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EDITORIAL

Dear Colleagues,

We are here again with a new issue. In this Issue, there are one review article about "Antiviral Treatment During Breastfeeding in Hepatitis B" and two case reports about "Telbivudine-related Myopathy" and "Chronic Hepatitis B Virus Infection in an Anti-HBC negative patient".

Also; "Methods of Male Circumcision Procedures and Prevalence of Viral Hepatitis", "Efficacy and Safety of Telbivudine in Chronic Hepatitis B", "Hepatitis Serology and Occupational Exposure Risk in Hospital Housekeeping Staff", "The Efficiency of Hepatitis C Virus Core Antigen Test", "Relationship Between ABO/Rh Blood Groups and Severity of Liver Fibrosis in Hepatitis B", and "Serum HCV RNA Titers and Biochemical Parameters in Chronic Hepatitis C Patients" subjects were included in the article in this issue.

Our aim is to have an open access for our journal so that everybody can hear and learn about all the latest developments. In line with this, we expect your contributions with articles, case reports, reviews, and letters to editor.

Prof. Dr. Fehmi TABAK **Prof. Dr. Mustafa ALTINDİŞ**

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Antiviral Treatment During Breastfeeding in Hepatitis B

Hepatit B'de Emzirme Döneminde Antiviral Tedavi

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ABSTRACT

From 1982, with the availability of hepatitis B vaccine, chronic hepatitis B infection rate and its complications have decreased dramatically. Today, transmission from an infected woman to her newborn still remains as one of the major problems about hepatitis B. Guidelines recommend quantification of hepatitis B virus (HBV) DNA in all infected pregnant women at the end of the second trimester. Mothers with high concentrations of HBV DNA (>1.000.000 copies/ml) should be considered for antiviral therapy. Since the immune system is activated after delivery, continuing this therapy during the postpartum period remains critical in highly viremic mothers.

Some antiviral drugs are recommended during pregnancy. However, safety of these drugs during breastfeeding interestingly remains unclear. There are several studies regarding the use of lamivudine (LAM) and tenofovir disoproxil (TdF) while breastfeeding in human immunodeficiency virus (HIV)-infected mothers. The World Health Organization guidelines on HIV recommend HIV-infected mothers to continue antiretroviral treatment while breastfeeding. Applicability of this recommendation for HBV-infected mothers must be clarified.

Both clinicians and patients face therapeutic decisions regarding breastfeeding in hepatitis B, which are not based on randomized controlled trials. They have to make a hard decision to choose the best option considering both the benefits of breastfeeding and the need for antiviral treatment, where indicated, to have a healthy mother, which seem to contradict to some extent. In the light of up-to-date literature, if a mother needs antiviral treatment for HBV, LAM and TdF raise as options with advantages of enabling breastfeeding. However, further studies are urgently needed in this issue to make a recommendation supported by evidence-based medicine.

Keywords: Hepatitis B, breastfeeding, antiviral treatment

ÖZ

1982 yılında hepatit B aşısının kullanılmaya başlanması ile kronik hepatit B enfeksiyonu ve komplikasyonlarında dramatik bir düşüş gözlenmiştir. Günümüzde hala enfekte anneden bebeğe bulaş, hepatit B ile ilgili en büyük problemlerden birini oluşturmaktadır. Hepatit B virüsü (HBV) ile enfekte gebelerde ikinci trimestırda HBV DNA kantitasyonu yapılması önerilmektedir. HBV DNA düzeyi 1,000,000 kopya/ml üzerinde olan gebelerin antiviral tedavi açısından değerlendirilmesi gerekmektedir. Postpartum dönemde gelişen immün sistem reaktivasyonu nedeniyle, antiviral tedavinin doğum sonrası dönemde de devam etmesi virüs titresi yüksek annelerde kritik öneme sahiptir. Bazı antiviral ilaçlar gebelik döneminde önerilseler de emzirme döneminde kullanımlarının güvenilirliği ile ilgili net bir veri bulunmamaktadır. Lamivudin (LAM) ve tenofovirin (TdF), insan bağışıklık yetmezlik virüsü (HIV) ile enfekte annelerde emzirme döneminde kullanımları ile ilgili çalışmaları vardır. Dünya Sağlık Örgütü HIV rehberinde HIV ile enfekte annelerin antiretroviral tedavi alırken emzirmeye devam edebilecekleri önerilmektedir. Bu önerinin HBV ile enfekte anneler için de net ortaya konması gerekmektedir.

Gerek klinisyenler gerekse hastalar günlük pratikte hepatit B ile enfekte annenin emzirme kararını, randomize kontrollü çalışmalara dayanmayan verilerle almak durumuyla karşı karşıya kalmaktadır. Hem emzirmenin faydalarını hem de hastaların antiviral tedavi gereksinimini göz önünde bulundururarak zor bir karar vermeleri gerekmektedir. Güncel bilgiler ışığında, bir annenin antiviral tedavi ihtiyacı varsa emzirmeye olanak sağlamaları nedeniyle LAM ve TdF iyi birer alternatif olarak karşımıza çıkmaktadır. Fakat yine de kanıta dayalı tıp ile desteklenmiş önerilerde bulunabilmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Hepatit B, emzirme, antiviral tedavi

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Introduction

Hepatitis B is a global health problem which affects approximately 400 million people worldwide. In spite of the global efforts to reduce hepatitis B infection, it is estimated that 240 million people are chronically infected with hepatitis B and approximately 780.000 persons die each year from hepatitis B infection (1).

From 1982, with the availability of hepatitis B vaccine, chronic infection rate and its complications have decreased dramatically. Today, transmission from an infected woman to her newborn still remains as one of the major problems about hepatitis B. Close screening of both mother and child during pregnancy and the postpartum period is essential for the prevention of transmission and hepatic flares in the mother. Guidelines recommend quantification of hepatitis B virus (HBV) DNA in all infected pregnant women at the end of the second trimester. Mothers with high concentrations of HBV DNA (>1.000.000 copies/ml) should be considered for antiviral therapy (2,3,4). After pregnancy, a significant increase in liver inflammation occurs. Since the immune system is activated after delivery, continuing this therapy during the postpartum period remains critical in highly viremic mothers (5). Some antiviral drugs are recommended during pregnancy, and there are several studies on this issue. However, safety of these drugs during breastfeeding interestingly remains unclear. Breast milk is a unique food for infants, and it is especially important in low-income countries. The advantages of breastfeeding for both mother and infant are unquestionable. Although the World Health Organization (WHO) recommends breastfeeding in chronic hepatitis B (CHB), unfortunately, 25-50% medical professionals (most of whom are hepatologists) do not encourage these mothers to breastfeed their babies (6,7). Even though HBV DNA is detected in breast milk (8), many studies suggest that breastfeeding is not a risk for mother-to-child transmission if the newborn is adequately managed for hepatitis B prevention at birth (9,10). Moreover, the majority of the mother-to-child transmission happens before deciding on infants' feeding modes (11). Breastfeeding during antiviral treatment in hepatitis B is an unclear issue. All of these drugs' labels include a warning stating that breastfeeding is not recommended while taking these drugs. There are several studies on the use of lamivudine (LAM) and tenofovir disoproxil (TdF) while breastfeeding in human immunodeficiency virus (HIV)-infected mothers. The WHO guidelines on HIV recommend HIV-infected mothers to continue antiretroviral treatment while breastfeeding (12). Since LAM and TdF are parts of antiretroviral treatment recommended for HIV-infected mothers who breastfeed their babies, applicability of this recommendation for HBV-infected mothers must be clarified. The aim of this review is to summarize the data regarding antiviral treatment during breastfeeding in CHB.

Lamivudine

LAM is a synthetic nucleoside analogue effective for both HBV and HIV-1. It is the first antiviral that was licensed for the treatment of HBV infection. Today, guidelines recommend using LAM in the treatment of CHB if more potent drugs are not available or appropriate (2). A randomized, placebo-controlled trial conducted on 150 hepatitis B surface antigen (HBsAg)-positive highly viremic pregnant women evaluated whether LAM prevented HBV transmission to newborns who received standard prophylaxis with hepatitis B immunoglobulin (HBIG) and vaccination. After a 52-week follow-up, 18% of babies from LAM-treated mothers were HBsAg-positive compared to 39% of those in placebo group (p=0.014). No adverse events were noted in the LAM-treated mothers and their infants. This study supports that LAM reduces HBV transmission from highly viremic mothers to their infants who received passive/active immunization (13).

The US Food and Drug Administration (FDA) included LAM in the pregnancy category C (Table 1, 2) (14). Although it is classified as C, LAM is the only antiviral against HBV and randomized controlled studies have proven the safety of LAM administration in pregnancy (13). Through 31 July 2015, the Antiretroviral Pregnancy Registry (APR) reported 4566 and 7263 women who have been exposed to LAM during the first and second/third trimesters, respectively. In these data, newborn defect rates were 3.1% for the first and 2.9% for the second/third trimesters, which are similar to the general population (15). In the Kisumu Breastfeeding Study, which evaluates antiretroviral concentrations at different time points in HIV-infected mothers, their breast milk, and infants, the median maternal plasma LAM concentration was 508 ng/ml and the breast milk concentration was 1214 ng/ml. The concentration of LAM in the infant was highest on the day of birth compared to the other postpartum sampling times, even though infants were breastfeeding (16). Although LAM is concentrated in breast milk (16,17,18), the amount that the infant has been exposed to is insignificant (which is approximately 2% of the recommended daily treatment dose of LAM) (16). Studies revealed that an infant is exposed to significantly higher LAM concentrations via umbilical cord than being exposed to via breast milk (13,14).

Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate is a prodrug used because of its better bioavailability than TdF. TdF is a nucleotide reverse transcriptase inhibitor. Since it has high barrier to resistance and potent inhibitory effect to HBV, it is one of the first-line therapies for CHB. TdF is labeled as pregnancy category B (Table 1) (19). Studies revealed that, like in LAM, infants are exposed to higher TdF concentrations via umbilical cord than that via breast milk (20). Benabound et al. (21) have reported in their study that among 5 women, the median maximal TdF concentration in breast milk was 14.1 ng/ml which is lower than the concentrations in both maternal serum and cord blood. Assuming that TdF in breast milk has low bioavailability because of not being a prodrug, the concentration of TdF in infants due to breast milk ingestion is probably insignificant. In an animal study among two lactating macaques, after the administration of a subcutaneous dose of TdF (30 mg/kg of body weight), it was observed that the TdF concentrations in breast milk of lactating macaques were unlikely to be toxic for the infant and that the small amounts of TdF in the milk were not likely to select for resistance in already infected infants (22). Similarly, Palombi et al. (23) reported in their long-term follow-up (12 months) study that passage of TdF into breast milk was negligible. It seems ironic that TdF has not been recommended while breastfeeding since its pregnancy risk is categorized as B. The APR reported 2608 and 1258 women who have been exposed to TdF during the first and second/third trimesters, respectively. In these data, newborn

defect rates were 2.3% for the first and 2.1% for the second/third trimesters, which are similar to the general population (15). A study among 74 infants which evaluated fetal bone effects of maternal TdF use, reported that TdF-exposed infants had significantly lower body bone mineral density compared with unexposed infants (24). However, further studies are required to reveal the effect of TdF on infants' bone mineral density. With its increasing safety data in pregnant women, TdF can be considered as an option for antiviral treatment during breastfeeding in hepatitis B. However, further studies are required to evaluate the pharmacokinetics and pharmacodynamics of TdF in breastfeeding.

Interferon-α

Interferon alpha (IFN-α) is an immunomodulatory and antiviral agent which is licensed for the treatment of HBV infection since 1992. With the modification through the attachment of a polyethylene glycol molecule, pharmacokinetics and pharmacodynamics properties of IFN has improved and enabled its once weekly administration. IFN is labeled as pregnancy risk category C (Table 1). There are limited data on its usage during both pregnancy and breastfeeding. Data on this issue are based on case reports. Therefore, the safety of interferon during both pregnancy and breastfeeding is not clear enough.

In 1995, Pons et al. (25) reported two HIV-seropositive pregnant women given a single intramuscular dose of IFN-alpha, just before the abortion in the second trimester. They found undetectable IFN levels in the fetal blood and amniotic fluid in both cases. In another case report evaluating the transfer of IFN-α (2B) into breast milk of a patient, who was receiving high intravenous doses for the treatment of malignant melanoma, the authors have reported that after 30 million IU administration, the amount of interferon in the breast milk was only moderately elevated (1551 IU/mL) when compared to control milk (1249 IU/mL). This report suggests that even following very high doses, interferon is not excreted in breast milk, probably due to its large molecular size (26). Despite the limited clinical and laboratory studies, the US Drugs and Lactation Database (LactMed) reports that it is unlikely that IFN use by a nursing mother presents any serious risk to the breastfed infant because of the low levels in milk and poor oral absorption by the infant (27).

Adefovir Dipivoxil

Adefovir dipivoxil (ADV) is the prodrug of adefovir, an acyclic nucleotide phosphonate analogue of adenosine monophosphate, which is converted by host enzymes to adefovir diphosphate. ADV is assigned to FDA Pregnancy Category C (Table 1) (28). There is no adequate data on the use of ADV during both pregnancy and breastfeeding. It is not known whether ADV is excreted in human milk. APR suggests that mothers should be instructed not to breastfeed if they are taking ADV (15).

Entecavir

Entecavir (ETV) is a guanosine nucleoside analogue which has activity against HBV reverse transcriptase. It is labeled as pregnancy risk category C (29). ETV has not been studied in both pregnancy and breastfeeding. Excretion of ETV to human breast milk is not known. Thus, its use in these situations cannot be recommended (26). Clinician together with the patient has to make a decision to discontinue breastfeeding or discontinue the drug.

