Research Article

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Investigation of Hepatitis B Surface Antibody Levels in Adults with Routine Hepatitis B Vaccination in Childhood

Çocukluk Döneminde Rutin Hepatit B Aşılaması Yapılan Erişkinlerde Hepatit B Yüzey Antikoru Düzeylerinin Araştırılması

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ABSTRACT

Objectives: Recombinant hepatitis B vaccines provide effective and long-term protection. It is not well known whether it reaches protective levels of antibodies in adulthood. In this study, it was aimed to investigate hepatitis B surface antibody (anti-HBs) levels in adults who received routine hepatitis B vaccination in the newborn period and to reveal its change with age.

Materials and Methods: The hepatitis B surface antigen (HBsAg) and anti-HBs levels of those who applied to our hospital's health board between 01.01.2017 and 31.12.2021 and were at least 18 years old were evaluated by retrospectively scanned from the board records. Those with anti-HB titers above 10 mIU/mL were considered to have a protective antibody level.

Results: The mean age was 20.0±1.5 (18-24). Anti-HBs result was found to be above 10 IU in 1,691 (70.8%) of 2,395 people who were HBsAg negative. In the study, the rate of those who were found to be anti-HBs negative at the age of 18 and 19 was significantly higher than the older age groups, and those with more than 1000 mIU/mL in the 23 and 24 age groups compared to the younger age groups ($p<0.001$). A significant correlation was found between age and anti-HBs levels ($p<0.001$; $r=0.219$).

Conclusion: Our study is one of the rare studies measuring the level of hepatitis B vaccine protection for up to 24 years. Our findings demonstrated that the antibody level was found to be above 10 IU in 71% of adults included in the routine hepatitis B vaccination program after birth, and the antibody level did not decrease but rather increased with increasing age.

Keywords: HBV, hepatitis B vaccine, anti-HBs titer

ÖZ

Amaç: Rekombinant hepatit B aşıları etkili ve uzun süreli koruyuculuk sağlamaktadır. Erişkin çağda rutin olarak koruyucu düzeyde antikor seviyelerine ulaşıp ulaşmadığı iyi bilinmemektedir. Bu çalışmada, ülkemizde yenidoğan döneminde rutin hepatit B aşılaması yapılan yetişkinlerde hepatit B yüzey antikoru (anti-HBs) düzeylerinin ve bu düzeylerin yaşla ilişkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Hastanemiz sağlık kuruluna 01.01.2017-31.12.2021 tarihleri arasında başvuran ve en az 18 yaşında olanların hepatit B yüzey antijeni (HBsAg) ve anti-HBs düzeyleri kurul kayıtlarından geriye doğru taranarak değerlendirilmiştir. Anti-HBs titreleri 10 mIU/mL'nin üzerinde olanlar koruyucu antikor düzeyine sahip kabul edilmiştir.

Bulgular: Ortalama yaşı 20,0±1,5 (18-24) idi. HBsAg negatif olan 2.395 kişinin 1.691'inin (%70,8) anti-HBs sonucunun 10 IU'nin üzerinde bulundu. Çalışmada 18 ve 19 yaşında olanlarda anti-HBs negatif saptananların oranı daha büyük yaş gruplarına göre, 23 ve 24 yaş gruplarında >1000 mIU/mL olanların olanı daha küçük yaş gruplarına göre anlamlı yüksekti ($p<0,001$). Yaş ve anti-HBs düzeyleri arasında anlamlı korelasyon saptandı ($p<0,001$; $r=0,219$).

Sonuç: Çalışmamız 24 yıla varan hepatit B aşı koruyuculuğu düzeyini ölçen nadir çalışmalardandır. Bulgularımız doğumdan sonra rutin hepatit B aşılama programına dahil olan erişkinlerin %71'inde antikor seviyesinin 10 IU'nun üzerinde saptandığı, yaş artıkça antikor düzeyinin azalmadığı aksine artığını göstermiştir.

