Research Article

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Investigation of Anti-HCV, Anti-HIV, and Anti-HAV IgG Seroprevalence in HBsAg-positive Patients

HBsAg Pozitif Hastalarda Anti-HCV, Anti-HIV, Anti-HAV IgG Seroprevalansının Araştırılması

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ABSTRACT

Objectives: The objective of this study was to evaluate serologic markers anti-hepatitis C virus (anti-HCV), anti-hepatitis A virus immunoglobulin G (anti-HAV IgG), anti-human immunodeficiency virus antibody (anti-HIV)] associated with HCV, HAV, and HIV in individuals with hepatitis B virus infection, with a view to contributing to the development of preventive strategies for disease control.

Materials and Methods: The study population comprised hepatitis B surface antigen (HBsAg)-positive adult patients admitted to the hospital between January 2015 and January 2024. Patients with complete anti-HCV, anti-HIV, and anti-HAV IgG tests were included in the study. The results were then subjected to retrospective analysis. Results identified as borderline and reactive in the anti-HIV test were referred to the National HIV-acquired immunodeficiency syndrome Confirmatory Reference Centre for confirmation by additional testing.

Results: In the present study, 733 patients were HBsAg-positive. Among these patients, anti-HAV IgG was detected in 23.1% (170/733), anti-HCV in 0.81% (6/733), and anti-HIV in 0.13% (1/733). Of the 733 patients who tested positive for HBsAg, 53% were male and 47% were female. The mean age of the cohort was found to be 50.49 (±14.32) years. The mean age of patients who tested positive for anti-HAV IgG was found to be 49.42 (±14.14) years. Among the included patients, 89 (52.4%) were male and 81 (47.6%) were female.

Conclusion: HAV seroprevalence should be investigated in HBsAg-positive patients due to the risk of a more severe HAV infection. Anti-HCV and anti-HIV tests should also be evaluated in HBsAg-positive patients because they have common transmission routes and increase mortality and morbidity. Guidelines recommend hepatitis A vaccination in seronegative cases and especially in the presence of chronic liver disease such as hepatitis B, hepatitis C

ÖZ

Amaç: Bu çalışmanın amacı, hepatit B virüs enfeksiyonu olan bireylerde; hepatit C virüsü (HCV), hepatit A virüsü (HAV) ve insan bağışıklık yetmezliği virüsü (HIV) ile ilişkili serolojik belirteçleri (anti-HCV, anti-HAV IgG, anti-HIV) değerlendirmeyi ve hastalıkların kontrolü için önleyici stratejilerin geliştirilmesine katkıda bulunmaktır.

Gereç ve Yöntemler: Çalışma popülasyonu, Ocak 2015 ile Ocak 2024 tarihleri arasında hastaneye başvuran hepatit B yüzey antijeni (HBsAg)-pozitif yetişkin hastalardan oluşmaktadır. Anti-HCV, anti-HIV ve anti-HAV IgG test sonuçları eksiksiz olan hastalar çalışmaya dahil edilmiştir. Sonuçlar daha sonra retrospektif analize tabi tutulmuştur. Anti-HIV testinde sınırda ve reaktif olarak tanımlanan sonuçlar, ek testlerle doğrulanması için Ulusal HIV-edinilmiş bağışıklık yetmezliği sendromu Doğrulama Referans Merkezine iletilmiştir.

Bulgular: Çalışmamızda 733 HBsAg pozitif hasta olup; bu hastalarda anti-HAV IgG %23,1 (170/733), anti-HCV %0,81 (6/733) ve anti-HIV %0,13 (1/733) oranında pozitif saptandı. HBsAg pozitif saptanan 733 hastanın %53'ünün erkek, %47'sinin kadın ve yaş ortalamasının 50,49 (±14,32) olduğu görüldü. Anti-HAV IgG pozitif olan hastaların yaş ortalaması 49,42±14,14 yıl olup, %52,4'ü erkek (n=89) ve %47,6'sı kadın (n=81) olarak tespit edildi.