Telbivudine

Telbivudine (LdT) is an HBV-specific synthetic thymidine nucleoside analogue. It is a potent inhibitor of HBV replication, but, due to a lower barrier to resistance, guidelines do not recommend LdT as the first-line monotherapy (2). A prospective study among 229 HBsAg-positive, HBeAg-positive pregnant women with high virus titers (>10^7 copies/mL) evaluated the efficacy and safety of LdT vs untreated controls (30). All infants in both arms received HBIG within 12 h postpartum and HBV vaccine at 0, 1, and 6 months. The mothers received LdT 600 mg/day from week 20 to 32 of gestation and continued for 4 weeks after delivery in the case of inactive disease and for 28 weeks in the case of active chronic hepatitis. The authors have reported that LdT treatment was associated with a noticeable decrease in serum HBV DNA and HBeAg levels and normalization of elevated alanine aminotransferase levels before delivery. Twenty-eight weeks after delivery, perinatal transmission was lower in the infants who born to the LdT-treated mothers than in controls. In this study, no serious adverse events were reported in the LdT-treated mothers or their infants. However, this study does not include any statement on

Table 1. Food and drug administration pregnancy risk categories (34)

Risk category	Explanation
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

Table 2. Pregnancy risk categories and recommendations of antivirals during breastfeeding

Antiviral	Pregnancy risk category	During breastfeeding
Lamivudine	C	Can be used based on clinical studies
Tenofovir	B	Can be used based on clinical studies
Interferon	C	Not recommended
Adefovir	C	Not recommended
Entecavir	C	Not recommended
Telbivudine	B	Not recommended

breastfeeding while taking LdT. Despite LdT is labeled as pregnancy risk category B (31), there are no adequate and well-controlled studies on the LdT usage in pregnant women. Moreover, excretion of LdT to human breast milk is not known. To recommend its use during breastfeeding, pharmacokinetics and pharmacodynamics of LdT have to be better known in the nursing mothers with HBV. All of these drugs mentioned above can be used in CHB. However, when the patient is a breastfeeding mother with hepatitis B, LAM and TdF remain as eligible treatment options. Although there are clinical studies on the use LAM both pregnancy and breastfeeding, due to high probability of resistance to LAM, TdF can be safer for a breastfeeding mother with CHB (32,33).

Conclusion

Since hepatitis B is a global health problem among women of reproductive age, both clinicians and patients face therapeutic decisions which are not based on randomized controlled trials. They have to make a hard decision to choose the best option considering both the benefits of breastfeeding and the need for antiviral treatment, where indicated, to have a healthy mother which seem to contradict to some extent. The benefits of breastfeeding for both mother and infant are unquestionable. On the other hand, antiviral treatment is crucial for the mother's health. In the light of up-to-date literature, if a mother needs antiviral treatment for HBV, LAM and TdF raise as options with advantages of enabling breastfeeding (34). Among these two antivirals, TdF seems to be more preferable due to its safer pregnancy risk category and high barrier to resistance. However, further studies are urgently needed in this issue to make a recommendation supported by evidence-based medicine.

Ethics

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Concept: Rahmet Güner, Design: Rahmet Güner Analysis or Interpretation: İmran Hasanoğlu, Literature Search: İmran Hasanoğlu, Writing: İmran Hasanoğlu, Rahmet Güner.

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Research Article

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The Relationship Between the Methods of Male Circumcision Procedures Used in the Past and the Prevalence of Viral Hepatitis

Erkeklerde Geçmişte Sünnet Yapılma Şekli ve Viral Hepatit Sıklığı Arasındaki İlişki

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ABSTRACT

Objective: The study was designed to evaluate the relationship between the methods of circumcision procedures used in the past and hepatitis B surface antigen (HBsAg), anti-HBs and anti-hepatitis C virus (HCV) positivity.

Materials and Methods: Within the scope of "Public Hepatitis Awareness Activities" executed by the Viral Hepatitis Society, volunteer participants who were admitted to primary healthcare centers across the Turkey, were screened for HBsAg, anti-HBs and anti-HCV positivity. A standard questionnaire form regarding their circumcision procedure in the past was applied via face-to-face interview method to each participant while their blood samples were collected for the analysis of hepatitis B virus and HCV positivity.

Results: HBsAg, anti-HBs and anti-HCV positivity rates were 3.6%, 9.9% and 0.6% respectively. HBsAg positivity was significantly higher in group of participants who have been circumcised by a traditional non-medical person than in the other group of subjects who have been circumcised by a health professional (3.3% vs 5.3%, p=0.003).

Conclusion: Circumcision is a widespread practice based on the existing cultural and religious traditions in islamic countries like Turkey. Mass circumcision and circumcision performed by traditional non-medical persons like barbers is still one of the important health-care problems with the risk of transmission of viral infections in Turkey. The results will help to take measures for preventing viral hepatitis transmission.

Keywords: Anti-HBs, anti-HCV, barbers, circumcision, hepatitis B surface antigen, hepatitis

ÖZ

Amaç: Bu çalışma, geçmişte sünnet yapılma şekli ve hepatit B yüzey antijeni (HBsAg), anti-HBs ve anti-hepatit C virüsü (HCV) pozitifliği arasındaki ilişkinin incelenmesi amacı ile dizayn edilmiştir.

Gereç ve Yöntemler: Viral Hepatitle Savaşım Derneği'nce hayata geçirilen "Toplum Hepatit Farkındalık Aktiviteleri" kapsamında, tüm Türkiye genelinde sağlık ocaklarına başvuran gönüllü katılımcılar HBsAg, anti-HBs ve anti-HCV pozitifliği açısından taranmıştır. Katılımcıların hepatit B virüsü ve HCV pozitifliği analizleri için kan örneklerinin alındığı sırada, geçmişteki sünnet prosedürü ile ilgili standart anket formu yüz yüze görüşme metodu ile her katılımcı için doldurulmuştur.

Bulgular: HBsAg, anti-HBs ve anti-HCV pozitiflik oranları sırası ile %3,6, %9,8 ve %0,6 olarak bulunmuştur. HBsAg pozitifliği sünneti geleneksel, sağlık personeli tarafından yapılmayan grupta sağlık personeli tarafından sünnet edilen gruba göre anlamlı olarak yüksek bulunmuştur (%3,3 vs %5,3, p=0,003). Gruplar arasında anti-HBs ve anti-HCV pozitifliği açısından anlamlı bir ilişki saptanmamıştır (%0,6 vs %0,8, p=0,533).

Sonuç: Sünnet, Türkiye gibi islam ülkelerinde, kültürel ve dini geleneklere dayanan oldukça yaygın bir uygulamadır. Türkiye'de, toplu sünnet ve geleneksel berberler gibi sağlık personeli olmayan kişilerce yapılan sünnet, viral enfeksiyonların bulaşma riski ile birlikte, hala önemli sağlık sorunlarından biridir. Sonuçlar, viral hepatit bulaşında önleyici önlemler almaya yardımcı olabilir.

Anahtar Kelimeler: Anti-HBs, anti-HCV, berber, sünnet, hepatit B yüzey antijeni, hepatit

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Introduction

Hepatitis infection is a major global public health problem with high mortality and morbidity rates due to serious complications, such as chronic hepatitis, cirrhosis and primary liver cancer (1). Almost one-third of the world population has been infected with hepatitis B virus (HBV) and about 350 million of these remain chronically infected. On the other hand, approximately 3% of the world population has been infected with hepatitis C virus (HCV) and 170 million people are chronic carriers of HCV (2,3). Traditional practices including rituals, such as circumcision, traditional medicine and the other activities which damage the skin, e.g. tattooing or body piercing have been considered among the potential sources of blood-borne infections like HCV in case of contaminated instrument usage (3). It is estimated that one out of three males worldwide is circumcised (4). Circumcision is mostly performed for social and religious reasons in 99% of the male population in Turkey (5). However, controversy surrounds the procedure and its benefits and risks to health (6). The incidence and nature of various complications resulting from unsafe male circumcision along with the potential benefits has been the subject of much discussion. In this regard, the availability of healthcare, trained staff and appropriate hygiene have been documented among significant factors to decrease complications related to circumcision (6,7,8).

Based on the role of population-based epidemiological studies on the estimation of the relative contribution of the various sources of infection, prioritization of preventive measures and making the most appropriate use of available resources in a particular country (9), this screening study was designed to evaluate the relationship between circumcision and hepatitis B surface antigen (HBsAg), anti-HBs and anti-HCV positivity.

Materials and Methods

Setting: This cohort study was conducted as a part of the "Public Hepatitis Awareness Activities" executed by the Viral Hepatitis Society of Turkey with the permission of the Turkish Ministry of Health. A descriptive questionnaire was used to obtain the sociodemographic features of the subjects and the method of circumcision. A detailed explanation concerning objectives and protocol of the study, application and interpretation of the blood analysis for viral hepatitis workup and questionnaire forms as well as contact details of the study coordinator was sent to the investigator (general practitioner or family physician) working at the primary healthcare centers across Turkey before the initiation of the study.

Laboratory Testing: Participants were screened in terms of HBsAg, anti-HBs, and anti-HCV positivity. A total of 8-10 ml of blood was collected from each participant to analyze serum samples for investigating HBsAg, anti-HBsAg and anti-HCV positivity by using immunochromatographic cassette test (Rapid Card Test Nanosign, Bioland, Chungbuk, Korea) and the screening method and the positive results were confirmed by enzymatic immunoassay (EIA).

Data Collection: Five thousand eight hundred eighty four male volunteers of 18-79 ages [mean age: 35.0 (standard deviation±14.1) years] were eligible to participate in the study from all over the cities in Turkey. Prior to data collection, oral informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study were implemented after the permission of the Turkish Ministry of Health. Five thousand eight hundred eighty four male participants completed the questionnaire prepared for investigating the relationship of the method of circumcision with HBsAg, anti-HBs and anti-HCV positivity. A standard questionnaire form was applied via face to face interview method to each participant. The questions about the type and place details of the circumcision included in questionnaire form.

Statistical Methods: Statistical analyses were made using SPSS version 13.0 (SPSS Inc. Chicago, IL, USA). Chi-square (x^2) test was used for the comparison of categorical data and the Mantel-Haenszel test was used for the analysis of linear relationship between ordinal variables. ANOVA and post-hoc Tukey test were used for the parametric variables. Data were expressed as mean (standard deviation), minimum-maximum and percent (%) where appropriate; a p value of less than 0.05 was considered statistically significant.

Results

HBsAg, anti-HBs and anti-HCV positivity were identified in 213 of 5.878 (3.6%), 231 of 2339 (9.9%) and 37 of 5.884 (0.6%) participants, respectively (Table 1).

When the subjects were classified as being circumcised by health professionals or nonmedical persons, HBsAg positivity was found to be significantly higher (n=165/4987 (3.3%) vs. 48/897 (5.3%); p=0.003) in the latter group, while there was no significant association for anti-HBs (10.0% vs. 8.8%, p=0.486) and anti-HCV (0.6% vs. 0.8%, p=0.533) positivity between groups (Table 2).

Table 1. Type of the circumcision with respect to serological findings

	HBsAg		Anti-HBs		Anti-HCV	
	Positive	Total	Positive	Total	Positive	Total
Type of circumcision	n (%)	n	n (%)	n	n (%)	n
Mass circumcision	27 (5.4)	501	19 (9.6)	198	0 (0.0)	503
Health technician	141 (3.4)	4113	157 (9.9)	1587	24 (0.6)	4115
Barber	21 (5.2)	405	10 (7.6)	131	7 (1.8)	394
Hospital	18 (3.4)	527	38 (14.2)	268	3 (0.6)	531
Outpatient clinic	6 (1.8)	332	7 (4.5)	155	3 (0.9)	341
Total	213 (3.6)	5878	231 (9.9)	2339	37 (0.6)	5884

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface, HCV: Hepatitis C virus

Discussion

Education and counselling programs have been suggested to inform practitioners of traditional and folk medicine (e.g. tattooing, body piercing and circumcision) as well as people using such services about the risk of hepatitis infection due to the use of non-sterile instruments or objects (1). Therefore, it seems more safe to make circumcision in the hospitals instead of other unhygienic places outside the hospitals in terms of medical complications (10). In our study, it was obvious that only a very small proportion of circumcisions were done in the hospitals (n=531) in compared to the outside the hospital in Turkey. Indeed, most of the circumcisions in Turkey have been documented to be performed at home, health centers or schools. Mass circumcisions are usually done as a part of religious ceremonies sponsored by charity organizations and local administrations or political societies. Although experienced doctors, health workers or technicians were identified to perform some of these circumcisions; in rural areas, most of the circumcisions have been reported to be performed by unexperienced staff (10). Likewise, in a previous study concerning frequency of hepatitis B and C in rural and periurban Sindh, only 14.8% of individuals, circumcision was identified to be performed by doctors, while in the remaining it was done by barbers using unsterilized instruments (11).

On the other hand, recent epidemiological studies have shown that male circumcision has a protective effect against sexually-transmitted diseases (12). However, usage of contaminated equipment during mass circumcision may cause transmission of blood-borne viruses such as HBV. In their study, Aweis et al. (13) investigated the prevalence hepatitis B and the risk factors of HBsAg-carriage among Somali population living in Liverpool and they found that a history of circumcision in Somalia was the most significant predisposing factor.

Mass circumcision is a very common practice, especially, in cases of charity; hundreds of children are being circumcised by traditional nonmedical people. In such cases, high probability of using the same surgical equipments for more than one child increases the risk of HBV infection (14). Otkun et al. (14) reported that the overall HBsAg-seropositivity was 1.7% and, notably, mass circumcision was documented as the only independent factor according to regression analysis comparing with uncircumcised children and those circumcised singly (anti-HBc positivity rates were 12.5%, 4.5% and 6.2%, respectively). Ozdemir (15) indicated that traditional nonmedical persons were responsible for 85% of the circumcision complications. The frequency of complication associated with mass circumcision was significantly higher than that related with circumcisions performed singly in operating room conditions. In our study, overall HBsAg-positivity in total population was 3.6%. We found that mass circumcision and circumcisions performed by barbers were associated with higher rates of HBsAg-positivity (5.4% and 5.2%, respectively). When the subjects were classified as being circumcised by a traditional non-medical person or a health professional, HBsAg positivity was significantly higher in the first group [5.3% (48/897) vs 3.3% (165/4987)] (p=0.003). There were no significant relationship between anti-HBs (8.8% vs 10%, p=0.486) and anti-HCV positivity (0.8% vs 0.6%, p=0.533).

Likewise, in a previous study about the prevalence and risk factors of hepatitis B and C virus infections in an impoverished urban community in Dhaka, Bangladesh, HBV positivity was identified in 84.1% of the patients with circumcision history. There was a significant association between circumcision with HBV-seropositivity (OR 3.21, p<0.001) (16).

Medhat et al. (17) researched risk factors for HCV infection in a village in Upper Egypt. They found that circumcision is a very common procedure and was not associated per se with anti-HCV presence, however, circumcision by a nonmedical person rather than a health professional was associated with anti-HCV among young male population (4.9% vs 0.5%, p<0.001). In our study, anti-HCV prevalence was not seemed to be associated with circumcision type or person.