Anahtar Kelimeler: HBV, hepatit B aşısı, anti-HBs titre

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Introduction

Hepatitis B virus (HBV) is a DNA virus that can cause serious disease in the liver. If an individual is infected with HBV, he/she may carry the virus asymptomatically for a lifetime, develop chronic liver disease, liver cirrhosis, liver cancer, and even progress to liver failure, which may result in death. In the latter case, liver transplantation may be required (1,2,3).

Today, HBV infection is a vaccine-preventable infectious disease. Recombinant hepatitis B vaccines developed against HBV provide effective and long-term protection. In many countries around the world, three doses of hepatitis B vaccine were included in the routine vaccination program in infancy in the 1990s. By ensuring that the first dose is given immediately after birth, protection against hepatitis B infection that may be present in the mother is provided (4,5,6,7).

Serum anti-HB titers decrease over the years after vaccination. However, it is stated that protection against HBV infection continues as long as this decrease does not decrease below the level of 10 mIU/mL. In the case the titer falls below this level, a booster dose of vaccine is recommended. In some patients who are considered to be at risk for hepatitis B infection due to some underlying diseases, it has been stated that antibody titers should be kept above 10 mIU/mL (4,5).

In most studies, antibody levels decrease with age or with the time elapsed after vaccination (5,8,9,10). However, while it has been about 20 years since the introduction of vaccination programs worldwide, there are very few studies investigating antibody and protection levels in individuals with 20 years of time elapsed since their infancy vaccination (11,12,13,14,15). Therefore, it is not well known whether it reaches protective levels of antibodies in adulthood. In this study, it was aimed to investigate anti-HB levels in adults who received routine hepatitis B vaccination in the newborn period and to reveal its change with age.

Materials and Methods

Approval for the study was obtained from the Samsun University, Clinical Research Ethics Committee (approval number: 2023/4/4, date: 01.03.2023).

Participants and Tests

Hepatitis B surface antigen (HBsAg) and anti-HBs levels of patients who were at least 18 years old and applied to our hospital's health board between 01.01.2017 and 31.12.2021 were evaluated retrospectively. Anti-HB titers that were above 10 mIU/mL using the ELISA method had a protective antibody level and were considered immune to the vaccine. All data of the participants were retrospectively obtained from the board records.

Statistical Analysis

The sample size of the study was calculated by power analysis using G-Power (version 3.1.9.6, Franz Faul, Universität Kiel, Germany). Effect size 0.34; the type1 error was 0.05 and the test power was taken as 0.99 and the sample size was calculated as 554, however 2,396 participants whose data were available were included in the study.

Since ELISA results for anti-HBs values above 1000 mIU/mL were reported as more than 1000 in the study, mean values for age groups could not be calculated and compared. Instead, the median values were compared. While preparing the box plot graph, all values more than 1000 mIU/mL were accepted as 1000 mIU/mL.

All statistical analyzes in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as numbers and percentages. Comparisons between groups in terms of categorical variables were performed by Pearson's chi-square test. Differences between groups in terms of continuous variables were performed by Kruskal-Wallis test. The relationship between continuous variables was evaluated by Spearman correlation analysis. The results were evaluated within the 95% confidence interval and $p<0.05$ values were considered significant.

Results

The mean age of the participants in the study was 20.0±1.5 (18-24). In the study, seven (0.3%) of 3,402 people who were evaluated for HBsAg had a positive HBsAg test, 1,691 (70.8%) of 2,395 people who were HBsAg negative had a positive anti-HBs result (≥10 IU), and 704 (29.3%) was found to be negative (Table 1).

When anti-HB positivity according to age is examined, it has been shown that as age increases, antibody positivity increases and negativity decreases ($p<0.001$) (Table 2).

