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Familial Clustering of Hepatitis B and C Viruses in Korea

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In order to evaluate the familial clustering of hepatitis B virus(HBV) and hepatitis C virus(HCV) infections and to elucidate the possible routes of HCV transmission among Korean adults with chronic liver disease, 137 household contacts of 51 chronic carriers of HBsAg and 111 household contacts of 38 controls, and 181 household contacts of 96 anti-HCV positives and 102 household contacts of 76 anti-HCV negatives were tested from July 1990 to March 1994. Of 71 non-vaccinated household contacts of HBsAg carriers, 10 gave positive result for HBsAg(14.1%), but none of the household contacts of the controls were positive for HBsAg($p<0.05$). Familial clustering of HBV infection was found, when the offspring of carriers and controls were compared. A significantly higher percentage of the offspring of carriers were positive for HBV infection(54.6% vs 15.4%, $p<0.05$) with OR of 6.6(95% CI ; 1.3-34.5). No evidence of familial clustering of HCV infection was found with 2.2%(4/181) anti-HCV positivity among the household contacts of index cases, similar to 1.0%(1/102) among those of controls. History of acute hepatitis(OR 3.2), transfusion(OR 3.2), and acupuncture(OR 2.5) were associated with an increased risk of HCV infection. In conclusion, HBV has strong familial clustering whereas HCV does not in Korea.

Key Words : *Familial clustering, Hepatitis B virus, Hepatitis C virus, Risk factor.*

INTRODUCTION

Chronic liver disease is the fourth most common cause of morbidity of inpatients in Korea(KMIC. 1991), and the age-adjusted incidence rates of liver cancer among Koreans were 30.5 and 7.6 per 100,000 in males and females, respectively(Ahn et al., 1989). In the total population, positive rates of hepatitis B surface antigen(HBsAg) are slightly lower in women(6.2%) than men(8.0%)(Ahn et al., 1992). Positive rates of anti-HCV were 0.9% in blod donors(Kim et al., 1990) and 1.7% in healthy adults without symptomatic liver disease(Kim et al., 1992). In patients with chronic liver disease 60-80% were positive for HBsAg(Suh, 1982 ; Kim et al., 1983) and 15-30% were positive for anti-HCV(Chi et al., 1990 ; Park et al., 1991 ; Chang et al., 1992).

Familial clustering of hepatitis B virus(HBV) infection is well known(Szmuness et al., 1973 ; Sampliner et al., 1981 ; Bernier et al., 1982), but familial clustering of hepatitis C virus(HCV) infection is not well documented.

The purposes of this study are to evaluate the familial clustering of HBV and HCV infections and to

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elucidate the possible routes of HCV transmission among Korean adults with chronic liver disease.

MATERIALS AND METHODS

One hundred and thirty seven household contacts of 51 chronic carriers who were positive for HBsAg more than 2 years, and 111 household contacts of 38 controls who were negative for all three markers of HBV(HBsAg, anti-HBs and anti-HBc) were included in group Ⅰ(Table 1) from July 1990 to October 1991. One hundred and eighty one household contacts of 96 anti-HCV positives confirmed by retest after more than 6 months and 102 household contacts of 76 anti-HCV negatives were included in group Ⅱ(Table 2) from July 1991 to March 1994. HBsAg carriers and controls were selected from a group of government employees, school teachers and staffs. Anti-HCV positives were selected from the patients who diagnosed clinically at the Asan medical Center. Ninety six anti-HCV positives consisted of 69 patients with chronic hepatitis, 6 with cirrhosis, 2 with hepatocellular carcinoma, and 19 with normal liver function. Anti-HCV negative subjects were selected from subjects who underwent a general check-up at the Asan Medical

Table 1. Sex and Age distribution of index cases of HBsAg carrier* and control#, and their household contacts(group Ⅰ)