Although, it is an important study for population healthcare, this study has some limitations. We don't have anti-HBs results for all participants, we had limited anti-HBs tests in some regions of the country during the study period. We could not get any information about pre-circumcision HBV and HCV serology results, hepatitis infections in related to other risk factors (tattoos, scarification, injection, drug use, surgical procedures, etc.) that may contribute the hepatitis infections. We could not have any medical records of participants related with the circumcision procedure to confirm the inquiry results. In our study population, circumcision was performed at childhood period but the mean age of the participants during the study was 35 years; so adults might not remember important informations about their circumcision, which were the questions they were asked for the study.

Table 2. Comparison of hepatitis serology in circumcisions performed by health professionals (health technician, in a hospital, in a private outpatient clinic) or nonmedical persons (barber, mass circumcision)

	HBsAg[a]		Anti-HBs[b]		Anti-HCV[c]	
	Positive	Total	Positive	Total	Positive	Total
Circumcision by	n (%)	n	n (%)	n	n (%)	n
Health professional	165 (3.3)	4972	202 (10.0)	2010	30 (0.6)	4987
Nonmedical person	48 (5.3)	906	29 (8.8)	329	7 (0.8)	897
Total	213 (3.6)	5878	231 (9.9)	2339	37 (0.6)	5884

[a]p=0.003, [b]p=0.486, [c]p=0.533 (c2 test)

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface, HCV: Hepatitis C virus

Conclusion

In conclusion, our findings, representing the first large-scale epidemiological data on circumcision and hepatitis transmission in Turkey, indicating mass circumcisions and circumcisions done by barbers that may pose a great risk for public health for their significant relationship with higher incidence of HBsAg positivity. Mass circumcision has been done for sociocultural and religious reasons for many years and it is usually done outside the health centers. For adequate infection controlling practices and prevention of infectious transmission, it is important to establish guidelines to ensure standardization of circumcision procedure and also maintain the educational collaborations of health officials with traditional non-medical circumcisers in Turkey.

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Ethics

Ethics Committee Approval: This trial done with permission of Basic Health Department of Ministry of Health. Informed Consent: Verbal consent was obtained from.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Concept: İsmail Balık, Fehmi Tabak, İrfan Şencan, Neşe Saltoğlu, Design: İsmail Balık, Fehmi Tabak, Necati Örmeci, Data Collection or Processing: Selma Tosun, Fehmi Tabak, Neşe Saltoğlu, Analysis or Interpretation: Selma Tosun, Literature Search: Selma Tosun, Neşe İnan, Writing:Selma Tosun, Neşe İnan.

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Research Article

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Efficacy and Safety of Telbivudine in Chronic Hepatitis B Treatment Throughout the Entire Pregnancy

Gebe Kadınlarda Tüm Gebelik Dönemi Boyunca Kronik Hepatit B Tedavisinde Telbivudinin Etkinliği ve Güvenilirliği

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ABSTRACT

Objective: Women of childbearing potential treated for chronic hepatitis B virus (HBV) infection may experience exacerbations during or after pregnancy. Infants may also acquire HBV infection through perinatal route. Currently, there is no antiviral agent approved for use in pregnancy. This makes it difficult to decide whether treatment should be withdrawn immediately or continued in women who become pregnant while on HBV antiviral therapy. The present study aims to establish the safety and, as a second measure, the efficacy of telbivudine in patients who became pregnant while they were on telbivudine treatment for chronic HBV infections and were maintained on the treatment throughout pregnancy.

Materials and Methods: Between 2010 and 2013, twenty-one patients, who became pregnant while receiving telbivudine treatment for chronic HBV infection and continued the treatment, were evaluated retrospectively.

Results: The mean age of the patients was 28.9±6.3 years (range: 18-41 years). All patients were hepatitis B envelope antigen-negative. The mean pre-treatment hepatic activity index was 9.4±1.6 (range: 7-13), and fibrosis and serum HBV, DNA measurements were 3.2±0.8 (range: 2-5) and $3.5x10^5±2.8x10^5$ IU/mL, respectively. No drug-related side effects were seen in any of the patients. All infants had normal birth weights and no abnormalities were observed in any of them. At the end of week 28, none of the infants was hepatitis B surface antigen-positive.

Conclusion: The use of telbivudine from the first trimester of pregnancy appears to be safe both for the mother and fetus and

ÖZ

Amaç: Kronik hepatit B virüsü (HBV) nedeni ile takip edilen doğurganlık çağındaki kadın hastalarda kronik karaciğer hastalığı gelişebilir, gebelik döneminde veya sonrasında alevlenmelere neden olabilir, bununla birlikte perinatal dönemde HBV bulaşı ile bebek infekte olabilir. Gebelik döneminde HBV enfeksiyonu için kullanımı onaylanmış bir antiviral ilaç yoktur. Bu nedenle, antiviral ilaç kullanırken gebe kalan kadınlarda tedaviyi sonlandırma ya da devam etme kararını vermek zordur. Bu çalışmada kronik HBV enfeksiyonu nedeniyle telbivudin tedavisi almakta iken gebe kalan ve tüm gebelik dönemi boyunca tedavi alan hastalarda telbivudinin ilk etapta güvenilirliğini daha sonra ise etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: 2010-2013 yılları arasında kronik HBV enfeksiyonu nedeniyle telbivudine tedavisi kullanırken gebe kalan ve tedaviye devam kararı verilen 21 hasta retrospektif olarak değerlendirildi. Tüm hastaların tedavi başlandığı andaki serum hepatit B yüzey antijeni, hepatit B zarf antijen, anti-HBe, HBV DNA, alanin aminotransferaz (ALT), aspartat aminotransferaz (AST) seviyeleri, hepatik aktivite indeksi ve fibrozis değerleri kaydedildi. Daha sonra hastaların gebelik başlangıcı, gebelik dönemi boyunca ve doğum sonrası 6. aya kadar 3'er ay ara ile serum hepatit B yüzey antijeni, hepatit B zarf antijen, anti-HBe, HBV, DNA, ALT, AST seviyeleri ölçüldü.

Bulgular: Hastaların yaş ortalaması 28,9±6,3 (yaş aralığı: 18-41) idi. Tüm hastalar hepatit B zarf antijen negatif idi. Tedavi öncesi hepatik aktivite indeksi ortalama 9,4±1,6 (yaş aralığı: 7-13), fibrozis 3,2±0,8 (yaş aralığı: 2-5), serum HBV DNA düzeyi $3,5x10^5±2,8x10^5$ IU/mL idi.

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to be efficient in preventing mother-to-child transmission of HBV infection. However, randomized, controlled studies involving a higher number of subjects are needed.
Keywords: Pregnancy, chronic hepatitis B, treatment, telbivudine

Hastaların hiçbirinde ilaca bağlı yan etki görülmedi. İnfantların hepsi normal doğum ağırlığına sahipti ve hiçbirinde anomali saptanmadı. Ayrıca 28. haftanın sonunda infantların hiçbirinde hepatit B yüzey antijen pozitifliği mevcut değildi.
Sonuç: Telbivudinin gebeliğin ilk trimesterinden itibaren kullanımı, hem anne hem fetus açısından güvenli, anneden infanta HBV geçişini önlemede de etkin görünmektedir. Bununla birlikte hasta sayısının daha fazla olduğu randomize kontrollü çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Gebelik, kronik hepatit B, tedavi, telbivudin

Introduction

About 350-400 million people worldwide are hepatitis B virus (HBV) carriers and about 1 million people die each year due to HBV-related complications (1). The prevalence of HBV infection varies by geographic region. Our country is in a intermediate-endemic area with a carrier rate of 2-10% (2). Transmission from mother to infant becomes a more important issue with increasing endemicity (3). Perinatal transmission is associated with a higher risk for chronic condition and occurrence of complications including cirrhosis and hepatic cancer (4). Therefore, it is important to prevent HBV transmission from mother to infant. Although pregnant women are screened for HBV and infants born to HBV-positive mothers are routinely vaccinated and given immunoglobulin, perinatal transmission may be an issue especially in pregnant women with a high level of viremia (5). Mothers may also experience exacerbations of chronic hepatitis B during or after pregnancy. Acute exacerbations of chronic HBV infection may have a severe course and may be associated with fatality rates of 20-30% (4,6). In pregnant women, who already started antiviral treatment, the treatment should be maintained if liver biopsy demonstrates advanced fibrosis as withdrawal of treatment may result in exacerbations (7).

There is currently no antiviral agent approved for the treatment of chronic HBV infection in pregnancy. This makes it difficult to decide whether the treatment should be discontinued or maintained in women who become pregnant while receiving an antiviral agent. The health of both the mother and infant should be taken into consideration when making this decision. The major concern for the fetus is drug exposure during embryogenesis, while the primary issue for the mother involves the risk of disease exacerbation and progression because treatment cannot be initiated or should be discontinued due to pregnancy. This effect on the health of the mother may also affect the health of the fetus and the lives of both the mother and the fetus may be compromised (8). Of the nucleoside and nucleotide analogues that are being widely used for chronic HBV infection, lamivudine, adefovir and entecavir are assigned to category C and telbivudine and tenofovir category B by the Food and Drug Administration (FDA) (8). Telbivudine is an oral nucleoside analogue and is one of the two agents that can be used in pregnancy. Clinical experience, however, is quite limited (9). There are a few studies in the literature on the efficacy and safety of its use particularly throughout the whole pregnancy. In the present study, we aimed to investigate the safety and, as a second measure, the efficacy of telbivudine in patients who became pregnant while they were on telbivudine treatment for chronic HBV infection and were maintained on the treatment throughout pregnancy.

Materials and Methods

This is a retrospective study performed with the participation of five hospitals from Turkey. A standard questionnaire was sent to each hospital participating in this study and the data were collected via a computerized database. Pregnant women receiving antiviral therapy and their partners were contacted with and, based on their prior treatment experiences, hepatitis B envelope antigen (HBeAg) status, HBV DNA values and fibrosis values with hepatic biopsy results, they were informed about the possible risks to the mother and the infant should the treatment is withdrawn or continued. Patients who were maintained on treatment underwent periodic checks by an obstetrician. Approval of the relevant ethics committee was received.

Patients

Medical files of 256 patients, who were examined for chronic HBV infection and received telbivudine treatment between 2010 and 2013, were reviewed. Twenty-one patients, who became pregnant while on telbivudine and decided to remain on treatment, were included in this study. The inclusion criteria were as follows;

1) The patient should have started telbivudine treatment before becoming pregnant and continued therapy throughout pregnancy,

2) Should have no other underlying condition,

3) Should be negative for human immunodeficiency virus, hepatitis C virus and hepatitis D virus. All patients were reviewed for toxoplasmosis, syphilis, rubella, herpes, and cytomegalovirus and, these diseases were excluded. All patients were given folic acid over the first trimester. Routine screening tests for phenylketonuria and hypothyroidism were also performed for all infants.

Data were retrieved by reviewing patient files retrospectively. Baseline serum HBsAg, HBeAg, anti-HBe, HBV DNA, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, hepatic activity index and fibrosis values were recorded for each patient. Further serum HBsAg, HBeAg, anti-HBe, HBV DNA, ALT, and AST measurements were performed at pregnancy onset, during and following pregnancy every 3 months up to post-natal month 6. In addition, all fetuses were monitored for abnormalities periodically throughout the intrauterine phase. To prevent chronic HBV infection, all infants were given 100 IU of intramuscular

hepatitis B immunoglobulin (HBIG, HyperHEP B solvent/detergent treated; Talecris Biotherapeutic, NC, United States) and 10 mcg of intramuscular hepatitis B (Recombivax HB; Merck Sharp and Dohme, NJ, United States) vaccines according to the relevant guidelines. Further doses of hepatitis B vaccine, one at week 4 and another at week 24, were administered. At the end of week 28, all infants were evaluated for HBsAg, anti-HBs and HBV DNA. In addition, all infants were monitored for any abnormalities and growth retardation for one year.

Laboratory Tests

HBV DNA was quantified using the Roche COBAS Amplicor HBV monitor assay which has a low limit of detection (LLD) of 500 copies/mL (Roche Molecular Diagnostics, Branchburg, NJ, United States). This assay was later replaced by the Roche COBAS TaqMan HBV test with a LLD of 50 copies/mL (Roche Molecular Diagnostics). HBV serological markers were detected by enzyme-linked immunosorbent assay kits on an Advia Centaur XP chemiluminescence immunoassay instrument (Siemens, Germany) according to the manufacturer's instructions.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences 19 (Computer Resource Center, Chicago, IL, United States). Measurement data were expressed as mean±standard deviation.

Results

The mean age of the 21 patients who became pregnant while receiving telbivudine for chronic HBV infection was 28.9±6.3 years (range: 18-41 years). In 8 patients (38.1%), at least one of the previous births was HBsAg-positive. All patients were HBeAg-negative. With pre-treatment measurements, hepatic activity index was 9.4±1.6 (range: 7-13), fibrosis was 3.2±0.8 (range: 2-5) and serum HBV DNA was $3.5x10^5$±$2.8x10^5$ IU/mL. ALT, AST, and HBV DNA values measured before treatment, at pregnancy onset and at later time points are provided in Table 1. None of the patients had abortion. Two of them developed urinary tract infection after the sixth month of pregnancy. None of them experienced drug-associated side effects. Triple screening test performed over the course of the pregnancy demonstrated risk for only one mother, with the test performed at month 4, for which amniocentesis was performed, revealing no pathology. All of the infants were of normal birth weight (2700-3800 g) and none had phenylketonuria, hypothyroidism or malformations. At the end of week 28, none of the infants were HBsAg-positive. Only two infants had anti-HBs <100 mIU/mL, while the remaining 19 infants had anti-HBs levels above 100 mIU/L.

