Relationship Between Age and Response to Immunization of Family Members of Chronic Hepatitis B Patients

Kronik Hepatit B Olgularının Aile İçi Bireylerinde Aşılamaya Alınan Cevabın Yaşla İlgisinin İncelenmesi

Alpay ÇAKMAK, MD[a]
Fatma SIRMATEL, MD[b]

Departments of [a]Pediatrics, [b]Clinical Bacteriology and Infectious Diseases, Harran University Faculty of Medicine, Şanlıurfa

Geliş Tarihi/*Received:* 27.05.2008
Kabul Tarihi/*Accepted:* 18.02.2009

Yazışma Adresi/*Correspondence:*
Alpay ÇAKMAK, MD
Harran University Faculty of Medicine, Department of Pediatrics, Şanlıurfa, TÜRKİYE/TURKEY
alpaycakmak@gmail.com

ABSTRACT Objective: First-degree relatives of patients with histological and serological diagnosis of chronic hepatitis B should be immunized; however, the response to immunization varies according to age. In this study, we evaluated the response to immunization in siblings of chronic hepatitis B patients. **Material and Methods:** HbsAg(-) family members of 100 index patients with chronic hepatitis B virus (HBV) were immunized with HBV vaccine at 0, 1, and 6 months, and were divided into three groups according to their ages, as follows: group 1, 0-10 years old; group 2, 11-20 years; and group 3, >20 years. After each vaccination, the responses to immunization, determined by anti-HBs positivity, were compared between the three age groups and were evaluated by the SPSS 12 computer program. **Results:** The study group comprised 205 cases 1-60 years old (mean 20.26 ± 12.18). The antibody responses at month 0, 1, and 6 were 4.3%, 66.7%, and 100% in group 1; 3.4%, 31.5%, and 85.6% in group 2; and 1.4%, 38.2%, and 74.6% in group 3, respectively. According to the Mantel-Haenszel chi-square test , the immune response of patients below 20 years of age was significantly higher than the response of those above 20 (Mantel-Haenszel chi-square= 14.54, p< 0.00013). **Conclusion:** Immunization in the first decade of life is important to prevent the spread of HBV infection. First-degree relatives of chronic HBV patients must be vaccinated and the immune response must be checked.

Key Words: Hepatitis B, chronic; vaccination; immunity, mucosal; hepatitis B antibodies

ÖZET Amaç: Histolojik ve serolojik olarak kronik hepatit B virüsü (HBV) tanısı almış olguların birinci derece yakınları, korunmak amacıyla aşılanmalıdır. Aşının cevabı yaşa göre değişmektedir. Bu sunumda kronik HBV tanısı alan hastaların kardeşlerinin aşıya karşı verdikleri cevabı değerlendirdik. **Gereç ve Yöntemler:** Kronik HBV tanısı almış toplam 100 indeks olgunun HBsAg negatif olan aile bireyleri, üç doz HBV aşısı ile 0, 1 ve 6. aylarda aşılandı. Yaş grubuna göre denekler üç grupta toplandı. Grup 1'in yaş aralığı 0-10, grup 2'nin yaş aralığı 11-20 ve grup 3'ün yaş aralığı 20 ve üzerindeydi. Her aşılamadan sonra anti-HBs pozitifliğine (>10 i.ü/mL) bakılarak, aşıya verilen cevap, yaş grupları arasında karşılaştırıldı. Yaş ve aşılamaya verilen cevap SPSS 12 bilgisayar ortamında istatistiksel olarak değerlendirildi. **Bulgular:** Toplam 205 olgunun yaşları 1-60 (ortalama 20.26 ± 12.18) arasındaydı. Aylara göre anti-HBs cevabı Grup 1'de %4.3, %66.7 ve %100; grup 2'de %3.4, %31.5 ve %85.6; grup 3'te ise %1.4, %38.2, %74.6 olarak bulundu. Mantel-Haenszel ki-kare testine göre erken yaşlarda aşıya cevap 20 yaş ve üstüne göre anlamlı ölçüde daha yüksek bulundu (Mantel-Haenszel ki-kare= 14.54, p< 0.00013). **Sonuç:** HBV enfeksiyonunun bulaşını önlemek için ilk dekadlarda aşılanmak daha önemlidir. Kronik HBV olgularının birinci derece yakınları mutlaka aşılanmalı ve aşı cevabı kontrol edilmelidir.