Sonuç: HBsAg pozitif hastalarda HAV seroprevalansı, klinik olarak daha şiddetli bir HAV enfeksiyonu riski nedeniyle araştırılmalıdır. HBsAg pozitif hastalarda, ortak bulaşma yollarına sahip olmaları ve mortalite ve morbiditeyi artırmaları nedeniyle anti-HCV ve anti-HIV testleri de değerlendirilmelidir. Kılavuzlar seronegatif olgularda ve özellikle hepatit B, hepatit C ve alkolik hepatit gibi kronik karaciğer hastalığı varlığında hepatit A aşılamasını önermektedir. Çalışmamızın bulguları bölgesel verilere katkı sağlayacaktır. Her merkezden seropozitiflik verilerinin toplanması ülkemizdeki gerçek

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and alcoholic hepatitis. The findings of our study will contribute to regional data. Collecting seropositivity data from each center will significantly help understand the real prevalence in our country.
Keywords: Hepatitis B, hepatitis A, hepatitis C, HIV/AIDS, HBV co-infection

prevalansın anlaşılmasına önemli ölçüde yardımcı olacaktır.
Anahtar Kelimeler: Hepatit B, hepatit A, hepatit C, HIV/AIDS, HBV ko-enfeksiyon

Introduction

Viral hepatitis is a prevalent hepatic disorder predominantly triggered by classical hepatitis viruses (A, B, C, D, E). The condition may be complicated by cirrhosis, liver failure, and hepatocellular carcinoma (HCC), which can result in morbidity and mortality (1). In the context of liver disease, viral hepatitis, particularly that attributable to hepatotropic viruses, has been observed to exhibit a propensity for more severe clinical presentations (2). Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infections can be observed concurrently because of shared modes of transmission (percutaneous transmission through blood and body fluids, sexual transmission via semen and vaginal secretions). This treatment has been shown to increase morbidity and mortality in patients. Hepatitis A virus (HAV), an acute and self-limiting infection of the liver, is transmitted through the primary fecal-oral route (3). According to the World Health Organization (WHO), the global prevalence of chronic hepatitis B (CHB) infection was estimated at 254 million in 2022. The study also reported that the annual incidence of new cases was 1,2 million, while 1,1 million deaths were attributed to cirrhosis and HCC associated with HBV infection (4). According to the WHO estimates, the global mortality rate from hepatitis A in 2016 was 7,134. This represents approximately 0.5% of viral hepatitis-related deaths (1). HAV superinfection exacerbates underlying liver disease in patients with chronic liver disease. Epidemiological studies conducted in Turkey demonstrated that hepatitis B surface antigen (HBsAg) seropositivity rates obtained from studies conducted with blood donors ranged from 2% to 7% (5). In 2015, it was reported that 71 million people, 1% of the global population, lived with HCV infection, 399,000 people died from cirrhosis or HCC caused by HCV infection, and 1,75 million new HCV infections developed (6). In the context of Turkey, the prevalence of HCV seropositivity exhibits a range of variation, with estimates ranging from 1% to 1.9%. (7). The issue of HIV infection as a significant public health problem persists, insofar as the condition has the capacity to affect individuals across all segments of society, reduce healthy life expectancy, and be transmitted from person to person. According to recent reports, the global prevalence of HIV is estimated to be 39 million (33,1 million to 45,7 million) (8). In the given country, the number of individuals with HIV and acquired immunodeficiency syndrome (AIDS) cases who were reported with positive confirmation tests between 1985 and November 8, 2023 was 39,437 and 2,295, respectively (9). It is recommended that serological markers associated with HCV, HIV, and HAV be assessed in individuals with HBV infection (10,11,12). The identification of co-infected cases is of paramount importance in the context of reducing mortality and morbidity, determining treatment strategies, and ascertaining the necessity for immunization and the development of preventive strategies for disease control. The present study aimed to ascertain the seroprevalence of anti-HCV, anti-HIV, and anti-HAV IgG in HBsAg-positive patients.