Discussion

The primary route of HBV transmission is via blood and skin and/or mucosal exposure to bodily fluids, but HBV is also present in the amniotic fluid, breast milk, vaginal secretions and cord blood (10). Perinatal transmission of HBV may be associated with significant rates of chronic infection and complications related to this infection, including cirrhosis and hepatocellular cancer (8). The prevalence of chronic HBV in pregnant women is 0.6% in low endemic areas and over 20% in high endemic areas (8,10). Studies from our country have reported HBsAg positivity rates of 2.1 to 12.3% among pregnant women (11,12,13,14). A woman of childbearing age infected with chronic HBV infection may develop chronic hepatic disease (fibrosis and/or cirrhosis) and may experience exacerbations during and following pregnancy and, furthermore, the infant may be infected via HBV transmission during the perinatal period. There is no conclusive information on the potential problems due to antiviral therapy in early pregnancy. However, if a patient has advanced fibrosis or elevated ALT levels, it may become necessary following a risk-benefit assessment to initiate treatment and to maintain the therapy throughout pregnancy (6,8,14). The FDA has defined risk categories regarding the use of medicines during pregnancy. Accordingly, telbivudine, an agent used in chronic HBV infection treatment, is included in the pregnancy category B (15). There are several studies in the literature on the use of telbivudine during pregnancy. However, most of these reports concern patients treated with telbivudine during the second or third trimesters of pregnancy to prevent transmission of HBV from the mothers with high viral load to their infants (16,17,18,19). To the best of our knowledge, there have been a very few reports on the safe use of telbivudine throughout the whole pregnancy, beginning from the first trimester (9,20). Treatment is challenging in women of childbearing potential. Given the 48-week treatment duration, interferons may be considered as the first choice if pregnancy is not being planned for the near future in these women. Problems are being encountered when deciding whether oral antiviral treatment should be started in situations where the women intent to become pregnant soon, have advanced hepatic disease and treatment delay would be risky. In case oral antiviral treatment has been initiated, the increased risk of mortality for both the mother and the infant due to possible acute chronic HBV infection exacerbation if the treatment is withdrawn when the patient becomes pregnant, presents another challenge. The present study examined the safe use of telbivudine throughout the whole pregnancy beginning from the first trimester during which embryogenesis takes place. A total of 21 patients who became pregnant while receiving telbivudine were evaluated in the study. Benefit to risk ratio was discussed with each individual patient since they all had advanced hepatic disease. An obstetrician also participated in the monitoring of patients who were maintained on

Table 1. Maternal laboratory investigation outcome

Maternal outcomes	Pre-treatment period	The beginning of pregnancy	6th month of pregnancy	Postpartum 3rd month	Postpartum 6 month
HBV DNA, (IU/mL)	$3.5x10^5$	Negative	Negative	Negative	Negative
ALT, (IU/L)	46.1	30.9	28.6	25.7	26.7
AST, (IU/L)	40.7	27.7	24	22.9	21.9

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

treatment. The mothers did not develop hepatic disease exacerbations throughout pregnancy and over the postpartum period and no side effects were observed. Congenital abnormalities were not observed in infants of the mothers treated with telbivudine. Maternal HBV transmission did not occur.

Conclusion

In conclusion, the use of telbivudine since the first trimester of pregnancy appears to be safe both for the mother and fetus and efficient in preventing HBV transmission from the mother to the infant. However, randomized, controlled studies involving a higher number of subjects are needed.

Ethics

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şafak Kaya, Selçuk Aksöz, Mehmet Cabalak, Eyüp Arslan, Şenol Comoğlu, Pınar Tantekin, Concept: Birol Baysal, Şafak Kaya, Design: Habibe Çolak, Recep Tekin, Data Collection or Processing: Birol Baysal, Şafak Kaya, Analysis or Interpretation: Birol Baysal, Şafak Kaya, Literature Search: Nuran Akmirza, Birol Baysal, Şafak Kaya, Writing: Birol Baysal, Şafak Kaya

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Research Article

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Investigation of Hepatitis Serology and Occupational Exposure Risk to Viral Hepatitis in Hospital Housekeeping Staff

Hastane Temizlik Çalışanlarının Hepatit Serolojileri ve Mesleki Viral Hepatit Temas Risklerinin Araştırılması

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ABSTRACT

Objective: Viral hepatitis is still an important health problem in our country. Healthcare workers (HCWs) are at a higher risk for acquiring viral hepatitis. Hospital housekeeping staff, working in similar conditions with HCWs, are a very difficult group in terms of training and follow up. In this study, it was aimed, It was aimed to investigate the serological status and occupational exposure risk of our hospital housekeeping staff to viral hepatitis.

Materials and Methods: A pre-prepared questionnaire was completed for each cleaning staff member working at the hospital through one-on-one interviews. The data regarding education level, job experience, attendance to previous training programs and vaccination status were collected in this questionnaire and for each staff one questionnaire form was filled. Serological tests for hepatitis A, B, and C were done.

Results: The hepatitis B surface antigen (HBsAg) positivity rate among our hospital housekeeping staff was 4.9%, and 8.9% of them tested negative for anti-hepatitis A virus (HAV) IgG. Anti-hepatitis C virus (HCV) positivity was 0%. 48.1% of the staff had completed primary school. 61.7% of the staff reported that they did not receive any training on the methods of protecting against blood-borne pathogens. 81.5% of them did not have any experience of working in a healthcare setting and only 8.6% of them have been previously vaccinated against hepatitis B.

Conclusion: HBsAg seropositivity rate in housekeeping staff in our sample was higher than in the normal population and was similar to that in other HCWs. Their anti-HAV IgG and Anti-HCV positivity rates were similar to that in the normal population. It was determined that the group had a low education level and did not have any experience of working in a healthcare setting and their hepatitis B virus immunization rate was low (8.6%). We concluded that annual health check, vaccination and frequency of training programs are not sufficient for hospital housekeeping staff and we suggest that serology testing, vaccination of sero-negative personnel and training related to blood and body fluid exposure risks, and protection methods should be performed at the time of job start.

Keywords: Occupational risk, hepatitis A, hepatitis B, hepatitis C, seroprevalence

ÖZ

Amaç: Viral hepatitler ülkemizde halen önemini koruyan bir sağlık sorunudur. Sağlık çalışanları viral hepatitler açısından riskli grupta bulunmaktadırlar. Hastanede çalışan temizlik çalışanları sağlık çalışanları ile benzer koşullarda çalışmakta olup, eğitimleri ve takipleri oldukça zor olan bir gruptur. Bu çalışmada hastanemizde çalışan temizlik elemanlarının bu konudaki riskleri ve hepatit serolojilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Hastanemizde çalışmakta olan temizlik görevlileri ile yüz yüze hazırlanmış olan anket formu dolduruldu. Bu ankette temizlik çalışanlarına eğitim durumları, deneyimleri, aldığı eğitimler soruldu ve her temizlik çalışanı için bir form dolduruldu. Hepatit A, B ve C serolojileri çalışıldı.

Bulgular: Temizlik elemanlarında hepatit B'nin yüzey antijeni (HBsAg) pozitiflik oranı %4,9, anti-hepatit A virüsü (HAV) IgG negatiflik oranı %8,9 ve anti-hepatit C virüsü (HCV) pozitiflik oranı %0 olarak tespit edildi. Çalışanların %48,1'inin ilkokul mezunu olduğu, %61,7'sinin kan ve vücut sıvılarıyla bulaşan patojenlere karşı korunma ile ilgili eğitim almadığı, %81,5'inin daha önce bu iş kolunda deneyimi olmadığı ve sadece %8,6'sının işe başlamadan önce hepatit B aşısı yaptırdığı tespit edildi.

Sonuç: Çalışmamızda temizlik elemanlarında hepatit A ve anti-HCV pozitiflik oranlarının toplumla benzer, HBsAg pozitiflik oranının ise toplumdan yüksek ve diğer sağlık çalışanları ile benzer oranlarda olduğu saptandı. Bu grubun eğitim düzeyinin çok düşük olduğu ve daha önce hastanede çalışma konusunda deneyimleri olmadığı, hepatit B aşılanma oranlarının çok düşük (%8,6) olduğu tespit edildi. Hastane temizlik çalışanları için uygulanan yıllık sağlık kontrolü ve eğitimlerin sıklığının yetersiz olduğu ve bu personelin işe başlarken hepatit serolojilerinin araştırılması, seronegatif olanların aşılanmaları ve kan ve vücut sıvılarıyla bulaşan patojenler, temas riskleri ile korunma yöntemleri hakkında eğitim almaları gerektiğine karar verildi.

Anahtar Kelimeler: Mesleki risk, hepatit A, hepatit B, hepatit C, seroprevalans

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Introduction

Viral hepatitis is still an important health problem in our country. Healthcare workers (HCWs) are at a higher risk for acquiring viral hepatitis. They can get infected through percutaneous injury from a contaminated sharp instrument or exposure to infected blood and body fluids (1,2). Among HCWs, sero-positivity rates in different age groups from different cities and different occupational groups have been reported to vary between 77.5% and 100% for anti-hepatitis A virus (HAV) IgG, 1% and 4% for hepatitis B surface antigen (HBsAg) and 0% and 2% for anti-hepatitis C virus (HCV) (3,4,5,6). At hospitals, housekeeping staff generally work as subcontracted laborers and often change between the business and health-care sectors. They are a very difficult group to follow up because of frequent job switches but they have similar risks of acquiring viral hepatitis with other HCWs. In this study, we aimed to investigate viral hepatitis transmission risk, serologic status and vaccination rates in our hospital housekeeping staff who do not get any specific education and have different working conditions but have similar environmental risks with other HCWs.

Materials and Methods

The study was conducted between January 2013 and May 2013 in Yenimahalle Training and Research Hospital, a 250-bed secondary-care hospital. All 81 members of the cleaning staff (46 male, 35 female) were included in our research. The mean age of the subjects was 35.8 years (range: 20-53 years). A questionnaire was completed through a one-on-one interview with each housekeeping staff member, and data regarding education level, previous experience in working in a healthcare setting, previous participation in training programs covering occupational exposure to blood-borne pathogens and protection methods, and hepatitis B vaccination status were collected. Serological tests for hepatitis A, B and C were done using the direct chemiluminescence sandwich immune test method (ADVIA Centaur® CP Immunoassay System, Germany) in our microbiology laboratory. The test results were added to the form.

Results

Four subjects (4.9%) were found to be HBsAg-positive, 24 (29.6%) were anti-HBs-positive and 51 (63%) subjects were anti-HAV IgG-positive. None of them tested positive for anti-HCV (Table 1). One of them was unaware of being HBsAg-positive. Only 7 (8.6%) of them have previously received hepatitis B vaccine and 17 (21%) of them had natural immunity against hepatitis B. Anti-HAV IgG testing was not performed in 25 (30.9%) of them. Anti-HAV IgG sero-positivity rate was 91.1% for the remaining. Nearly half of them (39/81, 48.1%) were primary school graduates, 18 (22.2%) had completed secondary school and 24 subjects (29.6%) were high-school graduates. Only 14 of them (16%) had 0-5 years' experience and only one subject (2.5%) had 5-10 years' experience of working in a healthcare setting (Table 2). We had 15 (%18.5) housekeeping staff members who had worked at another hospital previously and 4 of them reported previous participation in training covering occupational exposure to blood-borne pathogens and protection methods. Thirty-nine of the 66 cleaning staff with no previous experience reported that they had received no training. As a result, only 38.3% (31/81) in total had a previous training on exposure risks and protection methods. Two (2.5%) reported that they had had contact with contaminated material while not wearing gloves. Thirteen (16%) reported that they had been injured at least once with a sharp instrument (Table 2).

Discussion

HCWs, including housekeeping staff, are at risk of acquiring hepatitis following accidental exposure to blood and body fluids (1). This risk is higher in countries like Turkey where hepatitis is more common, since the HBsAg positivity rate in HCWs will be proportionate to the HBsAg positivity rate in the general population (7,8). In the literature, reported HBsAg sero-positivity rates among HCWs vary between 1% and 4.4%. Data from studies investigating the serologic status of hospital housekeeping staff revealed similar

Table 1. Hepatitis serology among the hospital housekeeping staff

	HBsAg	Anti-HBs	Anti-HCV	Anti-HAV IgG
Positive	4 (4.9%)	24 (29.6%)	0	51 (63%)
Not performed	0	0	0	25 (30.9%)
Negative	77 (95.1%)	57 (70.37%)	81 (100%)	5 (6.2%)

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HAV: Hepatitis A virus, IgG: Immunoglobulin

Table 2. The survey result among the hospital housekeeping staff

Number (%)	
Education	
Primary school	39 (48.1)
Secondary school	18 (22.2)
Highschool	24 (29.6)
Experience	
Nothing	66 (81.5)
0-5 years	14 (16.0)
5 <years	1 (2.5)
Training	
Had	28 (34.6)
Didn't have	50 (61.7)
Not remembering	3 (3.7)
Hepatitis B vaccination	
Had	60 (74)
Didn't have	17 (20.9)
Not remembering	4 (4.9)
Where got the vaccine	
At our hospital	53 (65.4)
Before starting the job	7 (8.6)
Not having the vaccine (natural immunity and HBsAg positive)	21 (26)
Contact with the medical waste without gloves	
Yes	2 (2.5)
No	79 (97.5)
Injury with a used instrument	
Yes	13 (16)
No	68 (84)

HBsAg sero-positivity rates between hospital housekeeping staff and HCWs, being between 1.5% and 4.4%. In our study, 4.9% of the hospital housekeeping staff were positive for HBsAg. To our knowledge, this is the highest encountered sero-positivity rate for this group when compared with the results of similar studies from Turkey (5,9). In the literature, reported anti-HBs sero-positivity rates and hepatitis B vaccination rates among HCWs ranges from 20.6% to 79.3% and from 44.4% to 90%, respectively (5,10,11,12). Vaccination rates were lower among HCWs working in private hospitals compared to those in state hospitals (5). Both in our study and in other studies, it has been shown that hepatitis B sero-positivity rate among HCWs is higher than in the normal population (13). One housekeeping staff member who was unaware of being HBsAg-positive was followed up by our infectious diseases clinic. It is important to test HCWs for HBsAg and follow up of sero-positives (11).

The rate of exposure to sharp injuries was 16% among hospital housekeeping staff in our study. This rate was lower than the rate reported in some of the previously published studies (80%). This might be due to the fact that the housekeeping staff were not questioned for repeated exposure to sharp injuries as well as underreporting and use of plastic boxes for the disposeal of used sharp instruments (13,14,15,16). Although our rate of exposure to sharp injuries among hospital housekeeping staff was lower than the rates reported in other studies, it was still high and when the high HBsAg sero-positivity rate in our population is taken into consideration, the risk of contacting to the viral hepatitis is higher than expected (12,16). Hospital housekeeping staff are considered an at-high-risk group for percutaneous injuries (15,17). Even if the rate of glove use is high in our study, the real exposure rate with blood and body fluids is not known and this poses a risk for infection (14).