Anahtar Kelimeler: Kronik hepatit B; aşılama; antikor cevabı; hepatit B antikoru

Turkiye Klinikleri J Med Sci 2009;29(6):1491-5

Chronic hepatitis B virus (HBV) infection is present in 5% of the world population. The probabilities of chronic HBV development in adults and newborns are 5-10% and >90%, respectively.[1] The

seroprevalence of HBsAg and anti-HBs in the normal population in Turkey ranges between 3.9–12.5% and 20.6-52.3%, respectively.[1]

HBV is primarily spread through four pathways: parenteral contact with infected blood or body secretions, transmission from an infected mother to the newborn (vertical), sexual transmission, and non-sexual close contact with infected people (horizontal).[2,3] Horizontal transmission is considered in the absence of identified parenteral, sexual, or perinatal contact. The risk groups for horizontal transmission include those who have a low socioeconomic level with a crowded living environment and poor standards of hygiene, the mentally disabled (because of abnormal social relations), children attending kindergartens, and individuals living in dormitories.[2] More infections have been detected in families in which chronic HBV infection is present than in the normal population, and horizontal transmission of HBV is most common in children and young adults.[3-5] When HBV infection develops in childhood, 90% of the cases become chronic. Immunization is the best way to protect against HBV infection. In Turkey, because the development of an immune response is better in childhood, the HBV vaccine is routinely administered during the first year of life.

In this study, we investigated the immunization levels and age-related immune responses of the family members of chronic HBV patients after vaccination.

MATERIAL AND METHODS

HBsAg (-) family members of 100 index patients with chronic HBV were immunized with HBV vaccine at 0, 1, and 6 months. Anti-HBs concentrations were measured and were reported in IU/mL using the World Health Organization (WHO) international reference standard. The lower limit of detection for the enzyme-linked immunosorbent assay (ELISA) was 5 IU/mL. Patients with anti-HBs levels ≥10 IU/mL were considered responsive. Negative serology for HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV), normal liver enzyme levels, and the absence of any underlying chronic, metabolic, or immunosuppressive disease were required in all cases. The subjects were divided into three groups according to their ages, as follows: group 1, 0-10 years old; group 2, 11-20 years old; and group 3, >20 years old. Hepatitis B vaccine (20 μg/mL) was administered at 0, 1, and 6 months. After each vaccination, the responses to the immunization were evaluated by serological testing for anti-HBs with a micro-ELISA method, and the results were compared between the age groups.

Inclusion criteria were verified by reviewing medical records. Persons were excluded from participation if they had received a dose of any hepatitis B vaccine. Additional exclusion criteria were: history of allergic reaction after receiving vaccine or hypersensitivity to any component of the hepatitis B vaccine used for the booster dose; history of HBV infection; existence of disease known to affect the immune system (e.g., human immunodeficiency virus infection, acquired immunodeficiency syndrome, severe combined immunodeficiency, chronic renal disease, cancer), current or recent (within 6 months) receipt of immunomodulatory therapy (e.g., systemic corticosteroids, chemotherapy) or blood products. Also excluded were those with alcohol, tobacco or other substance dependency and those who were either obese or malnourished. Study staff administered a questionnaire to the participants and their parents/guardians to collect demographic information and to verify eligibility. Written informed consent was obtained from the participants and their parents. The study protocol was approved by the Local Ethics Committee.

Statistical Analysis

Data were analyzed using the SPSS® for Windows computing program (Version 11.5). The values were expressed as mean ± SD for the patients. The differences between the age groups were analyzed by Mantel-Haenszel chi-square test. Statistical significance was defined for p values of less than 0.05.