Materials and Methods

In the present study, the results of anti-HCV, anti-HIV, and anti-HAV IgG tests of patients admitted to the hospital between January 1, 2015, and January 1, 2024 and found to be HbsAg-positive were analyzed retrospectively from the hospital information management system. In the present study, we sought to ascertain the most effective approach to the inclusion of test results to ensure the integrity of the study findings. To this end, a query was initiated within Microsoft Excel 2021, the objective of which was to identify and exclude patients who had repeated tests within the same year or between years. To exclude repeated patients from the study, a query was made with the Microsoft Excel 2021 program based on patient identity separately for positive and negative patient results, and repeated data were deleted. At the conclusion of the study, test results exceeding the reference value were designated as positive. Samples from patients who were found to be anti-HIV reactive in the enzyme-linked immunosorbent assay device were sent to the National AIDS Verification Center and Viral Hepatitis Laboratory of the General Directorate of Public Health for confirmation testing. In this facility, samples that were positive as a result of the HIV1/2 anti-body differential rapid confirmatory test were considered positive.

For this study, permission was obtained from Clinical Research Ethics Committee Balıkesir University Faculty of Medicine (date: 31.01.2018, approval number: 27).

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 statistical package program (IBM SPSS Corp.; Armonk, NY, USA) was used for data evaluation and analysis. Categorical variables are presented as frequency (n) and percentage (%), whereas numerical variables are presented as mean ± standard deviation. For comparison of categorical variables between the two independent groups, χ^2 and Fisher's exact test were applied. The independent sample t-test and Mann-Whitney U test were used to compare continuous variables between the two independent groups. The statistical significance level was set as $p<0.05$.

Results

In the present study, 733 patients with HBsAg positivity were included in the analysis. Among the included patients, 388 (52.9%) were male and 345 (47.1%) were female, with a mean age of 50.49 years (±14.32). Furthermore, the study revealed that 23.1% (170/733) of patients exhibited positive anti-HAV IgG, 0.81% (6/733)

demonstrated positive anti-HCV, and 0.13% (1/733) exhibited positive anti-HIV. The mean age of patients positive for anti-HAV IgG was 49.42 years (±14.14), 89 (52.4%) of whom were male and 81 (47.6%) of whom were female. No statistically significant findings were identified in the distribution of anti-HAV IgG and anti-HCV seropositivity according to age or gender (p=0.270, p=0.232, p=0.863, p=1, respectively). The seropositivity rates according to age and sex, along with the p-values, are presented in Figure 1, Tables 1 and 2.

Discussion

Viral hepatitis and HIV infection continue to be a global public health problem. It is estimated that approximately 296 million people worldwide are chronic carriers of HBV (4). In accordance with international guidelines, screening for HBV, HIV, and HAV co-infection is recommended for individuals with HBV infection, given the similarity of the transmission routes for these pathogens (10,11,12). HBV/HCV is important for the detection of HBV/HIV co-infection and for altering the natural course of chronic HBV infection. It is also imperative to be aware of HAV serology in patients with HBV to avoid the potentially fatal consequences of possible HAV infection and in light of the necessity for immunization. The present study was undertaken with the objective of determining the frequency of co-infection in individuals with HBV, eliminating any deficiencies that may occur during the diagnostic process and subsequent follow-up, and increasing awareness. The prevalence of co-infection varies geographically, with different regions exhibiting distinct endemicity patterns for the respective viruses. According to data provided by the WHO, Turkey is classified as an intermediate-endemic region for HBV. These data were primarily obtained from studies on blood donors (13). The prevalence of HBsAg positivity exhibits variability across diverse populations and geographical regions. Research findings have indicated that the global prevalence of chronic HBV infection, as indicated by the presence of HBsAg, is approximately 3.6%, with elevated rates observed in certain regions, including Africa (8.8%) and the Western Pacific (5.2%) (14). In a study conducted in the Central African Republic, the prevalence of HBsAg among 801 students was 15.5% (15). A number of epidemiological studies conducted in Turkey have demonstrated that the prevalence of HBsAg positivity ranges from 4% to 5% within the general population (16). It is imperative to acknowledge the significance of these rates and to take them seriously. Screening tests and seroepidemiological data are instrumental in guiding the management of patients with this disease, with the aim of reducing morbidity and mortality. In patients with hepatitis B, the investigation of hepatitis A is of two types. First, preventing the mortality of acute HAV co-infection. Second, determining the need for immunization in seronegative patients. A study conducted in Thailand reported fulminant liver failure and 25-55% mortality rates in HBsAg carriers with superinfection by acute hepatitis A (2). Chu and Liaw (17). found that the risk of developing fulminant liver failure in the event of acute infection with other hepatotropic viruses was approximately nine times higher in HBsAg carriers than in non-carriers. Hepatitis A seroprevalence exhibits significant interpopulation and interregion variability, with factors such as vaccination coverage, sanitation, and socioeconomic conditions playing a pivotal role in its distribution. For instance, a study conducted in Korea on patients with chronic viral liver disease revealed that 80% of those with chronic HBV infection were also infected with hepatitis A (18). A study conducted in Italy found that the levels of this substance were higher in the southern part of the country than in the northern part of the country. The researchers