In our study, the anti-HAV IgG positivity rate was similar to that in studies published previously and it was similar to that in the normal population (3,6). There are some reports on hospital outbreaks of hepatitis A. The seropositivity for hepatitis A is age-dependent and the rate of vaccination among sero-negatives is very low (3,11,18,19). Housekeeping staff and HCWs working in nursing homes, infectious diseases or pediatric clinics are at a higher risk for hepatitis A (20). Seronegative HCWs and housekeeping staff, especially those working in these high risk areas, should get vaccinated.

None of the housekeeping staff tested positive for anti-HCV. Data from studies performed between 2008 and 2012 among HCWs revealed anti-HCV positivity rates between 0% and 0.49% (4,6). In our study, none of the hospital housekeeping staff tested positive for anti-HCV. This result was similar to the normal population (4,10).

In our study, the rate of previous hepatitis B vaccination among hospital housekeeping staff was 8.6% which is very low and emphasizing the importance of hepatitis serology testing and vaccination in this group. In a study done in 2003 by Şencan et al., (21) the rate of hepatitis B vaccination among HCWs was 7.1%. In our study, the rate is similar reflecting that the attitude of HCWs towards vaccination did not improve in more than one decade. The rate of vaccination in hospital housekeeping staff was lower than in other HCWs (8,12). Not receiving any training on the risks of exposure to blood and body fluids and protection methods increases the risk of hepatitis transmission (8). Our results showed that although hepatitis serology screening tests were performed routinely and there was a training and vaccination program in place at our hospital, 61.2% of housekeeping staff did not receive any training and a high (16%) sharp injury rate was reported. We assume that this situation was due to high employee turnover.

We conclude that annual training, screening and vaccination programs are not sufficient for hospital housekeeping staff since they might miss the program as a result of employee turnover. We suggest that immediately upon starting the job, hepatitis screening tests, vaccinations and a training program about exposure risks and protection methods should be performed for this group of workers.

Ethics

Ethics Committee Approval: The study weren't approved by any Ethics Committee, Informed Consent: Consent form wasn't filled out by the participants.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Semiha Solak Grassie, Concept: Semiha Solak Grassie, Sümeyra Çetin Gevrek, Design: Semiha Solak Grassie, Data Collection or Processing: Sümeyra Çetin Gevrek, Analysis or Interpretation: Semiha Solak Grassie, Literature Search: Semiha Solak Grassie, Writing: Semiha Solak Grassie.

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Research Article

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The Efficiency of Hepatitis C Virus Core Antigen Test in the Diagnosis of Hepatitis C Infection

Hepatit C Enfeksiyonunun Tanısında Hepatit C Virüsü Kor Antijen Testinin Etkinliği

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ABSTRACT

Objective: It was aimed to investigate diagnostic value of hepatitis C virus (HCV) core antigen test in patients with positive or negative anti-HCV assay by comparing with HCV ribonucleic acid (RNA) assay.
Materials and Methods: Serum samples obtained from 189 patients who were admitted to Necmettin Erbakan University Meram Faculty of Medicine between December 2010 and February 2012, and HCV RNA assay were carried out for various reasons. Two mL of samples were stored under suitable conditions and anti-HCV, HCV core antigen and strip immunoblot assay [Commercial INNO LIA™ HCV Score (Innogenetics NV in Ghent, Belgium)] were performed. Genotyping was performed in the amplicons of the samples with positive HCV RNA test.
Results: The diagnostic sensitivity specificity, negative predictive value and positive predictive value of HCV core antigen test were 96.2%, 100%, 97.3%, and 100%, respectively. Sixty-five serum samples were genotyped and their distribution were detected: Fifty-nine samples were genotype 1b, 2-genotype 1a/1b, 1-genotype 3a, 1-genotype 4, 1-genotype 2a/2c, and 1 was genotype 1a.
Conclusion: It was concluded that HCV core antigen assay is highly specific, sensitive, reliable, reproducible, and easy to perform. It may be applied as a supplemental and confirmatory test in anti-HCV assays in the diagnosis of HCV.
Keywords: Hepatitis C virus, core antigen, hepatitis C virus ribonucleic acid, strip immunoblot assay

ÖZ

Amaç: Hepatit C virüsü (HCV) kor antijen testinin tanı değerinin anti-HCV testi pozitif veya negatif olan hastalarda HCV ribonükleik asit (RNA) ile kıyaslanarak araştırılmasıdır.
Gereç ve Yöntemler: Necmettin Erbakan Üniversitesi Üniversitesi Meram Tıp Fakültesi'ne Aralık 2010- Şubat 2012 tarihleri arasında başvuran ve çeşitli nedenlerle HCV RNA testi çalışılan 189 hastadan elde edilen serum örnekleri bu çalışmaya dahil edildi. İki mL serum örneği uygun koşullar altında saklandı ve anti HCV, HCV kor antijen ve strip immünblot testi [Ticari INNO LIA™ HCV Score testi (Innogenetics NV in Ghent, Belçika)] testleri çalışıldı. HCV RNA pozitif olan örneklere genotipleme yapıldı
Bulgular: Çalışmamızda HCV kor antijen testinin sensitivite, spesifite; negatif prediktif değer ve pozitif prediktif değerleri sırayla %96,2, %100, %97,3 ve %100 olarak tespit edildi. Genotipleme yapılan 65 örneğin 59'u genotip 1b, 2'si genotip 1a/1b, 1'i genotip 3a, 1'i genotip 4, 1'i genotip 2a/2c ve 1'i genotip 1a olarak tespit edildi.
Sonuç: HCV kor antijen testi sensitivitesi ve spesifitesi yüksek, kolay uygulanabilir, güvenilir bir testtir. Bu test HCV enfeksiyonunun tanısında anti-HCV test sonuçlarının konfirmasyon ve tamamlayıcı testi olarak kullanılabilir.
Anahtar Kelimeler: Hepatit C Virüsü, kor antijen, hepatit C virüsü ribonükleik asit, strip immünblot testi

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Introduction

Hepatitis C virus (HCV) is classified within the genus Hepacivirus in the Flaviviridae family. It is a single-stranded RNA virus with positive polarity (1,2). There are approximately 200 million individuals infected with HCV throughout the world. Moreover, HCV is considered as the most important reason for liver diseases in both developed and developing countries (3). HCV prevalence varies greatly in geographic distribution depending on the level of development of the country. High prevalence is found in Africa and Asia, whereas the ratio is lower in industrialized countries, such as Australia, North America, and Northern and Western Europe (4). It has been divided into six main genotypes and more than 80 different subtypes according to the nucleotide sequences of HCV (2). There is a close relationship between the genotypes and subtypes of HCV and pathogenesis and epidemiology of the disease (5,6).

Nowadays, anti-HCV assays, which detect antibodies against HCV and used as a screening test to detect HCV in blood and blood products, are performed in order to prevent transmission of HCV. Although screening tests are highly effective in reducing the risk of hepatitis C, they can give false-positive test results in some individuals without any clinical or laboratory findings related to HCV infection (7,8). However, strip immunoblot assay (SIA) is used as a supplementary test for positive anti-HCV assay results. This test has some disadvantages, such as difficulty of performing, high cost and a high percentage of indeterminate results (9). Although molecular methods are currently the most reliable method for determining HCV infection, they are time consuming and expensive and require high-technical equipment (10).

HCV core antigen is a protein which has 191 amino acids and its molecular weight is 21 kDa (11). HCV core antigen can be detected approximately 1-2 days after the emergence of HCV RNA and before the formation of anti-HCV antibodies in serum (12).

The aim of the study was to evaluate the diagnostic efficiency of HCV core antigen assay among anti-HCV-seropositive and seronegative individuals by comparing with HCV RNA assay.

Materials and Methods

This investigation was designed as a cross-sectional study. The study sample was collected from sera in which HCV RNA testing was performed for various reasons in our laboratory. One hundred eighty nine sera were obtained between December 2010 and February 2012. One hundred nine samples were taken from the HCV RNA-positive sera. As a control group, 80 samples were collected from HCV RNA-negative sera. The control group patients were admitted to the hospital for reasons not related to hepatitis infection.

The clinical research Ethics Committee of Meram Faculty of Medicine approved the study.

Anti-HCV assay was studied using commercial Architect® i2000SR chemiluminescence immunoassay (CIA) system (Abbott laboratories, diagnostics division, abbott Park, IL, USA) chemiluminescent microparticle immunoassay technology.

SIA was performed using Commercial INNO LIA™ HCV Score (Innogenetics NV in Ghent, Belgium).

HCV core antigen assay was carried out using Architect® i2000SR CIA system (Abbott laboratories, diagnostics division, and Abbott Park, IL, USA). This test is a new generation HCV core antigen assay. The test was performed following the manufacturer's instructions. 110 µl of each sample was used in the study and test period was 36-40 min. for each sample. The cut off value was 3.00 fmol/liter (0.06 pg/mL) according to manufacturer's instructions. Thus, <3.00 fmol/liter was considered as non-reactive and ≥3.00 fmol/liter was considered as reactive. The test results that were between ≥3.00 fmol/liter and <10.00 fmol/liter were retested. If both assays were nonreactive, test result was considered as nonreactive in terms of HCV core antigen. If one or both of the repeated tests were ≥3.00 fmol/liter, the test was considered as reactive (13).

Commercial COBAS® AmpliPrep/COBASv TaqMan® HCV Test (Roche Molecular Systems, USA), a nucleic acid amplification test, was applied in HCV RNA quantification. The assay features are low limit of detections (15 IU/mL) and quantification of HCV RNA, all genotypes, with a linear range of 43 to 69.000.000 IU/mL.

The samples were prepared using COBAS® AmpliPrep device, and amplification and detection was performed automatically by using COBAS® TaqMan® 48 analyzer device (Roche Molecular Systems, USA).

HCV genotyping was performed by a commercial Ampliquality HCV-TS (AB ANALITICA, Padova, Italy).

Statistical Analysis

Statistical analysis was carried out with SPSS version 16.0 (SPSS Inc, USA, IL). p value of less than 0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for statistical analysis of the data. Spearman's correlation coefficient was used to assess the linear relationship between HCV core antigen and HCV RNA concentrations. Pearson's correlation coefficient was used to assess the linear relationship between HCV core antigen concentrations and viral load values after log transformation.

Results

The study included 189 patients (80 male and 109 female). The mean age of the patients was 51.37±18.4 years.

Anti-HCV assay revealed that 148 serum samples were reactive and 41 were non-reactive.

Two samples were detected to be anti-HCV positive, HCV core antigen positive, SIA positive and, HCV RNA negative. When the HCV RNA assay was repeated with new serum samples 3 weeks later, positive HCV RNA results were obtained.

When the HCV core antigen test results of 8 samples with the values of ≥3.00 fmol/liter and <10.00 fmol/liter were retested, 6 were evaluated as non-reactive and 2 were evaluated as reactive. According to the results of SIA (Commercial INNO LIA™ HCV Score), 78 samples were positive, 103 were negative, and 8 samples were found to be indeterminate.

Study results are given in Table 1.

The HCV core Ag results are given according to HCV viral load in Table 2.

HCV RNA levels of three samples detected to be HCV RNA-positive and HCV core antigen-negative were 1.5 $x10^1$ IU/mL, 2.7 $x10^1$ IU/mL and 2.57 $x10^3$ IU/mL.

Spearman's correlation coefficient was calculated as 0.874, and a linear association was found between HCV RNA and HCV core antigen ($p<0.01$).

The correlation between the levels of HCV RNA and core antigen was significant (r=0.840, p<0.01).

The relationship between concentrations of HCV RNA and HCV core antigen is shown in Figure 1.

The results of the HCV core antigen test were compared to HCV RNA. Sensitivity, specificity, NPV, PPV, and accuracy of HCV core antigen test were 96.2%, 100%, 97.3%, 100%, and 98.4%, respectively.

Only 65 serum samples were genotyped. Their distribution were defined as follows: 59 were genotype 1b, 2 - genotype 1a / 1b, 1 - genotype 3a, 1 - genotype 4, 1 - genotype 2a/2c and 1 was genotype 1a.

Discussion

CIA and enzyme immunoassay (EIA), the most widely used methods in the diagnosis of HCV infection, have been used as a screening test (2). An important disadvantage of anti-HCV assay is that the rate of false-positive results is high especially at low anti-HCV value (8,14,15). According to the CDC guidelines, if anti-HCV results are low S/Co, a supplemental test is required (16).

Another disadvantage of anti-HCV assay is false-negative results. The reason for these cases are severe immunosuppression, hemodialysis, AIDS and agammaglobulinemia (17,18,19). In this study, HCV RNA ($5.2x10^6$ IU/mL), and HCV core antigen ($1.58x10^4$ fmol/L) were positive in serum of a chronic liver disease patient with a negative anti-HCV assay (0.12). Moreover, SIA (Commercial INNO LIA™ HCV Score) result of this sample was evaluated as negative. It was accepted as immunosuppression.

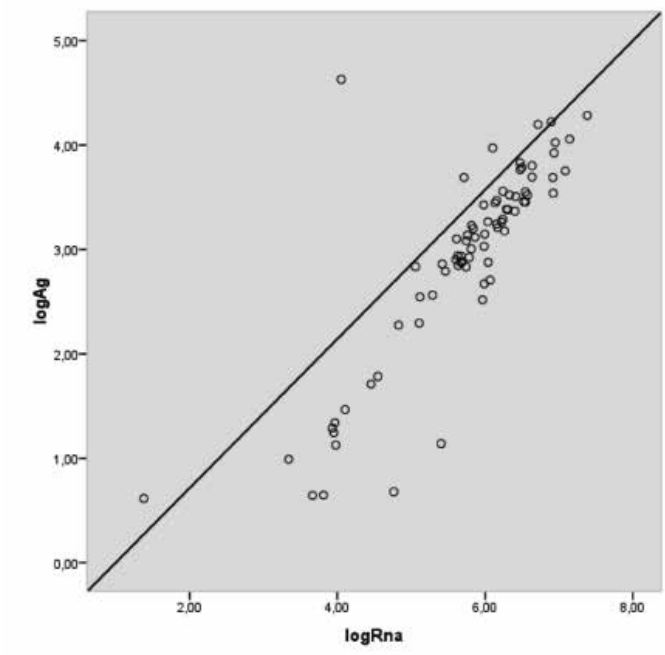

Figure 1. Correlation between hepatitis C virus ribonucleic acid (HCV RNA) and core Ag levels. Pearson's correlation coefficient showed a high correlation between the levels of HCV RNA and core antigen (r=0.840, p<0.01)

In recent years, confirmation of HCV replication has been shown to be possible by detecting and measuring HCV core antigen. While detection limit of the first generation HCV core antigen tests has been 1.5 pg/mL, that of the second generation test has been 0.06 pg/mL (3 fmol/L) (12,18,20).

