The Modes of Transmission of Hepatitis B Virus in Turkey; The Impact of Status of Liver Disease on Transmission

TÜRKİYE'DE HEPATİT B VİRÜSÜNÜN BULAŞ YOLLARI; KARACİĞERDE HASTALIK DERECESİNİN BULAŞA ETKİSİ

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Summary

A cross-sectional study was designed to evaluate the mode of transmission of HBV in household in Turkey. We also investigated the effect of the state of liver pathology of index cases on transmission. One hundred eight)' index cases (122 male and 58 female with a mean age of 36.8H0.6 years) and their 380 relatives were included as the study group and 100 individuals 148 male and 52 female cases with a mean age of 41.4 ->• 18.6 years) were recruited as a control group. We assaved the serological markers of HBV in participants. Biochemical tests, ultrasonography and liver biopsy were performed when necessary. The prevalence of HBs Ag positivity was 5"o in spouses, 41% in siblings, 18% in children, 17%, in relatives of healthy carriers, 19% in relatives of those index cases with chronic hepatitis (CH) while it was 7% in controls. HB V positivity among relatives of HBs Ag carriers and of those with CH were significantly higher than controls (p<0.05). There were more cases with liver disease among the relatives of' index cases with CH (62.5%,) than those of healthy carriers (29%) (p<0.05). HBs Ag carriage reaches a steady-state level of ¡4%, until the end of second decade. Considering the rate of HBs Ag positivity (4l'a) among siblings of index cases, horizontal way is the most important mode for HBV transmission in 'Turkey. The siblings and nude children are under serious risk)ot- horizontal transmission of HBV. Unless a mass vaccinatum program is available, at least a vaccination program should cover first necessarily those less than 20 years of age and siblings of index cases.

Key Words: HBs Ag, Horizontal transmission, Turkey, HBV carrier

T Klin J Gastrocnterohcpatol 1999, 10:97-104

Geliş Tarihi: 08.04.199

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Özet

Araştırma, HBV'niu aile içi geçişini incelemek için, kesitsel bir çalışına olarak düzenlendi. Ayrıca, indeks vakalarda karaciğerin hastalık durumunun bu geçişe etkisi incelendi. Çalışmaya 180 indeks vaka (122 erkek ve 58 kadın, yaş ortalamaları 36.8 ± 10.6 yıl) ve onların 380 yakını ile kontrol grubu olarak da 100 sağlıklı birey (48 erkek ve 52 kadın, yaş ortalamaları 41.4.^18.6 yıl) alındı. Katılanlarda HBV için serolojik belirteçler bakıldı. Biyokimyasal testler, ultrasonografı ve gerekliğinde karaciğer biyopsileri yapıldı. Eşlerde HBs Ag pozitifliği "¿5. kardeşlerde %,4f çocuklarda ",,18. sağlıklı taşıyıcı yakınlarında %17 ve kronik hepalitli (KH) hasta yakınlarında "d 19 olarak bulunurken kontrol grubunda bu oran %>7 idi. Taşıyıcı ve KH'H hasta yakınlarındaki HB]' pozitifliği kontrol grubuna göre anlamlı olarak yüksek bulundu (p<0.05). KH'li hasta ve taşıyıcı yakınlarından HBV pozitif saptananlar karşılaştırıldığında ilk gruptakiler arasında daha fazla hepatitli olguya rastlandı (sırasıyla %,62.5 ve %,29) (p<0.05). Genel olarak, HBs Ag taşıyıcılığı ikinci dekad sonuna kadar %,14 gibi sabit bir seviyeye ulaşmakta idi. Çalışına sonucuna göre, kardeşler arası bulaş (%>4T) gözönüue alındığında, horizontal yol HBV için Türkiye'de en önemli bulaş yoludur. Horizontal olarak HBV İmlasında kardeşler ve erkek çocuklar en yüksek riski taşımaktadır. Bu nedenle, tüm toplum aşılaması gerçekleştirilemiyorsa, yirmi yaş altındakiler ve indeks vakaların kardeşleri öncelikli olarak aşılanmalıdır.

