand by Alizadeh, Twelve (11%) of all family members of were HBsAg positive [12]. In the present study, the prevalence of HBs Ag positivity in the family members of hepatitis B patients (10.6%) was significantly higher than control group (0.2%) ($P < 0.0001$). The results of the present survey and the similar studies were evidences that household contacts of patients with hepatitis B are a risk group for acquiring HBV infection and thus becoming chronic carriers themselves. About Hepatitis C, while the reported prevalence is

0.3-2.2% worldwide [25, 28], the prevalence of acquiring hepatitis C in family members was 4.3% in a Turkish survey [29], 8.2% in an Italian survey [30], 20.5% in a study in Pakistan [31], and < 1% in Iran [32]. The higher prevalence of Hepatitis B in family members in comparison to hepatitis C suggests that, regarding the vaccination against HBV), the family members of the patients consider themselves immuned against HBV after vaccination and do not respect healthy behaviors in households contacts cautiously.

In the Indian study, prevalence of HBs Ag was 28.81% among mothers and 8.75% among spouses [17]. In Nahavand in Iran, the highest prevalence of HBsAg was in the brothers (25%) and fathers (12.5%) [12] which were similar to our study. In the present survey, prevalence of HBs Ag among family members of patients with Hepatitis B was 20% in brothers, 18.2% in sisters and 13.6% in spouses. But in the Turkish investigation, different from the present survey, the most prevalence of HBs Ag was reported in husbands [9]. The high prevalence of HBsAg infection among spouses may be due to sexual transmission in menstrual period in other countries. Due to cultural and religious aspects in Iran, this way of intra-familial transmission is not routine [12]. The high prevalence of HBs Ag among brothers suggests that probably prenatal and household contacts in the earliest years of life increases the risk of acquiring Hepatitis B.

In the Indian survey, the mean age of family members of Hepatitis B patients was 30 years old [17], while in the Turkish survey it was 35 years old [9], just like the present study (35.5 ± 13.5 years old). In the Iranian study in Nahavand the mean age of HBs Ag positive individuals in the family members group was 40.2 ± 18, but in our study it was 35.5 ± 12.9 years old [12].

HBV is transmitted through direct and indirect individual contacts and also some unknown oral, mucosal and dermal contacts between households. In an investigation in Ghana, the reported prevalence of hepatitis B was 20.9% and common use of towels, chew gums, toothpastes, and making excoriations on the skin were among behaviors which significantly were associated to the prevalence of Hepatitis B in family members of patients [33]. Also in a study in Korea, sharing of towels and handkerchiefs, and drinking vessels was associated with an increased risk of HBV infection via intrafamilial transmission [34], and in Brazilian survey, sharing toothpastes in family members was significantly related to the prevalence of Hepatitis B [20].

In our investigation, the most prevalent household contacts of patients with Hepatitis B were related to sharing common eating materials (37.2%) and sharing dress and towels (30.2%). It shows incomplete educations about the transmission routes of HBV.

In this study, the history of dentistry procedures (56.8%) and surgery (29.5%) were the risk factors which were associated to the prevalence of Hepatitis B among family members.

In the study in Bosnia and Herzegovina, only 8.7% of 172 family members had the history of vaccination against HBV [5]. Also in Nahavand, the vaccination rate among family members of patients with Hepatitis B was 16.7% [12]. In the current survey, most of the family members didn't have the history of HBV vaccination (47.7%) and the vaccinated individuals hadn't checked the HBs Ab titer. This is evidence that inattention toward vaccination against HBV is common among family members of the patients with Hepatitis B and it increases the risk of acquiring Hepatitis B in them and also those who are vaccinated consider themselves immuned against the risk of the disease and do not check the Ab titer.

In a survey in Greece, the risk of acquiring Hepatitis B was 15.8% in family members group and 10.85% in control group and the higher prevalence of Hepatitis B was reported in rural areas and lower educated groups [15], while in the present study all of the 44 HBs Ag positive family members were urban and only 3 (7.3%) of them were illiterate.

Such studies might be helpful in labeling asymptomatic patients with HBV infection who probably contracted HBV during childhood. The latter seems to be crucial from the clinical point of view, the earlier in life infection occurs, the greater the likelihood that the infected individual will become a chronic carrier of HBV and die from its sequelae [15]. It is important to note some limitations of this study. There are different studies about HBV intra-familial transmis-

sion in the world that in the strongest ones, phylogenetic sequence analysis and amino-acid variations of the HBV core gene. It is obvious that this genetic study is the only way to determine intra-familial transmission of HBV, but we didn't have sufficient resources to do this in the present study [12]. Also all of the cases from control group in our study were from one hospital. Although this hospital is a big referral hospital of the Province, these cases cannot necessarily represent the population of the Guilan province. So we suggest another survey with a control group from the general population to judge the prevalence of Hepatitis B in family members of Hepatitis B patients confidently.