HCV RNA levels have correlated with serum HCV core antigen. However, when the level of serum HCV RNA has decreased, number of false-negative results of HCV core antigen assay have increased (21,22,23,24). In this study, three serum samples with a low level of HCV RNA ($1.5x10^1$ IU/mL, $2.7x10^1$ IU/mL and $2.57 x10^3$ IU/mL) were detected with positive HCV RNA and negative HCV core antigen. The correlation between HCV RNA and HCV core antigen was significant (r=0.874, p<0.01).

In this study, two samples were detected to be anti-HCV-positive, HCV core antigen-positive, SIA-positive and, HCV RNA-negative. When the HCV RNA assay was repeated with new serum samples 3 weeks later, we obtained positive HCV RNA results. These results may appear in non-viremic HCV RNA period. In the presence of such a situation, HCV RNA should be repeated with new samples after several weeks (25,26)

In our study, SIA (Commercial INNO LIA™ HCV Score) was detected indeterminately and HCV RNA was detected negative in eight serum samples with positive anti-HCV assay. Anti-HCV S/Co results were ≤4.39 in the sera with indeterminate SIA results (Commercial INNO LIA™ HCV Score). These results suggest that results of positive anti-HCV and indeterminate SIA should be confirmed with HCV RNA. Nevertheless, the results of these sera samples with HCV core antigen assay were also non-reactive.

In this study, HCV core antigen sensitivity, specificity, PPV and NPV were found to be 96.2%, 100%, 100%, and 97.3%, respectively. These results were consistent with that of similar previous studies. Daniel et al. (27) found 85.3% sensitivity and 95.8% specificity, Miedouge et al. (23) found 100% sensitivity and 99.2% specificity,

Table 1. The results of SIA, HCV core antigen and anti-HCV assay

Test result	HCV RNA	Anti-HCV	HCV core Ag	SIA
Positive	80	148	77	78
Negative	109	41	112	103
Indeterminate	–	–	–	8

HCV: Hepatitis C virus, SIA: Strip immunoblot assay

Table 2. Hepatitis C virus ribonucleic acid core ag results according to hepatitis C virus ribonucleic viral load

		HCV core Ag	
		Negative	Positive
HCV RNA	Negative	109	0
	Positive	3	77
Viral load (IU/mL)	15-20.000	3	10
	20.000-100.000	0	4
	100.000-500.000	0	14
	500.000-800.000	0	9
	>800.000	0	40

HCV RNA: Hepatitis C virus ribonucleic acid, HCV: Hepatitis C virus ribonucleic

Kesli et al. (25) found 96.3% sensitivity and 100% specificity, Yuksel et al. (28) found 94.3% sensitivity and 97.9% specificity, Ergünay et al. (29) found 75.8% sensitivity and 95.1% specificity, and Arıdoğan et al. (30) found 86.5% sensitivity and 100% specificity.

PPV and NPV values in other studies were as follows: Daniel et al. (27) found 96.4% PPV and 83.1% NPV, Kesli et al. (25) found 100% PPV and 89.7% NPV, Yuksel et al. (28) found 99.1% PPV and 87% NPV, and Arıdoğan et al. (30) found 100% PPV and 59.4% NPV.

In this study, HCV core antigen sensitivity rate (96.2%) was higher than the results of Daniel et al. (27) (85.3%), Ergünay et al. (28) (75.8%), and Arıdoğan et al. (30) (86.5%), and was very close to the results of Kesli et al. (25) (96.3%), Yuksel et al. (28) (94.3%), and was lower than that of Miedouge et al. (23) (100%). In our study and other studies, specificity and PPV of HCV core antigen test were found to be quite high. This result suggests that positive core antigen test results are an important parameter in predicting the presence of the disease.

In conclusion, HCV antigen assay is highly specific, sensitive, reliable, reproducible, and easy to perform. It may be useful as a complementary and confirmatory test in anti-HCV assays.

Ethics

Ethics Committee Approval: The study were approved by Necmettin Erbakan University Meram Faculty of Medicine Ethics Committee, Informed Consent: Verbal consent was obtained.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Emin Demircili, Mehmet Özdemir, Bahadır Feyzioğlu, Bülent Baysal, Concept: Mehmet Emin Demircili, Mehmet Özdemir, Bahadır Feyzioğlu, Bülent Baysal, Design: Mehmet Emin Demircili, Mehmet Özdemir, Bahadır Feyzioğlu, Bülent Baysal, Data Collection or Processing: Mehmet Emin Demircili, Mehmet Özdemir, Analysis or Interpretation: Mehmet Emin Demircili, Mehmet Özdemir, Bahadır Feyzioğlu, Bülent Baysal, Literature Search: Mehmet Emin Demircili, Writing: Mehmet Emin Demircili

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Research Article

23

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Evaluation of the Relationship Between ABO/Rh Blood Groups and Severity of Liver Fibrosis in Patients with Chronic Hepatitis B

Kronik Hepatit B'li Hastalarda ABO/Rh Kan Grupları ile Karaciğer Fibrozisinin Ciddiyeti Arasındaki İlişkinin İrdelenmesi

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ABSTRACT

Objective: Studies on the severity of fibrosis in chronic viral hepatitis are scarce and limited with only hepatitis C infection. The aim of this study was to determine the role of ABO-Rh blood groups in the severity of fibrosis and progression to cirrhosis in patients with chronic hepatitis B (CHB).

Materials and Methods: This retrospective study was performed in patients who received the diagnosis of CHB in the infectious diseases clinics at Bezmialem Vakıf University Hospital. Age, sex, ABO-Rh blood groups and fibrosis scores of the patients were recorded. The patients were stratified according to severity of fibrosis (F0-2: No fibrosis/mild fibrosis and F3-6: Significant fibrosis) and the presence of cirrhosis (F0-4: No cirrhosis, F5-6: Cirrhosis).

Results: Four hundred one (59.5%) of 674 patients were male. The median age of the patients was 40 (±17.86) years. Twenty-five (3.7%) of the 171 (25.4%) patients, in whom liver biopsy was performed, the stage of the fibrosis score was ≥5 and, thus, were considered as having cirrhosis. AB0-Rh blood groups distribution in CHB cases was similar to that in blood donors in our hospital (p=0.152). It was found that O blood group significantly correlated with significant liver fibrosis (p=0.008) and the presence of cirrhosis (p=0.007). In addition, Rh positivity appeared to be related with the presence of cirrhosis (p=0.037).

Conclusion: O blood group may probably be involved in significant fibrosis and progression to cirrhosis as a host genetic factor in CHB.

Keywords: ABO blood group, chronic hepatitis B, liver fibrosis, cirrhosis

ÖZ

Amaç: Kronik viral hepatitlerde fibrozis ciddiyeti ilişkili çalışmalar hepatit C enfeksiyonu ile sınırlı olmak üzere çok azdır. Bu çalışmanın amacı, ABO-Rh kan gruplarının kronik hepatit B (KHB) hastalarında fibrozis şiddeti ve siroza gidişte rolünü saptamaktır.

Gereç ve Yöntemler: Bu çalışma Bezmialem Vakıf Üniversitesi Hastanesi Enfeksiyon Hastalıkları Kliniği'nde KHB tanısı alan hastalar arasında retrospektif olarak gerçekleştirilmiştir. Yaş, cinsiyet, ABO-Rh kan grupları ve fibrozis skorlarına ait hasta verileri kaydedilmiştir. Fibrozis ciddiyeti (F0-2: Fibrozis yok/hafif ve F3-6: Önemli fibrozis) ve siroz varlığı (F0-4: Siroz yok, F5-6: Siroz) açısından gruplandırma yapılmıştır.

Bulgular: Çalışmaya alınan 674 olgunun 401'i (%59,5) erkek idi. Yaşların ortalaması 40 (17,86) idi. Karaciğer biyopsisi uygulanan 171 (%25,4) olgunun 25'i (%3,7) fibrosis skoru ≥5 olup karaciğer sirozu kabul edilmiştir. KHB olgularının AB0-Rh kan grubu dağılımı hastanemiz kan bağışçıları verileri ile benzer saptanmıştır (p>0,05). O kan grubu ile önemli karaciğer fibrozisi (p=0,008) ve siroz varlığı (p=0,007) arasında anlamlı korelasyon saptanmıştır. Ayrıca, Rh varlığının ise siroz ile ilişkili olduğu görülmüştür (p=0,037).

Sonuç: O kan grubunun kronik hepatit B'de ileri fibrozis ve siroza gidişte konak genetik faktörü olarak rol oynayabileceği düşünülmektedir.

Anahtar Kelimeler: ABO kan grubu, kronik hepatit B, karaciğer fibrozisi, siroz

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Introduction

Blood group antigens represent hereditary polymorphic features transmitted between individuals and populations. Currently, 34 human blood group and hundreds of individual blood group antigens are known. Differences in expression of blood group antigens may affect host susceptibility to many infections. Blood groups may be directly involved in infection as a receptors or coreceptors (1). The relationship between ABO blood groups and diseases has always been an area of interest. In the early publications about this issue, cancer, peptic ulcer and thrombotic diseases were claimed to be related with ABO blood groups (2,3,4). Up to now, research on the relationship of ABO blood groups with coronary heart disease, hepatocellular carcinoma (HCC), stomach cancer, pancreatic cancer, acne vulgaris, chronic renal failure (CRF), brucellosis, malaria, Crimean-Congo haemorrhagic fever (CCHF), *Helicobacter pylori (H. pylori)* infection have been reported in the literature (5,6,7,8,9,10,11,12,13). Chronic hepatitis B virus (HBV) infection (CHB) is still considered as an important public health issue worldwide, despite the existing effective prophylactic vaccine and strong antiviral therapies. Globally 248 million patients are infected with HBV. Seroprevalance of HBV infection in Turkey is 4% (14). Liver fibrosis, which is a result of processes involved in stimulation of fibrogenesis and arrangement of fibrolysis, may lead to cirrhosis and, thus, has a major role in morbidity and mortality associated with hepatic disease. In the first step, liver fibrosis may be assessed by using experimental serum markers as an alternative to biopsy (15). There are studies showing the relationship between chronic viral hepatitis and blood groups (16,17). However, studies on the stage of fibrosis in chronic viral hepatitis are scarce and limited with only hepatitis C infection (18). Detection of ABO blood groups as a genetic risk factor is recommended during assessment of progression of hepatic fibrosis (19). In literature search, we could not find any study evaluating the stage of fibrosis and presence of cirrhosis in CHB patients and their relationship with ABO-Rh blood groups. In this manuscript, we aimed to evaluate the prevalence of ABO-Rh blood groups in CHB patients and the correlation of blood groups with severity of hepatic fibrosis and presence of cirrhosis.

Materials and Methods

Study Population

This study was conducted as a retrospective review of the records of patients diagnosed with CHB in the infectious diseases clinics at Bezmialem Vakıf University (BVU) via hospital information management system. Inclusion criteria were being ≥16 years old, hepatitis B surface antigen (HBsAg) positivity for at least 8 months and a known ABO-Rh blood group. Patients co-infected with hepatitis C virus (HCV), hepatitis D virus (HDV) and human immunodeficiency virus (HIV) were excluded from the study. Age, sex, ABO-Rh blood groups and fibrosis score were recorded. The distribution of ABO-Rh blood groups among CHB patients was compared with BVU hospital blood donors (20). The patients were evaluated in two distinct categories: severity of fibrosis (F0-2: No fibrosis/mild fibrosis and F3-6: Significant fibrosis) and presence of cirrhosis (F0-5: No cirrhosis and F5-6: Cirrhosis).

Laboratory Analysis

ABO-Rh blood groups were determined by the lam agglutination method using blood grouping reagent (Dia-Gast, Loos, France), microplate agglutination method using Galileo System (Stratec, Frankfurt, Germany), or gel centrifugation method using IH-1000 Fully Automated System (DiaMed, Cressier, Switzerland).

Histological Evaluation

Ultrasound-guided liver biopsy was performed by using a fully automated biopsy needle (18 G BioPinceTM, INTERV-MDTech, Gainesville, Florida). Biopsy samples were obtained by using Haematoxylin-Eosin and Masson's Trichrome staining on paraffin-embedded hepatic tissue fixed with formalin. All histological samples were assessed by a pathologist blind to patient characteristics by using Ishak staging scale and scored accordingly.

Statistical Analysis

Descriptive statistics of continuous numerical variables were expressed as ratio and interval; categorical variables were expressed as frequency distribution and number. The significance of association between ABO-Rh blood groups and significant fibrosis or presence of cirrhosis was assessed by Pearson's Chi-square test. Conformity of continuous variable to normal distribution was assessed by using the one-sample Kolmogorov-Smirnov test. Statistical analysis was performed using SPSS software, version 17. The results were considered statistically significant when the probability of findings occurring by chance was less than 5% ($p<0.05$). The study was approved by the BVU Ethics Committee for Clinical Research (20.05.2015/7591)

Results

Patients' Characteristics and Blood Group Distribution

Out of 1172 patients who were screened for eligibility, 674 patients were included in the study. Four hundred one patients were male (59.5%) and 273 were female (40.5%) and their median age was 40±17.86 years. Four hundred ten (60.8%) patients were with inactive CHB and 264 (39.2%) with active CHB. Liver biopsy was done in 171 (25.4%) patients. In 25 of them (3.7%), the stage of fibrosis was ≥5 and, thus, they were considered as having cirrhosis. Cirrhosis was found to be more frequent in males (n=20, p=0.009). The data about distribution of blood group antigens among CHB patients and that in BVU hospital blood donors was similar (Table 1) ($\chi 2=10.68$; p=0.152). When CHB patients with significant liver fibrosis and cirrhosis were evaluated according to their ABO blood group antigen status, it was observed that in O blood group, significant fibrosis and cirrhosis were more frequent than in other blood groups (Table 2) (p=0.008, p=0.007). Cirrhosis development was found to be more frequent in Rh antigen-positive patients (p=0.037).