Anahtar Kelimeler: HBs Ag, Horizontal bulaş, Türkiye, HBV taşıyıcısı

T Klin Gastroenterohepatol 1999, 10:97-104

Viral hepatitis is still a serious general health problem. Hepatitis B Virus (HBV) is the commonest cause for hepatocellular carcinoma (HCC) in Turkey (1,2) and world literature (3). Regarding the regional differences, we saw that the prevalence of

HBV carriage is 2-10% in Turkey (4-6). Today, we know that HBV is transmitted via blood and its products, homo and heterosexual contact, vertically (from mother to baby) and horizontally (via routes other than parenteral and vertical modes). Thus, the risk groups consist of relatives of carriers, homosexuals, babies of HBV infected mothers, health care workers, IV drug abusers and those require transfusions (7). It is very important to determine the main route of transmission countrywide, which helps programming the schedule of vaccination program especially in countries not executing a universal immunization program like our country. In this study we aimed 1. to determine the main mode of transmission in Turkey, 2. to assess the effect of the status of the liver disease on the rate of transmission, 3. able to draw the chart of age versus rate of carnage in relatives of index cases.

Material and Methods

One hundred eighty HBs Ag (+) index cases and their 380 first-degree relatives who applied to the department of Gastroenterology of Haccttcpe University Medical Center from August 1995 to June 1997 were enrolled. Additionally, another 100 outpatient admitted for non-specific dyspepsia were also included to this study as control group. The control cases had no history of personal or familial liver disease or hepatitis and any known risk factor. They had normal blood levels of transaminases, protrombin time and serum albumin. We detected HBs Ag, AntiHBc IgG, Anti HBs, HBc Ag, Anti HBc, Anti Delta antibody and measured Alanine Transaminase (ALT), Aspartate transaminase (AST) levels and protrombin time from the blood samplesY>f all index cases. On the other hand we detected only HBs Ag, Anti HBs and AntiHBc IgG from the relatives. Those with pure Anti HBc IgG positivity were excluded if they had a history of vaccination. The cases with a history of blood transfusion and any surgical intervention were not involved neither in the study (relatives meant) nor the control group. Ultrasonographic examination was also performed in all index cases. Patients without any symptoms and with normal liver biochemistry were assigned as healthy (asymptomatic carriers are indicated) carriers. Patients who had abnormality in liver biopsy samples compatible with chronic active hepatitis and those who denied biopsy but had abnormal transaminases (more than two times normal) for more than 6 months were assigned as chronic hepatitis (CH) group. The seldom patients with pathologically proven cirrhosis related to chronic HBV infections were excluded because of small sample size. The obtained sera were studied via enzyme linked immunosorbant assay (ELISA) with HBs Ag microelisa system (Hepanostika ® HBs Ag Uni-form **II,** Organon Teknika SA, France), HBs Ab microelisa system (Hepanostika ® anti-HBs, Organon Teknika SA, France), HBe Ag and anti HBe microelisa system(Hepanostika ® HBe Ag/anti HBe, Organon Teknika SA, France), and HBc Ab microelisa system (Hepanostika ® anti-HBc Uni-form, Organon Teknika SA, France). If any of HBs Ag, Anti HBs and AntiHBc IgG was detected positive, the case was assigned as seropositive otherwise as seronegative. The comparison of rates between groups was made by chi-square and Fischer's exact test.

Results

Among 180 index cases were 122 male and 58 female with a mean age of 36.8±10.6 (range 16-66) years old. In the control group, 48 male and 52 female cases with a mean age of 41,4±18.6 (range 18-69) years old were included. We had 59 healthy carriers and 121 patients with CH (58 of them were identified via biopsy, others via clinically by high plasma transaminases lasting more than six months) among index cases. The serological data of controls is shown in Table 1. Since it was not so easy to know which of the spouses was the initial source for the other, the table was made without considering the gender of the index case as seen in the Table 2, if one spouse was HBs Ag (+), the ratio of HBs Ag positivity of the couples was 5%, while seropositivity 76%. The HBs Ag positivity and seroposivity rates of spouses were not found significantly different from controls (p=0.72 and p=0.09) (Figure 1,2).