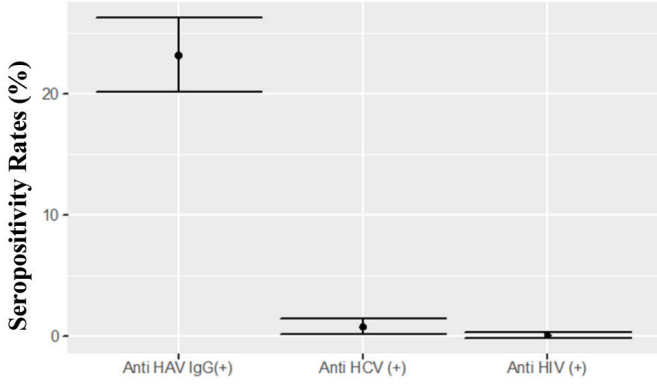

Figure 1. Anti-HCV, anti-HIV, and anti-HAV IgG seropositivity in HBsAg-positive patients

HBsAg: Hepatitis B surface antigen, HAV IgG: Hepatitis A virus immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Table 1. Prevalence of anti-HCV, anti-HIV, and anti-HAV IgG seropositivity in HBsAg-positive patients

	n	% (95% CI)
Anti-HAV IgG (+)	170	23.2 (20.14-26.26)
Anti-HCV (+)	6	0.8 (0.16-1.44)
Anti-HIV (+)	1	0.1 (-0.13-0.33)

HBsAg: Hepatitis B surface antigen, HAV IgG: Hepatitis A virus immunoglobulin G, CI: Confidence interval, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Table 2. Distribution of anti-HCV, anti-HIV, and anti-HAV IgG seropositivity in HBsAg-positive patients according to age and sex

	Total (n=733)	Anti-HAV IgG (+) (n=170; 23.2%)	Anti-HCV (+) (n=6; 0.8%)	Anti-HIV (+) (n=1; 0.1%)	p-value*	p-value**
Age (year)	50.49±14.32	49.42±14.14	57.33±12.30	49	0.270†	0.232µ
Sex						
Male	388 (52.9%)	89(52.4%)	3 (50%)	1 (100%)	0.863¶	1•
Female	345 (47.1%)	81 (47.6%)	3 (50%)	0 (0%)		

*: Anti-HAV IgG (+), **: Anti-HCV (+)
†: Independent samples t-test, µ: Mann-Whitney U test, ¶: Chi-square test, •: Fisher's exact test
HBsAg: Hepatitis B surface antigen, HAV IgG: Hepatitis A virus immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