Conclusion

Our data indicate that there is a significant difference in the prevalence of Hepatitis B in the general population and family members of Hepatitis B patients and this is an evidence for horizontal transmission of HBV among family members. It seems that healthy behaviors are disrespected in the family and the households are not aware of the exact time of the disease onset in the members with Hepatitis B. Also the vaccinated family members regard themselves immuned against the disease and do not avoid the high risk behaviors, while they do not check the Ab titer so that they are at the risk of contracting the disease from their relatives because of downfall of the Ab level in time. So it is absolutely necessary to investigate all family members of HBsAg carriers and patients for the presence of HBV markers and to immediately offer HBV vaccination in addition to checking Ab titer in vaccinated ones regularly.

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Disclosure of conflict of interest

None.

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References

[1] Alavian SM, Fallahian F, Lankarani KB. The changing epidemiology of viral hepatitis B in Iran. J Gastrointestin Liver Dis 2007; 16: 403-6.

[2] Ward JW, Hu DJ, Alter MJ, Kanwal F, Taylor C, Block JM, Caballero JB, Chase D, Saly M, Sandt L, Swan T. Transforming strategies for the prevention of chronic HBV and HCV infections. J Fam Pract 2010; 59: 23-8.

[3] Kao JH, Chen DS. Global control of hepatitis B virus infection. Lancet Infect Dis 2002; 2: 395-403.

[4] Lin CL, Kao JH, Chen BF, Chen PJ, Lai MY, Chen DS. Application of Hepatitis B virus Genotyping and phylogenetic Analysis in Intrafamilial Transmission of Hepatitis B virus. Clin Infect Dis 2005; 41: 1576-81.

[5] Salkic NN, Zildzic M, Muminhodzic K, Pavlovic-Calic N, Zerem E, Ahmetagic S, Mott-Divkovic S, Alibegovic E. Intrafamilial transmission of hepatitis B in Tuzla region of Bosnia and Herzegovina. Eur J Gastroentrol Hepatol 2007; 19: 113-8.

[6] Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004; 11: 97-107.

[7] Alavian SM. Networking for Overcoming on Viral Hepatitis in Middle East and Central Asia: "Asian Hepatitis Network". Hepat Mon 2007; 7: 181-2.

[8] Salkic NN, Zerem E, Zildzic M, Ahmetagic S, Cickusic E, Ljuca F. Risk factors for intrafamilial spread of Hepatitis B in Northeastern Bosnia and Herzegovina. Ann Saudi Med 2009; 29: 41-5.

[9] Erol S, Ozkurt Z, Ertek M, Tasyaran MA. Intrafamilial transmission of hepatitis B virus in the eastern Anatolian region of Turkey. Eur J Gastroenterol Hepatol 2003; 15: 345-9.

[10] Franco E, Bagnato B, Marino MG, Meleleo C, Serino L, Zaratti L. Hepatitis B: Epidemiology and prevention in developing countries. World J Hepatol 2012; 4: 74-80.

[11] Kowdley KV. The cost of managing chronic hepatitis B infection: a global perspective. J Clin Gastroenterol 2004; 38: 132-3.

[12] Mohammad Alizadeh AH, Ranjbar M, Ansari S, Alavian SM, Shalmani HM, Hekmat L, Zali MR. Intra-familial prevalence of hepatitis B virologic markers in HBsAg positive family members in Nahavand, Iran. World J Gastroenterol 2005; 11: 4857-60.