HBV serology of relatives is shown in Table 2. Total HBs Ag positivity rate of relatives was 15% and significantly higher than controls (p=0.04). On the other hand the seropositivity rate was the same with controls (p=0.85). The ratio of HBs Ag positivity of sons (18%) was significantly higher than daughters and controls (p=0.05), while the ratio of HBs Ag positivity of daughters (7%) was not significantly different than controls. Seropositivity

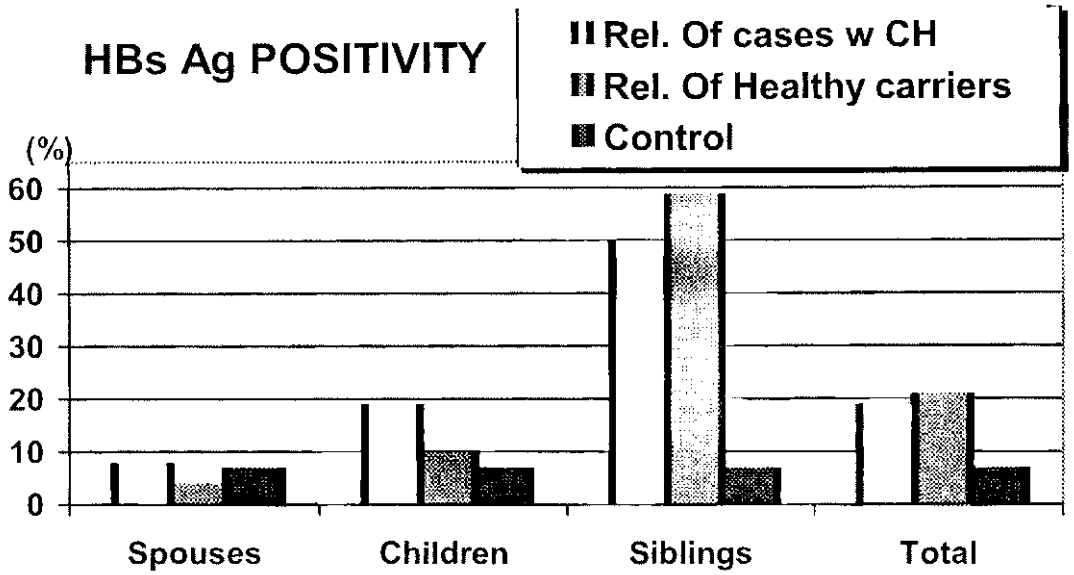

Figure 1. The ratios of HBs Ag positivity of the controls, and of relatives of healthy carriers and of index cases with CH.