RESULTS

A total of 205 cases, 100 (48.7%) women and 105 (51.3%) men, were included in the study. They

were 1-60 years old (mean 20.26 ± 12.18) and 178 (86.7%) cases were anti-HBs positive. Anti-HBs seropositivity seemed to decrease significantly with increasing age (Table 1). According to the Mantel-Haenszel chi-square test, the immune response of patients below 20 years of age was significantly higher than the responses of those above 20 (Mantel-Haenszel chi square=14.54, p< 0.00013).

DISCUSSION

HBV infection is prevalent worldwide and is associated with serious complications when it becomes chronic. Humans are the major reservoir of HBV, and Turkey is located in an intermediately endemic area for HBV infection. Therefore, the probability of exposure to HBV in Turkey is 20-60%.[2] The seroprevalence of HBsAg and anti-HBs in the general population of Turkey is 3.9-12.5% and 20.6-52.3%, respectively.[6] Early seroprotection is desirable for people at high risk of exposure and sometimes an accelerated vaccination schedule seems to provide a good response.[7,8] Immunization of susceptible persons against hepatitis B is necessary to prevent not only acute disease but also the carrier and chronic states of hepatitis B infection. The intrafamilial transmission of HBV infection is 3.3 times higher in families with chronic HBV patients than it is in the normal population.[1,4] Horizontal transmission is important in countries where HBV is endemic.[3] Parenteral transmission is the main pathway of HBV in low endemic countries, but non-parenteral transmission is more common in mid-endemic countries such as Turkey.[2] Thakur et al investigated the intrafamilial transmission of chronic liver disease related to HBV and reported the rates of horizontal–vertical, horizontal, and vertical transmission as 50%, 17%, and 33%, respectively.[5] Goth et al reported that the HBsAg prevalence rate in asymptomatic household members was 20% compared with 6% in the general population.[4] Chakravartya et al suggested that intrafamilial aggregation in Eastern Indian families indicated that the HBsAg carrier rate seemed to peak by the age of 5 years.[9]

TABLE 1: Anti-HBs positivity at months 0, 1, and 6, according to the age groups.

Months Age (years)	0	1	6
0-10	4.3%	66.7%	100%
11-20	3.4%	31.5%	85.6%
20 ≥	1.4%	38.2%	74.6%
p	0.633	< 0.00013	< 0.024

The groups were evaluated by the Mantel-Haenszel chi-square test. A p-value < 0.05 was considered significant.

Doğancı et al investigated horizontal transmission in children with chronic HBV infection and found HBsAg positivity in 38% of the fathers and 23% of the mothers of 302 children with chronic HBV infection.[3] They also reported a rise in HBV infection with increasing age and suggested that immunization programs were necessary not only in newborns but also in children to prevent horizontal transmission. Intrafamilial transmission is associated with socioeconomic and hygienic conditions and with the length of time of intrafamilial contact. Immunization of individuals at risk for HBV is necessary to prevent not only acute disease but also chronic HBV infection, and to diminish intrafamilial transmission and the spread of HBV. Clarifying the route of transmission is important for choosing the target population for immunization in countries where HBV is endemic.

A hepatitis B vaccine is in the immunization program of most countries and was shown to decrease the rate of chronic hepatitis B infection.[10] In a study of the immune responses after immunization in different populations, Chowdhury et al found 100% seropositivity 30 days after the first vaccine dose.[11] Chiaramonte et al reported a similar ratio of 99.6% at first month.[12] Euler et al found an antibody positivity of 97% in the immunized newborns of 879 mothers with hepatitis B; Staff et al studied 113 family members of 52 HBV patients and reported that 22 had hepatitis B, 67 were immunized and 17 were not.[13,14]