	Index Cases				Household Contacts of			
	HBsAg carrier		Control		HBsAg carrier		Control	
	No.	%	No.	%	No.	%	No.	%
Total	51	100.0	38	100.0	137	100.0	111	100.0
Sex								
Male	47	92.2	30	78.9	55	40.1	49	44.1
Female	4	7.8	8	21.1	82	59.9	62	55.9
Age(year)								
0— 9	—	—	—	—	35	25.5	28	25.2
10—19	—	—	—	—	43	31.4	38	34.2
20—29	5	9.8	2	5.3	13	9.5	3	2.7
30—39	22	43.1	19	50.0	28	20.4	27	24.3
40—49	17	33.3	15	39.5	12	8.8	9	8.1
50≤	7	13.7	2	5.3	6	4.4	6	5.4
Mean Age	40.0±8.3		38.9±7.0		22.7±15.1		23.5±16.0	

*HBsAg carrier : those who were HBsAg positive for more than 2 years
#control : those who were negative for all markers of HBV(HBsAg, anti-HBs and anti-HBc)

Table 2. Sex and age distribution of index cases of anti-HCV positive and negative, and their household contacts(group Ⅱ)

	Index Cases				Household Contacts of			
	anti-HCV(+)		Anti-HCV(−)		anti-HCV(+)		anti-HCV(−)	
	No.	%	No.	%	No.	%	No.	%
Total	96	100.0	76	100.0	181	100.0	102	100.0
Sex								
Male	58	60.4	36	47.4	77	41.6	42	42.2
Female	38	39.6	40	52.6	104	58.4	60	57.8
Age(year)								
0— 9	0	0	0	0	8	4.4	8	7.8
10—19	0	0	0	0	27	14.9	23	22.6
20—29	4	4.2	0	0	51	28.2	21	20.6
30—39	5	5.2	13	17.1	26	14.4	13	12.8
40—49	18	18.8	28	36.8	21	11.6	23	12.6
50—59	34	35.4	23	30.3	30	16.6	7	6.9
≥60	35	36.5	12	15.8	18	9.9	7	6.9
Mean Age	54.2±10.1		48.5±10.9		33.0±17.6		29.6±16.8	

Center and were not matched to the anti-HCV positive patient.

HBsAg, antibody to HBsAg(anti-HBs) and antibody to hepatitis B core antigen(anti-HBc) were tested by radioimmunoassay(AUSRIA, AUSAB and CORAB respectively, Abbott Laboratories). Anti-HCV was tested by second generation enzyme-linked immunoabsorbent assay(Abbott Laboratories).

Those who received hepatitis B vaccination were excluded from analysis for group I. Those who received hepatitis B vaccination were 66(48.5%) out of 137 household contacts of carriers, and 60(54.1%) out of 111 household contacts of controls.

All participants were interviewed for their past medical histories, which included operation, blood transfusion, acute viral hepatitis, dental procedures, sexually transmitted diseases, acupuncture use, endoscopy, tattoos, pierced ears and hepatitis B vaccination.

Familial clustering was examined by the difference in the prevalence of HBV and HCV infection among the household contacts of index cases and controls. We examined the odds ratios of possible risk factors of HCV infection in anti-HCV positive cases versus anti-HCV negative controls. Factors that were significant on univariate analysis were examined with Mantel Haenszel method using the Statistical Analysis System for personal computers (6.04).

RESULTS

Familial clustering of HBV infection

Of 71 non-vaccinated household contacts of HBsAg carriers, 10 tested positive for HBsAg(14.1 %), but none of 51 non-vaccinated household contacts of controls were positive for HBsAg($p<0.05$). Of the 10 who tested positive for HBsAg, 8 were the offspring of carriers(Table 3).

70.4% of non-vaccinated household contacts of

Table 3. Prevalence of HBsAg and hepatitis B virus infection# among non-vaccinated household contacts of carriers and controls by relationship to the index case

Relationship to the index case	Household contacts of carriers			Household contacts of controls		
	No. of Non-vaccinated	Positive of NHsAg No.(%)	Positive of HBV infection NO.(%)	No. of non-vaccinated	Positive of HBsAg No.(%)	Positive of HBV infection No.(%)
Parent	2	0(0.0)	2(100.0)	7	0(0.0)	6(85.7)
Spouse	33	1(3.0)	28(84.9)	26	0(0.0)	21(80.8)
Offspring	33	8(24.2)	18(54.6)*	13	0(0.0)	2(15.4)*
Sibling	2	1(50.0)	1(50.0)	4	0(0.0)	3(75.0)
Other relatives	1	0(0.0)	1(100.0)	1	0(0.0)	1(100.0)
Total	71	10(14.1)**	50(70.4)	51	0(0.0)**	33(64.7)