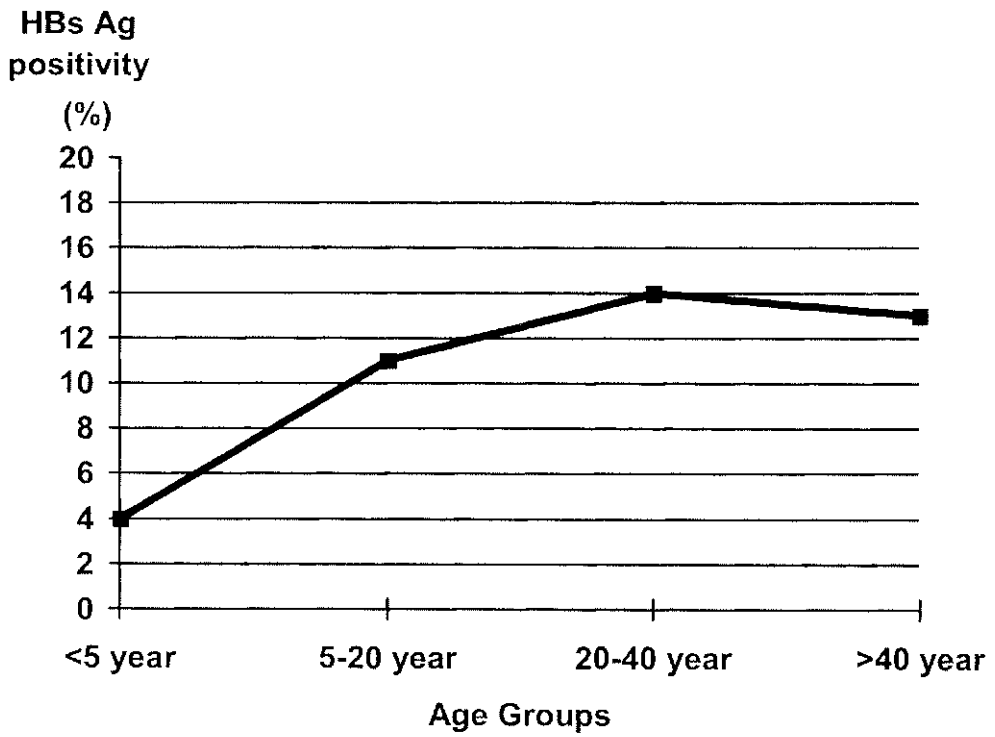

Figure 2. The change in HBs Ag positivity with age among the relatives of index cases.

rate was similar in the children of both sexes (p=0.21). The HBs Ag positivity among siblings (41%) was significantly higher than both children (18%) and spouses (5%) (p=0.003 and p<0.0001 respectively).

Overall HBs Ag positivity was 5% in the children of male index cases, this figure was not statistically different than controls (p=0.80). The ratio of

Table 1. The results of viral markers of control cases

Control Cases	H Bs Ag (+) n (%)	Anti FIBs (+) n (%)	Anti HBc IgG (+) n (%)	Sero (+) n (%)	Sero (-) n (%)
Male (n-48)	4 (8)	20 (41)	9 (18)	33 (68)	15 (15)
Female (n=52)	3 (6)	22 (42)	7 (13)	32 (61)	20 (20)
Total (n=100)	7 (7)	42 (42)	16 (16)	65 (65)	35 (35)

Table 2. The overall HBs Ag positivtty among relatives of index cases

Overall Relatives	HBs Ag (+) n (%)	Anti HBs (+) n (%)	Anti HBc IgG (+) n (%)	Sero (+) n (%)	Sero (-) n (%)	Total
Spouses	6 (5)	58 (48)	27 (22)	91 (76)	30 (25)	121
Children						
Male	19 (18)	16(15)	29 (27)	64 (60)	41 (40)	105
Female	6 (7)	22 (24)	21 (23)	49 (55)	40 (45)	89
Children total	25 (18)	38 (20)	50 (27)	113 (55)	81 (45)	194
Siblings	27 (41)	12 (18)	10 (15)	49 (75)	16 (25)	65
Relatives total	58 (15)	108 (28)	87 (22)	253 (67)	127 (33)	380
Controls	7 (7)	42 (42)	16 (16)	65 (65)	35 (35)	100

45% HBs Ag positivity belonging to siblings of male index cases was significantly higher than controls and than their children ($p<0.0001$, $p<0.01$ respectively). Comparing the HBs Ag positivity of children of male and female index cases (5% vs. 25%), there was a significant difference ($p<0.001$) if mother was the index case. Siblings of female index cases had a similar ratio of HBs Ag positivity with male index cases ($p=0.46$) and a higher ratio than controls ($p<0.001$). Without taking into consideration of the gender of the parents, male children had higher risk (18%) of acquisition of HBV than the female (7%) children ($p=0.03$).

As mentioned above, another aim of the study was to determine the effect of status of liver disease on the transmission rate of HBV. We tried to get the answer to whether index cases with chronic liver disease infect the others more vigorously than healthy carriers. The serocpidcmiological data from relatives of healthy index cases were presented in Table 3.

The ratio of HBs Ag positivity (4 %) in spouses of healthy carriers was not significantly different than controls ($p=0.74$). The sons of healthy carriers had significantly higher HBs Ag positivity (17%) than controls ($p<0.05$), whereas the daughters of healthy carriers had similar ratio of HBs Ag positivity to the controls ($p=0.15$). Meanwhile, the daughters had significantly lower ratio (48%) of seropositivity ($p=0.03$). We observed that the ratio of HBs Ag positivity of the siblings (59%) in this group had been significantly higher ($p<0.0001$) than controls.

The scroepidemiological data from the relatives of index cases with CH arc shown in Table 4. The ratio of HBs Ag positivity (8%) of spouses was not significantly different than controls ($p=0.74$). Similarly there was no significant difference between the ratio of HBs Ag positivity in daughters and in controls. On the other hand, this ratio was significantly higher in sons (28%) and siblings (50%) of the index cases with chronic hepatitis ($p<0.005$ and $p=0.05$ respectively) compared to that of controls.