attributed this discrepancy to the higher socioeconomic standards in the north and the lower consumption of raw or partially cooked shellfish in the region (19). In a multicenter study conducted in Turkey, 4,793 CHB patients were examined, and the anti-HAV IgG positivity rate was found to be 93.5%. The study reported that 26.2% of patients were under the age of 19, 15.5% were in the 20-25 age group, and 12.5% were in the 26-29 age group. All patients were HAV seronegative (20). In a further study conducted in our country, the data of 137 adult male patients (aged ≥20 years) who were HBsAg-positive and had not received HAV vaccination were analyzed. The study revealed that 83.2% (114/137) of the serum samples from the study group were anti-HAV IgG positive, with higher percentages observed in the Marmara Region (61.5%, 8/137), the Aegean Region (83.3%, 10/12), and the Central Anatolia Region (81.3%, 13/16). The lowest percentages were found in the Black Sea Region (66.7%, 8/12), Eastern Anatolia region (87.5%, 21/24), and Southeastern Anatolia region (94.1%, 32/34) (21). In the study by Kepenek et al. (22), the presence of anti-HAV IgG was examined in a cohort of 923 patients who were monitored for HBsAg positivity between 2010 and 2019. The overall positivity rate was 89.9% (830/923), indicating a high prevalence of the infection (22). In a separate study, the presence of anti-HAV IgG was identified in 105 (94.6%) of 111 patients diagnosed with CHB (23). In the present study, the anti-HAV IgG positivity rate was 23.2%. The results of a study conducted on a smaller sample from the same center in 2018 yielded similar outcomes, and this rate was found to be lower than that of other studies conducted in our country. Consequently, it was hypothesized that the level of awareness regarding hepatitis A vaccination among the study population was inadequate. Conversely, the low rate of anti-HAV IgG positivity may be attributable to disparities in socioeconomic status, hygienic practices, sanitation infrastructure, and familial size across different regions (24). In the United States, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends hepatitis A vaccination in seronegative cases and in the presence of chronic liver disease, especially hepatitis B, hepatitis C, and alcoholic hepatitis (25). In consideration of the data obtained from our own research, it was recommended that patients with a hepatitis B infection who were seronegative for hepatitis A should receive vaccination as initial controls.

In comparison with patients infected with HBV alone, those with HBV/HCV, HBV/HIV, and HBV/HAV infection demonstrated a more unfavorable prognosis with regard to elevated HBV replication, frequent and rapid progression to cirrhosis, the development of HCC, and fulminant liver failure (2,26,27). It has been established that patients suffering from both HBV and HCV infections face an elevated risk of progressive liver disease, cirrhosis, and HCC when compared with individuals who are infected with a single virus (27,28). Therefore, it is recommended that anti-HCV be requested during the diagnostic process and throughout the treatment phase. As a general rule, these patients should be treated for the virus during its replication phase. However, it is important to note that treatment of HCV with direct-acting antivirals may result in the reactivation of HBV. Consequently, in cases of co-infection, the prescription of direct-acting antivirals should be accompanied by the administration of a nucleotide analog, provided that the patient fulfills the treatment criteria for CHB. In patients with chronic HBV infection, the concurrent administration of direct-acting antivirals and a nucleotide analog is recommended, with treatment continuing for a period of up to 12 weeks following the cessation of direct-acting agent therapy (29,30). In the event of co-infection, a comprehensive evaluation is imperative to ascertain the necessity of treatment and prophylaxis. The anti-HCV seroprevalence rate in HbsAg-positive patients has been the subject of investigation in various populations. In a study conducted in China between 2018 and 2020, 44 (0.4%) of 10,560 HbsAg-positive patients were found to be anti-HCV-positive (31). A study conducted in China found that 14.9% of 712 HBV patients exhibited HCV co-existence (32). In a separate study, Chu and Lee (33) discovered that HCV was present in 2-10% of individuals who were carriers of HBV. In their report, Benvegnù et al. (34) stated that the 10-year cumulative risk of developing HCC was 45% in patients with cirrhosis with co-infection and 16% in patients with HBV-related cirrhosis. Consequently, the potential for HCV infection should be assessed in patients with HBV-related chronic liver disease. A comprehensive study was conducted in 15 centers to investigate the prevalence of HBV/HCV co-infection in our country. The prevalence rate was approximately 0.974% (974/100,000) (28). In the present study, the anti-HCV seroprevalence rate was 0.8% in HBsAg-positive patients, which is consistent with the findings of previous studies. Despite the absence of a vaccine against the HCV, the low prevalence observed in our country and within our patient group appears to be advantageous.