#Positive for at least one hepatitis B marker(HBsAg, anti-HBs, or anti-HBc)
*$P<0.05$ by Fisher's exact test, Mantel Haenszel estimates of odds ratio ; 6.6 with 95% CI of 1.26-34.54
**$P<0.01$ by Fisher's exact test. 95% CI ; 7.8-24.0% for household contacts of carrier and 0.0-7.0% for those of control.

Table 4. Anti-HCV positive rates among household contacts of anti-HCV positives and negatives by relationship to the index case

Relationship to the index case	Household contacts of anti-HCV positives			Household contacts of anti-HCV negatives		
	No. tested	anti-HCV(+)	(%)	No. tested	anti-HCV(+)	(%)
Parent	3	0	(0.0)	1	0	(0.0)
Spouse	65	4	(6.2)	45	1	(2.2)
Offspring	85	0	(0.0)	52	0	(0.0)
Sibling	5	0	(0.0)	2	0	(0.0)
Other relatives	23	0	(0.0)	2	0	(0.0)
Total	181	4	(2.2)	102	1	(1.0)

Table 5. Distribution of the index anti-HCV positives and negatives by some variables

Variables	anti-HCV(+) No. (%)	anti-HCV(−) No. (%)	Crude OR	adjusted[a] OR	(95% CI)
Total	96	76			
Surgical operation	47 (49.5)	33 (43.4)	1.3		
Blood transfusion	34 (36.6)	11 (14.7)	3.4	3.2**	(1.4- 7.3)
History of acute hepatitis	18 (20.7)	4 (5.5)	4.5	3.2*	(1.0-10.0)
History of STD[b]	24 (25.8)	18 (24.7)	1.1		
Endoscopy	67 (70.5)	61 (82.4)	0.5		
Acupuncture	77 (81.1)	49 (66.2)	2.2	2.5*	(1.2-5.1)
Tooth extraction	64 (68.8)	56 (73.7)	0.8		
Tattooing	18 (8.5)	14 (18.7)	0.4		
Ear piercing	11 (11.7)	19 (25.7)	0.4		

[a]adjusted by age & sex
[b]sexually transmitted disease
*P<0.05 **P<0.01

HBsAg carriers were positive for HBV markers. This was not significantly different from the 64.7% HBV infection rate of household contacts of controls(P> 0.05).

Familial clustering of HBV infection was found, when the offspring of carriers and controls were compared. A significantly higher percentage of the offspring of carriers were positive for HBV markers(54.6% vs 15.4%, p<0.05) with OR of 6.6(95% CI ; 1.3-34.5)(Table 3).

Familial clustering of HCV infection

No evidence of familial clustering of HCV infection was found with 2.2%(4/181) anti-HCV positivity among the household contacts of index cases, similar to 1.0%(1/102) among those of controls(Table 4).

Risk factors associated with HCV infection

History of acute hepatitis(OR 3.2), transfusion(OR 3.2) and acupuncture(OR 2.5) were associated with an increased risk of HCV infection in Korea(P< 0.05) (Table 5). The following factors were not associated with an increased risk of HCV infection ; operation, history of sexually transmitted disease, endoscopy, tooth extraction, tattooing and ear piercing.