The overall comparison of the ratio of transmission among controls, healthy carriers and cases with CH is presented in Table 5. The ratios of HBs Ag positivity among spouses of two groups and the controls were not significantly different than each others ($p>0.05$). Although the overall transmission

too

Table 3. Data from relatives of healthy index cases

Relatives of 1 lealthy Carriers	HBs A g (+) n (%)	Ami-HBs (+) n (%)	Anti HBc lgG (+) n (%)	Sero (+) n (%)	Sero (-) n (%)	Total
Spouses	3 (4)	34 (47)	14 (19)	51 (70)	21 (30)	72
Children						
Male	11 (17)	10 (15)	19 (29)	40 (62)	24 (38)	64
Female	2 (4)	10 (18)	15 (27)	27 (48)	29 (52)	56
Children total	13 (11)	20 (16)	34 (28)	67 (56)	53 (44)	120
Siblings	26 (59)	7 (15)	5 (11)	38 (86)	6 (14)	44
Total	42 (17)	61 (25)	53 (22)	156 (66)	80 (34)	236

Table 4. Data from relatives of index cases with chronic hepatitis

Relatives of Index Cases With CFI	HBs Ag (+) n (%)	AntiHBs (+) n (%)	AntiHBe IgG (+) n (%)	Sero (+) n (%)	Sero (-) n (%)	Total
Spouses	4 (9)	24 (51)	10 (21)	38 (81)	9 (19)	47
Children						
Male-	8 (28)	6 (21)	6 (21)	20 (72)	8 (28)	28
Female	4 (11)	6 (17)	8 (23)	18 (53)	16 (47)	44
Children total	12 (19)	12 (19)	14 (22)	38 (62)	24 (38)	62
Siblings	8 (50)	3 (18)	3 (18)	14 (88)	2 (12)	16
Total	24 (19)	39 (31)	27 (22)	90 (72)	35 (28)	125

rates for index cases with CH compared to healthy carriers were not statistically significant (p=0.85), there were significantly higher number of relatives having chronic liver disease (15 of 24; 62.5%) in the index group with CH than in the healthy earners (12 of 41; 29%) (p<0.05). The overall HBs Ag positivity rates (Chart 1) among relatives of both healthy carriers and cases with CH were significantly higher than controls (p=0.005). The seropositivity among relatives of index cases with CH, the relatives of the healthy carriers and the controls was not different (p=0.43) The children of cases with CH demonstrated a significantly higher ratio of HBs Ag positivity than controls (p=0.04). There was no difference in the HBs Ag positivity between the relatives of healthy carriers and those with CH (p=0.45). HBe Ag positivity in index cases with CH was 24% and it was 19% in healthy carriers (p=0.70).

Regarding the distribution of transmission rate with the advancement of age groups (Chart 2). We noticed that the most dramatic increase was seen between 5-20 years age group.

Discussion

It has been estimated that two billion people have been infected with HBV worldwide and 400 millions of them have become carrier (8). The same numbers for Turkey are 30 millions and 4 million respectively. Meanwhile, Turkey takes place among the countries of moderate endemicity with a ratio of 5-6‰ for carrier state (9). Considering these numbers, it is obvious that HBV is still an important health problem in Turkey and worldwide as well.

After routine screening of blood products for HBV, the remaining important modes for the transmission of this virus have become vertical and horizontal ways. For vertical transmission. HBe Ag positivity of mother has an impact in the transmission of the virus to the newborn. The rate of transmission from a HBe Ag negative mother was found to be 10-40% with 40-70% of chronicity while the same figures from HBe Ag positive mothers were 70-90% for both transmission and chronicity (10).