When the anti-HBs values were analyzed by grouping, significant differences were found in terms of the distribution of anti-HBs groups according to age groups, according to this, the rate of those with negative results in 18 and 19 years old was higher compared to the older age groups, and those with more than 1000 mIU/mL in the 23 and 24 age groups was significantly higher than the

Table 1. The distribution of HBsAg and anti-HBs results

HBsAg	Anti-HBs	n	%
Positive (n=7)	Negative	3	0.12
	Positive	4	0.18
Negative (n=2395)	Negative	704	29.3
	Positive	1691	70.4

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

Table 2. The distribution of anti-HBs results by age in HBsAg-negative patients

Age	Negative, n (%)	Positive, n (%)	p
18	223 (44.6)	277 (55.4)	<0.001
19	188 (36.2)	332 (63.8)	
20	131 (25.1)	390 (74.9)	
21	100 (22.1)	352 (77.9)	
22	42 (16.0)	220 (84.0)	
23	18 (15.1)	101 (84.9)	
24	2 (9.5)	19 (90.5)	
Total	704 (29.3)	1691 (70.7)	-

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

younger age groups (p<0.001). The rate of negativity and low-level positivity was higher at younger ages, whereas the rate of high-level positivity was higher at older ages. There were no participants in the 23 and 24 age groups with a score of 0. Only 3.8% of the 18-year-olds had more than 1000 mIU/mL levels (Table 3).

When the median anti-HBs levels were analyzed between age groups, it was found that there was an increase in anti-HBs levels with age, accordingly, the median values of 18, 19 and 20 year olds were significantly lower than all other age groups older than them (p<0.001) (Table 4) (Figure 1).

It was found that the mean age was significantly higher in the groups with antibody titers above 100 mIU/mL compared to the groups with antibody titers 10-100 mIU/mL and <10 mIU/mL (p<0.001) (Table 5).

In the correlation analysis, it was found that there was a positive but weak correlation between age and anti-HBs levels (p<0.001; r=0.219).

Discussion

In the 1990s, the hepatitis B vaccine began to be included in the routine vaccination program from birth in many countries around the world. It has been stated that anti-HB levels decrease rapidly in the first year after hepatitis B vaccination in children, but this decrease slows down in the following years. In addition, it has been reported that as long as the anti-HBs level remains above 10 mIU/mL, its protection continues for up to 23 years, and even below this level, protection might still be sustained (4,5,6). In our study, anti-HBs levels were examined in adults who were born after the addition of hepatitis B vaccine to the routine vaccination program in our country and who are up to 24 years old today, and it was observed that antibody levels did not decrease as expected in older patients.

In our study, seven (0.3%) of 3,402 people who were examined for HBsAg were found to be positive for HBsAg. This finding shows that it is important to examine the hepatitis B antigen of mothers during pregnancy because HBV can be transmitted from mother to baby during delivery.

Shakeri et al. (8) showed that 10 years after the hepatitis B vaccine, the protection rate was 96.5%, and Kazemeini and Owlia (16) showed that it was 90%. Floreani et al. (10) found 10-year antibody positivity rates between 81-88% after routine vaccination with two different vaccines. In the study of Qawasmi et al. (9) in which they examined people aged 0-19 years, they found that 37% of the 17-19 age group had a protective level of antibody positivity. The antibody positivity at a protective level 20 years after the first vaccination was reported to be 37% by Bagheri-Jamebozorgi et al. (12); 48% by Lin et al. (13); 49.3% by Fonzo et al. (15); 66.9% by Dini et al. (11); 71.8% by Lu et al. (14). In our study, it was found that anti-HBs was negative in 29.2% of adults who received a routine vaccination program during the neonatal period. This finding shows that despite the routine vaccination program, the protection rate against hepatitis B in the general population is at a very low

Table 3. The distribution of anti-HBs titer groups by age in HBsAg-negative patients

Age	Anti-HBs titres (titers/mL)						Total
	Negative, (0)	Negative, (0.1-9.9)	Positive, (10-19.9)	Positive, (20-99.9)	Positive, (100-1000)	Positive, (>1000)	
18	18 (3.6)	205 (41.0)	63 (12.6)	110 (22)	85 (17.0)	19 (3.8)	500 (100)
19	11 (2.1)	177 (34.0)	58 (11.2)	100 (19.2)	108 (20.8)	66 (12.7)	520 (100)
20	16 (3.1)	115 (22.1)	45 (8.6)	109 (20.9)	144 (27.6)	92 (17.7)	521 (100)
21	18 (4)	82 (18.1)	34 (7.5)	91 (20.1)	149 (33.0)	78 (17.3)	452 (100)
22	2 (0.8)	40 (15.3)	22 (8.4)	56 (21.4)	92 (35.1)	50 (19.1)	262 (100)
23	0 (0)	18 (15.1)	10 (8.4)	28 (23.5)	34 (28.6)	29 (24.4)	119 (100)
24	0 (0)	2 (9.5)	2 (9.5)	5 (23.8)	7 (33.3)	5 (23.8)	21 (100)
Total	65 (2.7)	639 (26.7)	234 (9.8)	499 (20.8)	619 (25.8)	339 (14.2)	2395 (100)