Discussion

Our study evaluating the correlation of ABO-Rh blood groups with the severity of fibrosis and presence of cirrhosis has shown that such a significant correlation does exist with blood group O. Rh positivity was observed to be related with cirrhosis. Distribution of ABO blood groups in CHB patients was similar to that in healthy blood donors. O blood group may serve as an independent genetic

risk factor predicting hepatic fibrosis. In their study comprising 346 French patients with a diagnosis of chronic hepatitis C (CHC), Poujol-Robert et al. (19) have found that the non-O blood group was more common in patients with advanced fibrosis and they have considered this finding as an independent risk factor.

Shavakhi et al. (18) have found a significant association between severe hepatic fibrosis and non-O blood group. In a study focusing on a serum hepatitis epidemic limited to patients and staff of a haemodialysis unit, O blood group was found to be dominant particularly in severe cases, leading to a suggestion that host factors may be important in the genesis of this disease (21). In another study, HBsAg seroprevalance was the highest in patients with O blood group among a cohort of 330 blood donors, however, the association was not statistically significant (22). Siransy et al. (23) have found that O blood group of individuals were infected with HIV and HBV infection more frequently than those with non-O blood group. In a comprehensive study including antenatal screening tests, B and AB blood groups were observed to be associated with increasing HBV infection (24). Behal et al. (16) have determined HCV seropositivity in 68 of 20.000 blood donors and have reported that HCV seroprevalence was higher in O blood group and lower in AB blood group. Omar et al. have compared 12 HBV, 71 HCV and 371 healthy blood donors and found that HBV and HCV seroprevalence was higher in subjects with Rh positivity and in those of O blood group (25). Pourhassan (26) have found no association between CHB and ABO blood groups in a study including a cohort comprising 200 patients with CHB, 200 with CHC and 200 healthy individuals, however, they have observed that the rate of O blood group was significantly higher in CHC group. Naeini et al. (17) have found no correlation in their study comparing patients CHB and CHC and blood donors according to their ABO-Rh blood groups. Exact underlying mechanism for the association between HBV infection and ABO blood groups is not clearly known, but blood groups may affect HBV susceptibility via receptor-mediated binding affinity (27).

ABO blood group antigens, known as first human genetic markers, are complex carbohydrate molecules expressed from red blood cells and other cell lineages and tissues. Increasing evidence indicates that ABO antigens, in addition to their crucial role in transfusion medicine, may have a probable interaction with pathogenesis of many infectious, neoplastic and cardiovascular diseases (28). The risk of cerebral vein thrombosis is higher in non-O blood group individuals (29). Hazendonk et al., (30) in their study evaluating the extent and predictors of underdosing and overdosing in perioperative hemophilia A patients, found that blood O patients had a higher risk of perioperative bleeding complications compared to those with blood group non-O. A synergism between blood group A and HBV infection in the development of extrahepatic cholangiocarcinoma has been suggested (31). In their case-control study including 1.538 patients with newly diagnosed HCC, Shim et al. (6) from Korea have concluded that blood group A and genotype AA showed the highest risk of HCC. In a study of 339.432 individuals conducted in Taiwan, A blood group was found to be associated with increased risk of stomach cancer and non-O blood types with pancreatic cancer (7). Kurt et al. (9) have reported that CRF was less frequent in 0 Rh (+) patients but more frequent in B Rh (-) patients (9). Ansari et al. (13) have found that O blood group is a risk factor in the development of *H. pylori*-associated gastroduodenal disease and ulcer. A blood group has been found to be significantly associated with CHB and pancreatic cancer and, B blood group has been found to be significantly associated with ovarian cancer (27,32). It has been found that patients with O blood groups were more susceptible to gastrointestinal infection epidemic due to *Escherichia coli* O 157 and mortality was higher among this group (33). It has been reported that O blood group was prophylactic against malaria (11). In their study, Jang et al. (34) have reviewed 108.898 medical records of ABO and HBsAg results and found that blood group A was more prone to have positive results with HBsAg, on the other hand, blood group O was more prone to *Clostridium difficile* toxin. Güven et al. (12) have reported that in CCHF cases, bleeding tendency was more common in patients with O blood group. Most of these studies have shown that O blood group may lead to an increase or decrease in susceptibility to certain diseases as a host factor.

Table 1. Distribution of blood groups among chronic hepatitis B patients and the Bezmialem Vakıf University Hospital blood donors

ABO-Rh blood groups	CHB patients n (%)	BVU blood donors (20) n (%)
A Rh +	244 (36.2)	2305 (38.2)
O Rh +	218 (32.3)	1746 (28.9)
B Rh +	89 (13.2)	744 (12.3)
AB Rh +	48 (7.1)	397 (6.6)
A Rh -	23 (3.4)	319 (5.3)
O Rh -	30 (4.5)	249 (4.1)
B Rh -	12 (1.8)	162 (2.7)
AB Rh -	10 (1.5)	119 (1.9)
Total	674 (100)	6041 (100)

CHB: Chronic hepatitis B, BVU: Bezmialem Vakıf University

Table 2. Correlation of ABO-Rh blood groups with significant fibrosis (F3-6) and the presence of cirrhosis (F5-6)

Parameter	Severity of fibrosis			Presence of cirrhosis		
	F0-2 n (%)	F3-6 n (%)	p value	F0-4 n (%)	F5-6 n (%)	p value
A blood group	41 (23.8)	14 (8.1)	0.209	50 (29.1)	5 (2.9)	0.292
O blood group	45 (26.2)	33 (19.2)	*0.008	59 (34.3)	18 (10.5)	*0.007
B blood group	19 (11)	6 (3.5)	0.355	23 (13.4)	2 (1.2)	0.548
AB blood group	12 (7)	2 (1.2)	0.138	14 (8.1)	0 (0)	0.257
Rh positivity	109 (63.4)	46 (26.7)	0.051	135(78.5)	19 (11)	*0.037

F: Fibrosis

The limitations of our study include the absence of any other study criticizing the literature for the correlation between blood groups and liver fibrosis with CHB to compare our findings in detailed manner, the sampling restrictions duo to absence of any other involved center except our hospital, and to discharge patients with HCV and HDV infection. Briefly, we assume that multicenter studies may be more effective to criticize the relationship between hepatic fibrosis and ABO-Rh blood groups in patients with CHB.

Conclusion

Our study suggests that O blood group and Rh antigen positivity in CHB cases may be a genetic host risk factor for severe hepatic fibrosis and progression to cirrhosis. In order to clarify this assertion, further studies that include larger cohorts are needed.

Ethics

Ethics Committee Approval: The study was approved by Bezmialem Vakıf University Ethic Committee for Clinical Research (2015/7591), Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İsmail Necati Hakyemez, Concept: İsmail Necati Hakyemez, Design: İsmail Necati Hakyemez, Turan Aslan, Data Collection or Processing: İsmail Necati Hakyemez, Bülent Durdu, Analysis or Interpretation: İsmail Necati Hakyemez, Sibel Bolukçu, Bülent Durdu, Literature Search: İsmail Necati Hakyemez, Bülent Durdu, Writing: İsmail Necati Hakyemez, Language Editing: Turan Aslan.

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Research Article

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The Relationship Between the Serum RNA Titers of Hepatitis C Virus and Biochemical Parameters in Chronic Hepatitis C Patients

Kronik Hepatit C Hastalarında Serum Hepatit C Virüs RNA Titreleri ile Biyokimyasal Parametreler Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: Liver biopsy, as well as some non-invasive biochemical parameters are also used in monitoring patients with chronic hepatitis C (CHC). The aim of this study was to investigate the relationship between serum biochemical markers and HCV RNA titers in patients with previously untreated CHC.

Materials and Methods: We performed a retrospective study on anti-HCV and HCV-RNA-positive 82 patients with CHC. Eighty two healthy subjects constituted the control group. Complete blood counts, total protein (TP), albumin (ALB), C-reactive protein (CRP), γ-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and HCV RNA levels were recorded for each patient and control subject. Neutrophil-lymphocytes ratio (NLR) and the fibrosis index based on the 4 factors (FIB-4 index) were calculated using formulas.

Results: There was a significant difference in ALT, AST, GGT, TP, CRP, red cell distribution width (RDW), lymphocytes (LYM), platelets (PLT), FIB-4, and NLR between CHC patients and controls (p=<0.05). Values of HCV RNA viral load were correlated with ALT (r=0.271; p=0.014), TP (r=-0.256; p=0.02), WBC (r=-0.365; p=0.001), NEU (r=-0.362; p=0.001) and NLR (r=0.282; p=0.01) levels.

Conclusion: We have shown that ALT, AST, GGT, TP, CRP, RDW, LYM, FIB-4, and NLR values are increased in CHC patients but, LYM and PLT levels were decreased. Also, levels of ALT and NLR have correlated with HCV RNA titers in CHC patients. These results have implied that noninvasive biochemical parameters may contribute to monitoring patients with CHC.

Keywords: Biochemical parameters, HCV RNA titers, chronic hepatitis C

ÖZ

Amaç: Karaciğer biyopsisinin yanı sıra noninvaziv bazı biyokimyasal parametreler de kronik hepatit C (KHC) takibinde kullanılmaktadır. Bu çalışmanın amacı, daha önce tedavi edilmemiş kronik HCV hastalarında serum biyokimyasal belirteçler ve HCV RNA titreleri arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Anti-HCV ve HCV-RNA pozitif 82 KHC hastası retrospektif olarak incelendi. Hastaneye başvurmuş herhangi bir hastalığı olmayan 82 sağlıklı birey kontrol grubu olarak belirlendi. Hasta ve kontrol grubundaki her bir bireyin, tam kan sayımı, total protein (TP), albumin (ALB), C-reaktif protein (CRP), γ-glutamil transpeptidaz (GGT), aspartat aminotransferaz (AST), alanin aminotransferaz (ALT) ve HCV RNA düzeyleri kaydedildi. Nötrofil-lenfosit oranı (NLR) ve 4 faktöre dayalı fibroz endeksi (FIB-4 endeksi) formüller kullanılarak hesaplandı.

Bulgular: KHC hasta ve kontrol grubu arasında ALT, AST, GGT, TP, CRP, kırmızı hücre dağılım genişliği (RDW), lenfositler (LYM), trombositler (PLT), FIB-4 ve NLR değerlerinde anlamlı bir fark vardı (p<0.05). HCV RNA viral yük değerleri ile ALT (r=0,271; p=0,014), TP (r=-0,256; p=0,02), NEU (r=-0,365; p=0,01), WBC (r=-0,362; p=0,001) ve NLR (r=0,282; p=0,01) seviyeleri korelasyon gösterdi.

Sonuç: ALT, AST, GGT, TP, CRP, RDW, LYM, FIB-4 and NLR değerlerinin CHC hastalarında arttığını, LYM ve PLT değerlerinin ise azaldığını bulduk. Ayrıca, ALT ve NLR seviyeleri KHC hastalarında HCV RNA titreleri ile korelasyon gösterdi. Bu sonuçlar noninvaziv biyokimyasal parametrelerin kronik hepatit C hastalığının takibine katkı sağlayabileceğini göstermektedir.

Anahtar Kelimeler: Biyokimyasal parametreler, HCV RNA titreleri, kronik hepatit C

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Introduction

Hepatitis C virus (HCV), a family member of Flaviviridia, is a single-stranded 9.600 kb RNA virus (1,2,3). HCV RNA genome has genetic heterogeneity with its 6 major genotypes which are divided into more than 80 subtypes. HCV genotype distribution varies according to geographical location or route of transmission (4). HCV is mainly transmitted via parenteral route, by blood transfusion, substance abuse and accidental needle pricks. Dental surgery, acupuncture, hemodialysis and procedures such as tattooing also pose a risk of transmission of HCV (1,5,6).

HCV infection is a significant public health issue. Currently, it is estimated that worldwide there are 175 million chronic hepatitis infection cases and 350.000 patients die every year due to complications of HCV such as cirrhosis and hepatic cancer (7). HCV infection is an insidious disease with slow progression. HCV infection can be manifested as an acute infection and in around 20% of the patients, the disease spontaneously resolves, but becomes chronic in 80% of cases (3,8,9). HCV infection can lead to chronic hepatitis C (CHC), liver cirrhosis and hepatocellular carcinoma (HCC) (10,11). Mechanism of liver injury due to acute or chronic HCV infections has not been fully understood. The high rate of chronicity in HCV infections is explained by escape of virus from immune control as a result of genetic heterogeneity due to tendency to rapid mutation (12). The natural history of HCV infection is affected by a number of host and virus variables (13,14). The duration and route of transmission of the disease, viral genotype, viral load, alcohol abuse and co-infection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are among the factors affecting the progression of the disease (5,9). Chronic hepatitis B (CHB) is usually indolent and incidentally recognized during routine serological tests, blood biochemistry tests or histological tests (5,15). The diagnosis of HCV infection is established by detecting antibody formed against the virus (anti-HCV) and by measuring HCV RNA by nucleic acid amplification method (1).

Liver biopsy is considered as the gold standard for grading and staging (9,11,14,16,17). In general, liver biopsy is a reliable method, however, it is invasive, costly and has risk of complication though minimal (9,11,16,17). Because of these limitations, numerous studies have focused on developing simple, inexpensive and, most importantly, non-invasive biochemical markers as an alternative to liver biopsy (11,17).

There are non-invasive methods evaluating hepatic inflammation and fibrosis (9). In HCV-positive patients, complete blood count, routine biochemical blood tests, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate (ALP) and measurement of serum HCV RNA levels are carried out (18,19). There are several studies that have investigated the association between liver injury and serum ALT levels, HCV viral load and HCV genotypes but the results were inconsistent (11,14,20,21,22,,23,24,25,26).

The objective of this study was to evaluate and determine the potential correlation between HCV viral load and different biochemical parameters in chronic hepatitis C.

Materials and Methods

The current study is a retrospective analysis of 82 patients, who were known to be HCV antibody (anti-HCV)- and HCV-RNA-positive, admitted to Ahi Evran University Training and Education Hospital between July 2014 and December 2015 and received the diagnosis of CHC. The control group was consisted of 82 volunteers from similar age groups and sex who attended the hospital during the same time period for any reason and had normal biochemistry tests and negative anti-HCV results.

Serum anti-HCV was analyzed by chemiluminescence enzyme immunoassay (Roche Modular Analytics, cobas 6000 analyzer; Roche Diagnostics, Germany). HCV-RNA test was performed by real time polymerase chain reaction (PCR) with an automated system (Roche/Cobas TaqMan System) according to the manufacturer's instructions. The linear range of the HCV RNA assay was 25 to 391.000.000 IU/ml. HCV genotypes were determined using the Linear Array Hepatitis C Virus Genotyping Test (Roche Molecular Systems).