Table 5. The viral markers among the relatives of healthy carriers, cases with CH and controls

	HBs Ag positivity	The ratio of Scropositivity
Spouses		
Control	(7/100) %7	(65/100) %65
Healthy carriers	(3/72) %4	(51/72) %70
Index cases with CH	(4/47) %9	(38/47) %81
P	0.60	0.14
Children		
Control	(7/100) %7	(65/100) %65
Healthy carriers	(13/120) %11	(67/120) %56
Index cases with CH	(12/62) %19*	(38/62) %62
P	0.04	0.25
Siblings		
Control	(7/100) %7*	(65/100) %65*
Healthy carriers	(26/44) %59	(38/44) %86
Index eases with CH	(8/16) %50	(14/16) %88
P	0.001	0.01
Total		
Control	(7/100) %7*	(65/100) %65
Healthy carriers	(42/236) %17	(156/236) %66
Index cases with CH	(24/125) %19	(90/125) %72*
P	0.005	0.01

*p <0.05

Evidence for horizontal transmission has been evolving in recent years both in foreign and national literature. The virus has been detected in various body fluids; it has been proven to rise the counts in semen, sera and saliva enough to be in infective capacity (11). Since the virus can resist to the environmental conditions up to one week, the transmission is possible during this period (12). Local skin infections, eczema, bites, shared razors and toothbrushes are the means for horizontal transmission. It is very important that one should avoid these factors as much as possible in a family having an index case (13, 14). In a large sample sized study, it was reported that the behaviors most strongly associated with prevalence of HBV were sharing of bath towels, sharing of chewing gum or partially eaten candies, sharing of dental cleaning materials, and biting of fingernails in conjunction with scratching the backs of carriers (15).

In one study from Turkey done with hemodialysis patients, the rate of HBs Ag positivity in the relatives of hemodialysis patients was found to be 11%, while it was 6.6% for controls. The authors attributed this transmission mostly to the horizontal relations (16). It was reported that horizontal transmission occurred mostly between the ages of 6 month-6 years and it was a common way of transmission in communities with a low socio-economic status (17). We also noticed in our study that the rate of HBs Ag positivity had reached a steady state of 14% between the ages of 20-40 years. Thinking of approximately 75 % seroposivity, it seemed that most of the population met the virus until that age. In a study, it was found that the detected scropositivity for HBV in a child care center had been 25% in 0-6 age group, while it had been 63% in 7-12 years and 60% in 13-22 years age groups (18). Again, it was noticed in this study that the rate of transmission at 7-12 years age group had already risen to the same rate as the adults. It could be speculated that duration of seven years would be enough for horizontal mode of transmission to show its full-blown effect. Until this age group, we believe that many of the people met the virus.

The efficiency of horizontal transmission among Turkish children was also supported by a study of Back and et al (19). In that study, the rates of HBs Ag positivity of Turkish children born in

Sweden to earner mothers were compared to the rates of those born in Turkey, lived sometimes and immigrated to Sweden, The later group had an HBs Ag positivity of 6% while those born in Sweden were seronegative. All the children involved in the study had HBs Ag positive mothers.

We suggest for a various reasons that the horizontal way is the most important and effective mode for HBV transmission in Turkey. First of all, we found that the highest HBs Ag positivity in siblings of index cases (41%). Secondly, the HBs Ag positivity displayed the strongest incline during the ages of 5-20 years. In this age group, considering in Turkey the low incidence rate of homosexuality, drug abuse, the absence of marriages below those ages we could explain the peak in the transmission rate only by the horizontal mode. The horizontal transmission was said to be the main mode for infectivity in the foreign literature as well (13,20). In a study done in USA, similar results were obtained. One hundred nineteen index cases and their 449 relatives involved in that study. They found the carnage rate of HBs Ag was 0.8% in controls, 6.7% among relatives, 3.4% in spouses and 19.7% among siblings (21). In another study supporting horizontal transmission, it was reported that a child HBs Ag negative at birth from an index mother would have the chance of being infected of 40% by the age of 5 years (22).

This was the study executed with one of the largest sample size in Turkey by far, dealing with the horizontal transmission, and also investigating the effect of liver disease status on horizontal transmission. Generally we obtained parallel results with the literature. But we also detected some striking features as well.

In our study, comparing with girls (7%) the sons posses a higher risk (18%) to be infected with the virus in both cases whether the index case was mother or the father. In a study this ratio was found to be 6 times higher for sons (8,20). These might be attributed to that boys play much more vigorous games so that they exposed to more open and exudative wounds.

We found that there was no difference between the rates of HBV transmission of spouses of index cases with CH and those healthy carriers and controls. Palabiyikoglu and colleagues declared similar results with respect to transmission between spouses (23). This might be explained that spouses acquire the virus in adulthood when people are more resistant to infections.