P<0.001. HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

Table 4. Mean and median anti-HBs titer values by age in HBsAg-negative patients

Age	n	Mean ± SD	Median	Minimum	Maximum
18	500	109.3±239.8	**12.750**	0	>1000
19	520	213±346	**25.700**	0	>1000
20	521	290.3±380.3	**67.900**	0	>1000
21	452	310±378.4	102.750	0	>1000
22	262	340.9±384.4	144.350	0	>1000
23	119	358.9±409.2	111.200	0.1	>1000
24	21	352±395.7	166.500	0.2	>1000
Overall	2395	248.9±359.2	46.600	0	>1000

P<0.001. SD: Standard deviation, HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

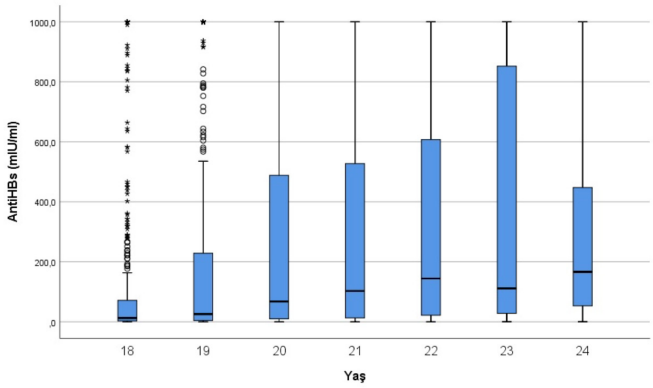

Figure 1. Mean and median anti-HBs titre values by age in HBsAg-negative patients

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

Table 5. Comparison of mean ages between anti-HBs titer groups in HBsAg-negative patients

Anti-HBs, (mIU/mL)	Age, mean ± SD (year)
Negative (0-9.9)	19.4±1.4
Positive (10-100)	19.9±1.5
Positive (>100)	20.4±1.4
Overall	20±1.5

P<0.001. SD: Standard deviation, HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

level of 70%. This finding also suggests that hepatitis vaccines should be tested for protection status after administration and booster doses should be given to those who do not develop antibodies and to those who become negative as antibody levels fall. Moreover, it appears in general that the administration of a booster dose can largely prevent anti-HB negativization in the general population and enhance collective immunity.

In European countries, recurrent hepatitis B vaccine has been recommended in risk groups, and it has been stated that antibody titers above 100 mIU/mL can also provide protection against HBV genotypes not included in the vaccine (17). In our study, the rate of those in the 18-24 age groups with antibodies above 100 mIU/mL was found to be 40%. This finding indicates that the proportion of adults with high levels of protection after vaccination in infancy is acceptable.