The anti-HBs response to hepatitis B vaccine in patients who are >40 years of age, smokers, males, and immunodeficient has been investigated.[15] Leroy et al reported that the seropositivity rate in 77 chronic HCV patients was 63.6% after immunization, but it was 93.9% in 231 healthy adult controls.[16] Craxi A, et al investigated HBV

vaccination in relatives of chronic HBV patients and found that low responders to the vaccine were mostly among parents and spouses.[17] Wiedman et al immunized 59 chronic hepatitis C patients with a mean age of 42 for hepatitis B; seropositivity in the study and control groups was 69% and 91%, respectively.[18] In a study of 100 chemotherapy patients, 1-16 years old, Emir et al found 72% seropositivity.[19] Das et al found 85.3% seropositivity after hepatitis immunization in 102 volunteers >40 years of age.[20] In our study, the antibody response was higher in children compared to adults.

A review of the literature revealed that the anti-HBs titer was positive after immunization in 95% of babies born to HBsAg-positive mothers. Vranckx et al concluded that the seropositivity of babies born to HBeAg-positive and negative mothers was 85% and 100% after immunization, respectively.[21] In a study of 1436 patients, after three doses of vaccination, McMahon et al found anti-HBs positivity in 94%.[10] In this same study, the anti-HBs positivity values in group 1 (6 months-19 years old), group 2 (20-49 years), and group 3 (>50 years old) were 99%, 91%, and 68%, respectively. Adwan et al detected 100% anti-HBs seropositivity after the immunization of 161 family members of hepatitis B carriers.[22] Zhang et al reported that the protection after immunization in healthy adults 18–50 years old was 82.7%.[23] Panhotra et al detected 92.2% seropositivity after the immunization of 1302 healthy individuals.[24] Pazdiora et al found 78.3% seropositivity in 410 family members, 0-89 years old, who were in close contact with 453 hepatitis B carriers (253 males, 200 females).[25] In our study, where the participants aged 1-60 years (mean 20.6), the anti-HBs seropositivity after immunization was 86.7%. The high anti-HBs seropositivity may be due to the low mean age level. We investigated the anti-HBs responses of the family members of individuals with chronic hepatitis B and found that, after the third dose of vaccine, the seropositivity values in the 0-10, 11-20, and >20 years age groups were 100%, 85.6%, and 74.6%, respectively. We found a significant decrease in anti-HBs seropositivity with increasing age that was consistent with the data in the literature.

In studies of healthy children the seroconversion rate after 3 vaccinations was 100%, 90.8% and 94%.[26-28] The antibody response rate of the group not in contact with chronic hepatitis B patients and the antibody response in our study group of children seemed to be similar.

The seroconversion rate was reported 81-88% in adults after three vaccinations of two different vaccines.[29] Another study reported a seroconversion rate of 71-82% in adults after three doses of two different vaccines.[30] The protection rate was 88-98% in another study where adults received three doses of two different vaccines.[31] The seroconversion rate in the adult group was similar to that in our study group. The immunization responses were similar in the healthy group and in those who had familial contact with chronic hepatitis B and the seroconversion rate decreased as age increased.

The transmission of HBV infection in intermediately endemic areas like Turkey occurs more through non-parenteral pathways. HBV infection at birth or in early childhood is associated with a high risk of developing chronic HBV infection. Starting vaccination at birth prevents perinatal and early childhood acquisition of HBV infection and is expected to provide protection throughout adolescence and young adulthood.[32,33]

In antibody-negative family members of HBV patients, the immune response to vaccination is better in childhood.

CONCLUSION

In addition to genetic factors, long-term virus contact and a low socioeconomic status has an effect on the chronic nature of HBV infection. Intrafamilial close contact, in particular, and inadequate hygienic conditions may facilitate the spread of HBV infection. To prevent HBV infection and to decrease the number of carriers, HBV immunization starting from childhood is necessary. Free vaccination should be administered to HBsAg (+) family members. Through this protocol, expensive tests and treatment modalities, in addition to workforce losses, may be significantly decreased.

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