[13] Farzadegan H, Harbour C, Ala F. The prevalence of Hepatitis B surface antigen and its antibody in blood donors and high risk groups in Iran. Vox Sang 1979; 37: 182-6.
[14] Merat S, Malekzadeh R, Rezvan H, Khatibian M. Hepatitis B in Iran. Arch Iran Med 2000; 3: 192-201.
[15] Zervou EK, Gatselis NK, Xanthi E, Ziciadis K, Georgiadou SP, Dalekos GN. Intrafamilial spread of hepatitis B virus infection in Greece. Eur J Gastroenterol Hepatol 2005; 17: 911-5.
[16] Amini S, Mahmoodi MF, Andalibi S, Solati AA. Seroepidemiology of hepatitis B, delta and human immunodeficiency virus infections in Hamadan province, Iran: a population based study. J Trop Med Hyg 1993; 96: 277-87.
[17] Chakravarty R, Chowdhury A, Chaudhuri S, Santra A, Neogi M, Rajendran K, Panda CK, Chakravarty M. Hepatitis B infection in Eastern Indian families: Need for screening of adult siblings and mothers of adult index cases. Public Health 2005; 119: 647-54.
[18] Zampino R, Lobello S, Chiaramonte M, Venturi-Pasini C, Dumpis U, Thursz M, Karayiannis P. Intrafamilial transmission of hepatitis B virus in Italy: phylogenetic sequence analysis and amino-acid variation of the core gene. J Hepatol 2002; 36: 248-53.
[19] Dumpis U, Holmes EC, Mendy M, Hill A, Thursz M, Hall A, Whittle H, Karayiannis P. Transmission of hepatitis B virus infection in Gambian families revealed by phylogenetic analysis. J Hepatol 2001; 35: 99-104.
[20] Lobato C, Tavares-Neto J, Rios-Leite M, Trepo C, Vitvitski L, Parvaz P, Zoulim F, D'Oliveira A Jr, Paraná R. Intrafamilial prevalence of hepatitis B virus in Western Brazilian Amazon region: epidemiologic and biomolecular study. J Gastroenterol Hepatol 2006; 21: 863-8.
[21] Hollinger FB, Liang TJ. Hepatitis B virus. In: Knipe DM, Howley PM, eds. Fields Virology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. pp: 2971-3036.
[22] Thakur V, Guptan RC, Malhotra V, Basir SF, Sarin SK. Prevalence of hepatitis B infection within family contacts of chronic liver disease patients: does HBeAg positivity really matter? J Assoc Physicians India 2002; 50: 1386-94.
[23] Milas J, Ropac D, Mulić R, Milas V, Valek I, Zorić I, Kozul K. Hepatitis B in the family. Eur J Epidemiol 2000; 16: 203-8.
[24] Pourshams A, Nasiri J, Mohammadkhani A, Nasrollahzadeh D. Hepatitis B in Gonbad-e-Kavoos: prevalence, risk factors, and intrafamilial spreading. Govaresh 2004; 9: 222-5; [in Persian].
[25] Mansour-Ghanaei F, Fallah MS, Jafarshad R, Joukar F, Salari A, Tavafzadeh R. Prevalence of hepatitis B surface antigen and hepatitis C virus antibody and their risk factors among Guilan's volunteer blood donors (1998-2003). Hepat Mon 2007; 7: 239-41.
[26] Szmuness W, Prince AM, Hirch RI, Brotman B. Familial clustering of hepatitis B infection. N Eng J Med 1973; 289: 1162-6.
[27] Honda M, Kaneko S, Unoura M, Kobayashi K, Murakami S. Risk of hepatitis C virus infections through household contact with chronic carriers: analysis of nucleotide sequences. Hepatology 1993; 17: 971-6.
[28] Carrilho FJ, Moraes CR, Pinho JR, Mello IM, Bertolini DA, Lemos MF, Moreira RC, Bassit LC, Cardoso RA, Ribeiro-dos-Santos G, Da Silva LC. Hepatitis B virus infection in Haemodialysis Centres from Santa Catarina State, Southern Brazil. Predictive risk factors for infection and molecular epidemiology. BMC Public Health 2004; 4: 13.
[29] Saltoghlu N, Tasova Y, Burgut R, Dundar IH. Sexual and non-sexual intrafamilial spread of hepatitis C virus: intrafamilial transmission of HCV. Eur J Epidemiol 1998; 14: 225-8.
[30] Demelia L, Vallebona E, Poma R, Sanna G, Masia G, Coppola RC. HCV transmission in family members of subjects with HCV related chronic liver disease. Eur J Epidemiol 1996; 12: 45-50.
[31] Aktar S, Moatter T, Azam SI, Rahbar MH, Adil S. Prevalence and risk factors for intrafamilial transmission of hepatitis C virus in Karachi, Pakistan. J Viral Hepat 2002; 9: 309-14.
[32] Alavian SM, Gholami B, Maserrat S. Hepatitis C risk factors in Iranian volunteer blood donors; case – control study. J Gastroenterol Hepatol 2002; 17: 1092-7.
[33] Martinson FE, Weigle KA, Royce RA, Weber DJ, Suchindran CM, Lemon SM. Risk Factor for horizontal transmission of hepatitis B virus in a rural district in Ghana. Am J Epidemiol 1998; 147: 478-87.
[34] Kim YS, Ahn YO. Factors associated with intrafamilial transmission of hepatitis B virus infection in Korea. J Korean Med Sci 1993; 8: 395-404.