Dini et al. (11) found that 20 years after the first vaccination, those with antibody titers above 100 mIU/mL had a significantly higher mean age compared to the groups with a mean age of 10-100 mIU/mL and <10 mIU/mL. Mastrodomenico et al. (18) also found that the mean postvaccination period was significantly higher in individuals with anti-HBs titers >10 mIU/mL compared with those with antibody titer <10 mIU/mL (22.4 years vs. 21.8 years). Similarly, in our study, it was found that those with antibody titers above 100 mIU/mL were found to be significantly higher than the groups with a mean age of 10-100 mIU/mL and <10 mIU/mL. These findings suggest that antibody titers are higher in individuals with older age or with a longer time since hepatitis vaccination. When anti-HB positivity according to age is examined, it has been shown that as age increases, antibody positivity increases and negativity decreases. This finding shows that there is a more significant decrease in the protectiveness of those who are younger. In addition, in our study, when the anti-HBs values were analyzed by grouping, significant differences were found in terms of the distribution of anti-HBs groups according to age groups; accordingly, the proportion of negative results detected in those aged 18 and 19 was found to be significantly higher compared to older age groups, and those with more than 1000 mIU/mL in 23 and 24 age groups compared to younger age groups. While the ratio of negativity and low-level positivity was higher at younger ages, the ratio of high-level positivity was higher at older ages. In the 23 and 24 age groups, there were no participants with an antibody level of "0". Only 3.8% of 18-year-olds had antibody levels more than 1000 mIU/mL. All these findings suggest that antibody negativity is more frequent in younger individuals, whereas antibody positivity ratios are significantly higher in older individuals. Therefore, it is important to determine the level of protection against hepatitis B in younger patients.

Bagheri-Jamebozorgi et al. (12) found the mean anti-HBs titer as 55.4 mIU/mL 20 years after infancy vaccination. In our study, the mean antibody titer after approximately 20 years were found to be at a higher level of 248.9 mIU/mL. This difference may be attributed to various factors such as the population included in the study and the brand of vaccine administered in infancy.

Shakeri et al. (8) showed that anti-HBs levels were significantly lower in individuals with more than 16 years elapsed since last hepatitis B vaccination compared with those with a shorter period of time elapsed after last hepatitis B vaccination and reported that antibody levels decreased with age and older age was a negative predictive factor for antibody levels. Kazemeini and Owlia (16), however, found no relation between age and anti-HBs titer, but found a relation between the last vaccine dose and antibody titer Some other studies have also shown that there is a significant decrease in antibody titer during the time since the last vaccine (9,16,19,20,21). However, in our study, significant differences were found between age groups in terms of median anti-HBs levels, accordingly, the median values of those aged 18, 19 and 20 were found to be significantly lower than all other age groups who were older than them. This finding indicates that antibody levels are generally lower at younger ages and less protective in general terms. Furthermore, correlation analysis showed that there was a positive but weak relationship between age and anti-HB levels. This finding shows that as age increases, antibody levels are generally higher and the level of protection is better. It is rather unexpected that the antibody levels are higher in older patients, that is, higher anti-HBs levels are found despite a longer period of time since hepatitis B vaccination. This may be due to increased exposure to hepatitis B virus with age.

Qawasmi et al. (9) reported that the mean anti-HBs level in the 17-19 age groups was 5.3 mIU/mL. In our study, the mean anti-HB titer was found to be 109.3±239.8 mIU/mL in the 18-year-old group, and 213±346 mIU/mL in the 19-year-old group, and much higher antibody titers were observed in the older age groups. The fact that the mean values in our study were much higher than those in the aforementioned study may be attributed to the differences in regional and participant characteristics.

Study Limitations

There were limitations to our study. Since information on whether the subjects included in the study received the booster hepatitis B vaccine was not available, it could not be clarified whether the high anti-HBs levels were associated with the booster vaccine. The number of participants was kept very high to avoid statistical errors. In addition, individuals over the age of 24 could not be included in the study and changes in antibody levels could not be observed at older ages because the study was related to the introduction of a routine vaccination program.

Conclusion

To the best of our knowledge, our study is one of the rare studies measuring the level of hepatitis B vaccine protection for up to 24 years. Our findings showed that people who were included in the routine hepatitis B vaccination program after birth had 71% protection when they reached adulthood, and the antibody level did not decrease with increasing age, on the contrary, it increased**.** Further immunological studies are needed to explain the reason.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Samsun University, Clinical Research Ethics Committee (approval number: 2023/4/4, date: 01.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S., Concept: E.S., E.M.Y., Design: E.M.Y., Data Collection or Processing: E.S., M.A.O., Analysis or Interpretation: E.S., E.M.Y., M.A.O., Literature Search: E.S., E.M.Y., M.A.O., Writing: E.S., E.M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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