We have noticed that the rates of HBs Ag positivity in children of mother index cases were 25%, while it was 5% for those of father index cases. This finding indicates that horizontal plus vertical modes of mothers are more effective than only horizontal mode of fathers ($p<0.01$). In the same manner, the seroprevalence rate in children of mother index cases (75%) was higher significantly than that (47%) of father index cases ($p<0.01$). The important role of mother index cases in transmission of HBV in our country was reported in several other studies as well (24,25).

In our study, we found that the relatives of index cases with CH or healthy carriers were under higher risk for HBV infection. Furthermore if index cases had CH, their HBV positive relatives had more chance to develop chronic liver damage. This finding was supported in a study by Habu and colleagues (26). Subjects with HBV in a family with members who had normal liver function and who were seronegative for HBcAg were less likely to develop chronic hepatitis B than such subjects in a family with members having chronic liver damage. Thus the presence of intrafamilial clustering might affect the chance of subjects with HBV developing liver damage. The mode of infection and some genetic factors in the infected subjects seem to contribute to the natural history of the infection. Depending on the age they were exposed, they could clear the virus or become carrier or develop hepatitis. Those met the virus at an early age are candidate to be affected more severely. That is why they should be taken into consideration first while planning a national vaccine program.

We observed that the relatives of both patients with CH and healthy carriers were significantly more prone to be infected by HBV and to become carriers, compared to controls (19%. 17% and 7%) respectively). But there were no significant difference between the ratio of HBs Ag positive relatives of the patients with CH and healthy carriers. This may be explained by the fact that patients with CH would be much more symptomatic and in turn be noticed by the relatives earlier so that they would

have more chance to take some precautions for the infection. On the contrary, the relatives of a healthy carrier would live longer under risk until they recognized the situation of the index case.

Conclusively we suggest that horizontal mode is the most effective way in transmission of H B V in Turkey. At first, the siblings and secondarily the children of the index cases are under significant risk. It is especially of importance to know that the chance of developing chronic liver disease is higher if the index case has chronic hepatitis. Up to the age of 20 years, HBs Ag positivity reaches a steady state level (14%) m Turkey. Considering the relatively higher prevalence rates of H B V and thus its overall economic cost on the country, the execution of strict national vaccination program should be recommended strongly. Until a mass vaccination program is taken into effect, siblings and children of index cases should be the first groups to be included in a limited vaccination program. Meanwhile we want to point out that further studies aimed at describing the factors that limit the upper threshold of HBs Ag positivity (that is 14% for Turkey) rate are needed.