The prevalence of HIV infection has increased worldwide, which has resulted in a concomitant increase in the number of studies investigating HBV and HIV co-infection (26). It is important to note that HBV and HIV can occur in parallel due to the similarity of their respective transmission routes. In patients with HBV and HIV infection, both types of infection should be treated, irrespective of CD4 levels. The combination of tenofovir disoproxil fumarate and tenofovir alafenamide has proven efficacious in combating both HIV and HBV and is therefore recommended for incorporation into therapeutic regimens. However, it is crucial to emphasize that discontinuation of treatment can lead to HBV reactivation, emphasizing the necessity for strict adherence to treatment guidelines. It is imperative to emphasize that treatment should aim to be suppressive and lifelong (29,30). In a study conducted in Taiwan, 57 (18.9%) of the anti-HIV-positive sample group consisting of 301 intravenous drug users were found to have HBV/HIV co-infection (35). A recent meta-analysis of HBV infection among people with HIV reported that the prevalence of HBV/HIV co-infection was highest in the Western Pacific region (11.4%) and sub-Saharan Africa (10.0%) and lowest in Europe (6.7%) and the Americas (5.3%) (36). The prevalence of hepatitis B infection and HIV in Senegal was 8.8% in a study conducted in the region (37). In Turkey, the prevalence of HBV and HIV co-infection was reported to be 4.2% and 4.4%, respectively (38,39). In the present study, the anti-HIV seroprevalence rate was 0.13% among patients positive for HBsAg. The risk of developing CHB infection increases by up to 23% in the presence of HIV infection (40). While studies investigating HBV and HIV co-infection have predominantly concentrated on HBV in HIV-positive individuals. Consequently, co-infection may be detected at a higher rate in patients with HBV

than in studies investigating HIV. This underscores the necessity of incorporating risk factors and specific population demographics when evaluating co-infection rates.

In the present study, no statistically significant difference was identified between the distribution of anti-HAV IgG and anti-HCV seropositivity according to age (p=0.270, p=0.232) and gender (p=0.863, p=1.00). These findings underscore the importance of hepatitis A vaccination, particularly among older seronegative patients. In Turkey, hepatitis A and B vaccinations are included in the childhood vaccination schedule. A Turkish study conducted among a cohort of children born after 1998, when the national programme for free hepatitis B vaccination was initiated, and who had received cancer treatment, found that HBsAg positivity was not observed in 100 children (41). Although the present study was conducted in a cohort of patients with hepatitis B, it is nevertheless incumbent upon us to eradicate the virus. The decline in HBsAg positivity in Turkey is a significant public health achievement, which can be attributed to the success of vaccination campaigns targeting high-risk groups, public health initiatives, and the commitment of healthcare workers to combat HBV transmission (42).

The objective of this study was to contribute to the regional data. It is acknowledged that seropositivity rates may vary among countries, regions, and even centers. The collection of seropositivity data from each center will facilitate a more comprehensive understanding of the actual prevalence in our country. From a clinical perspective, in the presence of co-infection, HAV seroprevalence should be investigated in HBsAg-positive patients because of its severe course, and seronegative cases should be vaccinated. It is hypothesized that enhancing public awareness regarding the modes of transmission, augmenting knowledge concerning vaccination, and undertaking further research into immunization will result in a substantial decline in the incidence of these infections.

Study Limitations

This study is subject to several limitations. Due to its retrospective nature, the study did not achieve a sufficient sample size, and the available data were limited in scope. To contribute to the epidemiological data of our country, it is thought that the study needs more patients and should be supported by a multicenter study.

Conclusion

In conclusion, individuals living with HBV must undergo meticulous monitoring for co-infections. Co-infections are of particular significance due to their capacity to increase morbidity and mortality. Relevant tests should be requested and followed up to determine disease management and treatment priorities. It is recommended that each center evaluate its own epidemiological data and raise awareness.

Ethics

Ethics Committee Approval: For this study, permission was obtained from Clinical Research Ethics Committee Balıkesir University Faculty of Medicine (date: 31.01.2018, approval number: 27).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Ç., E.D., Concept: Y.Ç., E.D., Design: Y.Ç., E.D., Data Collection or Processing: Y.Ç., E.D., Analysis or Interpretation: Y.Ç., E.D., Literature Search: Y.Ç., E.D., Writing: Y.Ç., E.D.

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