DISCUSSION

Familial clustering of HBV infection is well known. HBsAg prevalence among the household contacts of acute cases of hepatitis B was 3.3 times higher than that of the general population(Goh et al., 1985). Prevalence of HBsAg and any one of the HBV markers among household contacts of chronic carriers was 6.8 and 3.4 times higher than those of household contacts of controls respectively(Bernier et al., 1982). Mother to child transmission is also well documented in Hong Kong(Lok et al., 1987) and Taiwan(Stevens et al., 1975). Father to child transmission(Szmuness et al., 1973), transmission among siblings(Kashiwagi et al., 1984), and transmission among spouses(Szmuness et al., 1975) are also documented. Our study confirmed the household transmission of HBV infection, especially from parents to offspring when one of the parents was a carrier, which resulted in familial clustering. As much as 6.6 times higher prevalence of HBV infection among the offspring of carriers was found compared to controls. The HBV infection rate of the spouses of carriers did not differ from that of the spouses of controls. This is consistent with the findings of Lok et al.(1987), who studied a population with a high prevalence of HBV infection. However, this conflicts with the findings of Szmuness et al.(1975), who studied a population with a low pre-

valence of HBV infection and found a relative risk of 2.5 among the spouses of carriers. In Korea, the HBV infection rate among persons in their 20's is estimated at 59-73%(Ahn et al., 1992), most of the spouses of the carriers may have already been infected with HBV prior to marriage with relative reduction of the risk of new infection from HBV carriers after marriage. Parents, siblings, and other relatives of carriers and controls also did not differ in the HBV infection rate in our study. Most of them were adults who already have a high prevalence of HBV infection in Korea(Ahn et al., 1992). The sample size was too small to make a significant conclusion, and a larger study with more parents, siblings and other relatives needs to be done.

Intrafamilial transmission of HCV is still controversial. Ideo et al.(1990) and Kiyosawa et al.(1991) report the presence of intrafamilial transmission of HCV but our study shows similar results of Everhart et al.(1990) where no intrafamilial transmission was found. Although they(Ideo et al., 1990 ; Kiyosawa et al., 1991) found intra-familial transmission of HCV the differences between cases and controls were much smaller than those of HBV infection. Perinatal transmission of HCV was found in the studies by Wejstal et al.(1990) and others(Kamitsukasa et al., 1989; Kuroki et al., 1991). However, Reinus et al.(1992) and Novati et al.(1992) suggested passive transfer of anti-HCV rather than vertical transmission as the explanation for this finding. While mother to child transmission of HCV may be possible it may not be as important a route as in the transmission of HBV. Spouse to spouse transmission of HCV was reported by Kamitsukasu et al.(1989) but not by Everhart et al.(1990). and Kiyosawa et al.(1991) Having multiple heterosexual partners was reported as a risk factor for sexual transmission of HCV(McHutchison et al., 1992) but homosexuality was not(Melbye et al., 1990). Such controversial results might be due to the low possibility of sexual transmission of HCV in view of the report by Hsu et al.(1991) in which HCV was not found in semen or saliva. Thus, intrafamilial transmission of HCV which includes all forms of close contacts(i.e. mother to child and sexual), is not as common as in HBV infection and does not manifest in familial clustering. Therefore the parenteral route remains as the major route of transmission of HCV.

In our study, transfusion, as the classic form of parenteral transmission, has an odds ratio of 3.2 and is consistent with findings by Esteban et al.(1991) and Serfaty et al.(1993). History of acute hepatitis is found to be a significant risk factor, which is consistent with the findings of Serfaty et al.(1993). Acupuncture is also found to be a significant risk factor of HCV infection. This finding was supported by various reports in the literature(Alexis et al., 1988 ; Kent et al., 1988) which considered acupuncture as a significant route of transmission of hepatitis viruses. Lee et al.(1991), McHutchison et al.(1992) and Serfaty et al.(1993) report intravenous drug use as a significant route of transmission. Our study was not able to adequately evaluate intravenous drug use as a risk factor due to very low incidence of intravenous drug users in our study population and also due to poor responses to questions regarding intravenous drug use. We also attempted to evaluate tattooing as a possible risk factor as reported by Ko et al.(1992). However tattooing was not found to be a risk factor.

The limitations of our study are the lack of confirmation of anti-HCV positivity with other methods such as recombinant immunoblot assay(RIBA) or polymerase chain reaction(PCR) and the sample size which was inadequate to fully evaluate the various routes considered. Even with these limitations, we are able to conclude that HBV has strong familial clustering whereas HCV does not. Parenteral routes such as transfusion and acupuncture remain the major routes of transmission of HCV in Korea.

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