REFERENCES

1. Özdemir S, Sosyal T, Senturk H, Bczgal M, Sonsuz A, Göksel S et al. Primary liver tumors in Turkey. Gastroenteroloji (Turkey) 1993; 4: 397-8.
2. Aygcnccl SG, Akean Y. Hepatoselliiler karsinomlu 50 olgunun değerlendirilmesi. Türkiye Tıp Dergisi 1998; 5: 66-7.
3. Beasley RP. Hepatitis B Virus. The major etiology of hepatocellular earcinoma. Canecr 1988; 61; 1942-56.
4. Mistik R. Balık 1. Tiirkiyede viral hematitlerin epidemiolojisi; Bir mctaa"iliz. In: Kılıçturgay K. Ed. Viral Hepatit 98. Viral Hepatitle Savaşım Derneği Yayını, Bursa, 1998: 9-40.
5. Çakaloğlu Y. Ökten A, Yalçın S. Türkiye'de Hepatit B virüsü seroepidemiolojisi (taşıyıcılık-seropozitiflik prevalansı). T Klin üastroenterohepatoloji 1990; 1: 49-53.
6. Türkdoğan M K , Berktaş M, Tuncer I, Akdeniz H, Hekim H, Mete R, ve ark. Van yöresinde viral hepatit B seroepidemıyolojisi. Viral Hepatit Dergisi 1996; 1: 38-9.
7. Szumuness W, Marley EJ. İkram H, Stevens CE. Soeiodemographic aspects of the epidemiology of Hepatitis B. In: Vyas C N , Cohen SN, Schimed R, eds. Viral hepatitis. Philadelphia: Franklin Institude Press, 1978: 297-320.
8. Sherlock S. Dooley J. Viral hepatitis. In ed. Sherlock S, Dooley J. Diseases of the Liver and Biliary System. 9th ed. Blackvvell Scientific Publications, Oxford, 1993: 260-80.
9. Badıır S. Ülkemizde viral hepatitlerin durumu (Viral Hepatitle Savaşını Derneği Raporu). Ed. K. Kılıçturgay. Viral Hepatit '94. VHSD Nobel Yayıncılık 1994; 15-37?
10. Xu Z Y , Liu C B , Francis DP, Purcell RII. Gun Z L , Duan SC, et al. Prevention of perinatal acquisation of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double blind placebo-controlled and comperative trial. Pediatrics 1985; 76:713-8.
11. Shikata T, Karasaw T. Abe K, Uzawa T, Suzuki H, Oda T. et al. Hepatitis B e antigen and infectivity of hepatitis B virus. J Infect Dis 1977; 136:571-6.
12. Bond WW, Favcro MS, Petersen NJ. Gravellc CRr. Ebert JW Maynard JE. Survival of hepatitis B virus after drying and storage for one week. Lancet 1981; 1(8219): 550-1.
13. Dhorje SP, Pavri K M , Prasad SR, Sehgal A, Phule D M . Horizontal transmission of hepatitis B virus infection in household contacts, Pune, India. J Med Virol 1985; 16:183-9.
14. Shapiro NC. Transmission of hepatitis viruses. Ann Intern Med 1994; 120:82-4.
15. Martinson FE, Weigle K A , Royce RA. Weber DJ, Suchindran C M , Lemon SM, Am J. Risk factors for horizontal transmission of hepatitis B vims in a rural district in Ghana. Epidemiol 1998; 147: 478-87.
16. Yazanel O, Canoruç F, Kaplan A. Hemodializ hastaları vc aile bireylerinde hepatit B, C ve HIV serolojik işaretleri. Turk J Gastroenterol 1995; 6:335-58.
17. Uc A, Ozsoylu S. Age-prevelance of HBsAg positivity in children seen at Hacettepe Children's hospital. Turk J Med Res 1992; 10:264-6.
18. Mıkla Ş, Fıçıcıoğlu C, Midilli K, Çam H, Ozdemir S, Aydın A, et al.Istanbul bölgesi Çocuk Esirgeme ve Çocuk Yetiştirme Yurtlarında hepatitis B virus infeksiyonu seroepidemiyolojisi. Turk J Gastroenterol 1995; 6:414-6.
19. Back E, Danielsson D, Lunquist B. Difference in prevalance of hepatitis B markers in children bom either in Sweden or in Turkey of Assyrian immigrants. Scand J Infect Dis 1985; 17:147-50.
20. Davis L G , Weber DJ, Stanley M L . Horizontal transmission of hepatitis B virus. Lancet 1989; 1(8643): 889-93.
21. Szumuness W, Prince A M , Hırsch R L , Brotman B. Familial clustering of hepatitis B infection. N Eng J Med 1973; 29:1162-66.
22. Beasley RP, Hwang LY. Postnatal infectivity of hepatitis B surface antigen-carrier mothers. J Infect Dis 1987; 147:185-90.
23. Palabıyıkoğlu 1, Kocagül A, Durmaz NO, Acar N , Erbas O. Hepatit B virüsünün aile içi geçişi. Gastroenteroloji (Turkey) 1994; 5:603-6.
24. Ateş BJ, Dolar M E . Karahan M. Caner E. Aile içinde hepatit B virüsünün geçiş yolları. Gastroenteroloji (Turkey) 1992;3:15-8.
25. isler M, Akın D, Ertem S, Tekesin O. Hepatit B virüs infeksiyonun aile içi geçişinin araştırılması. XI. Ulusal Türk Gastoenteroloji Kongresi 6-9 Kasım. Antalya 1994; 365.
26. Habu D, Monna T, Saitoh S, Kuroki T, Kobayashi K. Relationship between the condition of the liver in patients and carriers with hepatitis B virus (HBV") and whether there is intrafamilial clustering of HBV. Nippon Shokakibyo Gakkai Zasshi 1991 ;88(8): 1545-53.