The biochemical assessment included serum total protein (TP), albumin (ALB), C-reactive protein (CRP), γ-glutamyl transpeptidase (GGT), AST, and ALT which were measured on a AU5800 analytical system (Beckman Coulter, FL, USA) using commercially available reagents and an enzyme-based kit. A complete blood count of hemoglobin (HB), hematocrit (HTC), white blood cells (WBC), neutrophils (NEU), lymphocytes (LYM), platelets (PLT), mean platelet volume (MPV) and red cell distribution width (RDW) was determined using a ABX Pentra DX 120 cell counter (Horiba Ltd., Kyoto, Japan). NEU-LYM ratio (NLR) was calculated as the ratio of NEUs and LYM, both obtained from the same automated blood sample at the time of admission to the study. The fibrosis index based on the 4 factors (FIB-4 index) was calculated using the following formula (16):

FIB-4 index=age (years) × AST (IU/L)/PLT count ($\times 10^9$/L) × (ALT [IU/L])$^{1/2}$

Statistical Analysis

All statistical analyses were carried out using the SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables were presented as frequencies and percentages; continuous variables were expressed as means and standard deviation. Statistical comparison of clinical data between the two groups consisted of unpaired t-tests for parametric data. Correlations were assessed with the Pearson's correlation coefficient, and a chi-square test was used for categorical variables. A p value of less than 0.05 was considered statistically significant.

Results

Eighty-two patients with CHC (37 male, 45 female) and 82 control subjects (43 male, 39 female) were included in the present study. The median age of CHC and control patients was 59.84±16.22 and 58.78±12.76, respectively. There was no statistically signiŞcant difference in sex and age between the groups (p>0.05). The mean HCV-RNA level in the serum was 3.747.400±6.527.860. The distribution of HCV genotypes was as follows genotype 1: 59.3%; genotype 2: 13%; genotype 3: 11% and genotype 4: 16.7%. Dominant genotype in our study group was genotype 1 which is significantly higher than other genotypes. The demographic characteristics and some biochemical features of the participants are shown in Table 1. There was a significant difference in ALT, AST, GGT, TP, CRP, RDW, LYM, PLT, FIB-4 and NLR between the groups. Biochemical values in patients with CHC and controls are also shown in Table 1.

When the correlation between serum HCV RNA levels and various biochemical parameters were evaluated, it was observed that serum HCV RNA titers correlated with ALT (r=0.271; p=0.014), TP (r=-0.256; p=0.02), WBC (r=-0.365; p=0.001), NEU (r=-0.362; p=0.001), and NLR (r=0.282; p=0.01) levels (Table 2).

Discussion

In this study, we have determined that there was a significant difference in ALT, AST, GGT, TP, CRP, FIB-4, RDW, LYM and NLR parameters between HCV-positive patients and control group and we have also found that ALT, TP, WBC, NEU and NLR levels significantly associated with the indicator of viral load, namely HCV RNA level.

As it is known, HCV infection affects nearly 3% of the whole population; and 80% of the cases becomes chronic and its mortality rate is getting higher (1,27). Clinical consequences of HCV infection depend on the balance between replication rate of the virus and specific, rapid and effective response of immune system to the virus (21,28). A number of clinical, biochemical and histological parameters are used in the evaluation of CHC progression (29). Although liver biopsy is considered as the gold standard in determining the effect of HCV on liver, in recent years, studies have focused on developing a non-invasive marker to replace liver biopsy (10,16,17,30,31,32,33,34,35).

Systemic inflammatory response can be evaluated by the increase in NLR. NLR is a simple and inexpensive marker that can be measured by using the results of routine complete blood count. Previous studies have revealed that NLR is related to cardiovascular diseases associated with systemic inflammation and pathologies such as cancer and is a predictor of disease severity and mortality (10,36,37). In their study, Abdel-Razik et al. (38) have found a relationship of NLR with disease severity and hepatic fibrosis in patients with nonalcoholic steatohepatitis (NASH). In their study, Kuo et al. (10) have investigated the association between NLR and response of CHC patients to antiviral therapy and have found a significant correlation between HCV RNA viral load and NLR increase. This finding led to the conclusion that high NLR has a negative impact in evaluation of antiviral therapy (10). In our study, consistent with the literature, CRP and NLR levels were significantly higher in CHC patients compared to controls and also, there was a significant correlation between HCV RNA levels and NLR.

RDW is a measure for variations in circulating red blood cell size. Elevated RDW has been reported to associate with higher mortality risk among the general population (39). Cengiz et al. (40) have also reported a positive correlation between RDW values and fibrotic scores in patients with NASH. Hu et al. (41) have observed that RDW increased in chronic patients with CHB and have suggested that RDW may serve as a potential prognostic index in liver disease. We have also investigated a probable relationship

Table 1. Baseline demographic and biochemical characteristics of study populations

Variables	Chronic hepatitis C patients (n=82)	Control group (n=82)	p value
Age(mean ± SD) (yr)	59.84±16.22	58.78±12.76	0.642
Male sex % (n)	45 (37)	52 (43)	0.435
HCV-RNA (IU/mL)	3.747.400±6.527.860	-	
ALT (IU/L)	41.65±37.68	19.30±7.73	<0.001
AST (IU/L)	39.17±21.24	21.12±5.15	<0.001
GGT (IU/L)	51.45±54.97	22.32±9.14	<0.001
TP (g/dL)	7.30±0.98	6.81±0.42	<0.001
ALB (g/dL)	3.95±0.55	3.95±0.28	0.916
CRP (mg/dL)	0.53±1.07	0.22±0.13	0.012
WBC (10^3/µL)	6.63±3.77	6.21±1.21	0.344
HB (mg/dL)	13.72±2.70	14.34±1.49	0.075
HTC (%)	41.74±5.41	41.78±5.91	0.962
RDW (%)	15.05±1.88	13.76±1.05	<0.001
NEU (10^3/µL)	4.08±3.24	3.38±0.87	0.063
LYM (10^3/µL)	1.75±0.64	2.12±0.66	<0.001
PLT (10^3/mm^3)	207.06±63.62	236.02±49.01	0.001
MPV (fL)	8.87±0.80	8.77±0.81	0.414
FIB-4	2.39±2.40	1.29±0.49	<0.001
NLR	2.43±1.57	1.75±0.73	<0.001

Data are presented as median (range) or mean ± SD, TP: Total protein, ALB: Albumin, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: γ-glutamyl transpeptidase, HB: Hemoglobin, HTC: Hematocrit, WBC: White blood cells, NEU: Neutrophils, LYM: Lymphocytes, PLT: Platelets, MPV: Mean platelet volume, RDW: Red cell distrubition width, NLR: Neutrophil-lymphocytes ratio, TP: Total protein, FIB-4: Fibrosis-4, SD: Standard deviation

Table 2. Correlation between serum HCV RNA levels and various biochemical parameters in patients with chronic hepatitis C

Variables	r value	p value
ALT (IU/L)	0.271	0.014
AST (IU/L)	0.032	0.774
GGT (IU/L)	0.131	0.242
TP (g/dL)	-0.256	0.02
ALB (g/dL)	-0.177	0.111
CRP (mg/dL)	0.201	0.071
WBC (10^3/µL)	0.365	0.001
HB (mg/dL)	0.045	0.688
HTC (%)	-0.029	0.793
RDW (%)	-0.032	0.778
NEU (10^3/µL)	0.362	0.001
LYM (10^3/µL)	0.086	0.442
PLT (10^3/µL)	0.076	0.496
MPV (fL)	0.082	0.466
FIB-4	-0.064	0.567
NLR	0.282	0.01

TP: Total protein, ALB: Albumin, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: γ-glutamyl transpeptidase, HB: Hemoglobin, HTC: Hematocrit, WBC: White blood cells, NEU: Neutrophils, LYM: Lymphocytes, PLT: Platelets, MPV: Mean platelet volume, RDW: Red cell distrubition width, NLR: Neutrophil- lymphocytes ratio, PLT: Platelets, MPV: Mean platelet volume, FIB-4: Fibrosis-4

between RDW and liver disease associated with HCV and have observed that RDW increased in CHC patients similar to that in patients with hepatitis B.

As it is known, FIB-4 index is a non-invasive test used for evaluation of hepatic fibrosis. A score of <1.45 is considered as absence of fibrosis or presence of moderate fibrosis (F0-F1-F2-F3), and >3.25 is considered as presence of severe fibrosis or cirrhosis. It is accepted that like other non-invasive tests, FIB-4 index may replace biopsy in 70% of cases (16). McCombs et al. (42) have shown in their study that patients with a FIB-4 value of >3.25 had significantly higher risk of mortality and clinical course of hepatic disease was worse in these patients. In our study, we could not find a correlation between HCV RNA viral load and FIB-4, however, consistent with the above mentioned studies, FIB-4 value was significantly higher in the CHC group compared to the control group.

It is a generally accepted predication that in patients with CHC, higher HCV-RNA and serum ALT levels indicate presence of active HCV replication in liver and, thus, liver injury implies a clinical risk. The grade of elevated ALT is accepted as a marker of liver injury and it is used as a criterion in starting antiviral therapy or monitoring response to therapy (14,21,28). It has also been determined that HCV RNA titers are correlated with response to antiviral therapy (18,43). In recent years, various studies investigated the association between the grade of liver injury and serum ALT levels, HCV RNA titers in CHC patients and HCV genotype were performed, but the results were inconsistent. In some studies, no clinically feasible association was found between ALT level and liver injury or liver fibrosis (23,24,25). In a study by Lee et al. (21) there was no association between HCV RNA level and grade of liver injury in chronic HCV carriers but serum ALT level was associated with portal inflammation and periportal necrosis.

Fanning et al. (29) have found that serum HCV RNA viral load and ALT level were significantly correlated with the grade of liver inflammation but no such correlation was found between these parameters and liver fibrosis. Al Swaff (20) have found an association between grade 1 and grade 4 liver fibrosis and higher ALT levels in patients with CHC (genotype 4) infection and have detected higher HCV RNA levels in grade 3 liver fibrosis.

Zechini et al. (14) have found a significant correlation between HCV RNA and ALT. in CHC patients and have also found a correlation between histological activity index (HAI) and HCV RNA levels as well as between HAI and AST and ALT levels. They have reported in their study that particularly AST might be associated with liver injury. Shahid et al. (11) have found that HCV RNA titers, AST, ALP and total bilirubin were correlated with grade of fibrosis in patients with CHC (genotype 3a) infection (11). In our study, serum ALT levels in CHC patients were higher than in control group. There was also a significant correlation between HCV RNA titer and ALT levels (p=0.014).

Conclusion

Some limitations should be considered when evaluating our study. The primary limitation is the relatively small sample size. A larger sample size could provide stronger statistical data. Another limitation is the possible effect of medications that were used by CHC patients was not evaluated. Finally, we did not evaluate our patients in terms of ultrasonography and histopathological investigation which are reference methods of hepatic injury.

We have shown that ALT, AST, GGT, TP, CRP, RDW, LYM, FIB-4, and NLR values are increased in CHC patients, but LYM and PLT were decreased. Also, levels of ALT and NLR have significant correlation with HCV RNA titers in CHC patients. These results have imply that noninvasive biochemical parameters may contribute to monitoring of CHC disease and evaluation of its grade. However, further studies including larger patient population and measuring biochemical parameters and HCV RNA titers simultaneously with histopathological evaluation are needed.

Ethics

Ethics Committee Approval: The study did not need to get Ethics Committee approval.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Concept: Rukiye Nar, Design: Rukiye Nar, Fikriye Milletli Sezgin, Data Collection or Processing: Rukiye Nar, Fikriye Milletli Sezgin, Analysis or Interpretation: Rukiye Nar, Fikriye Milletli Sezgin, Literature Search: Rukiye Nar, Fikriye Milletli Sezgin, Writing: Rukiye Nar.

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

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Case Report

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A Case of Chronic Hepatitis B Virus Infection in an Anti-HBc-negative Patient: An Atypical Serological Profile

Atipik Serolojik Profil Olarak Anti-HBc Negatif Kronik Hepatit B Virüs Enfeksiyonu Olgusu

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ABSTRACT

Antibodies against hepatitis B virus (HBV) core antigen (anti-HBc) are assumed to be the best serologically reliable markers of HBV infection. However, chronic HBV infection can be seen with an atypical serological profile, such as anti-HBc negativity with the presence of hepatitis B surface antigen (HBsAg). Anti-HBc negativity during HBV infection has been observed in a few different circumstances, such as infections with HBV variants, in infants born to hepatitis B envelope antigen positive carrier mothers and immunocompromised patients. In this case, we described a 21-year-old anti-HBc-negative male patient with chronic HBV infection.
Keywords: Anti-HBc, hepatitis B virus, atypical serology

ÖZ

Hepatit B virüs (HBV) core antijenine (HBcAg) karşı antikorlar (anti-HBc), HBV enfeksiyonu için güvenilir serolojik belirteçlerden biridir. Ancak HBV enfeksiyonu bazen hepatit B yüzey antijeni (HBsAg) varlığına rağmen anti-HBc negatifliğinin görüldüğü atipik bir serolojik profil ile ilişkili olabilir. HBV enfeksiyonu süresince anti-HBc üretiminde defekt, HBV varyantları ile enfeksiyon, hepatit B envelope antigeni pozitif anneden doğan infantlar ve immünsüpresif hastalar gibi birkaç durumda gözlenmiştir. Bu olgumuzda, 21 yaşında bir erkek hastada anti-HBc negatif kronik HBV enfeksiyonu tariflenmektedir.
Anahtar Kelimeler: Anti-HBc, hepatit B virüsü, atipik seroloji

Introduction

The diagnosis of hepatitis B virus (HBV) infection is established by the serological detection of HBV antigens and host produced antibodies against them. If HBV surface antigen (HBsAg) persists for more than six months, the infected individual is considered to be a chronic HBV carrier (1).

HBV core antigen (HBcAg), not a secreted protein, exists primarily in the liver and in serum within HBV particles, not being in the blood directly accessible to the immune system. Antibodies to HBcAg (anti-HBc) are considered to be the best serologically reliable markers of HBV infection. Not only chronic HBV carriers, but also healthy individuals, who have natural immunity to HBV due to past infection, are positive for anti-HBc. Therefore, anti-HBc is the most important marker indicating past HBV infection as well as ongoing infection (2).

Anti-HBc levels can show significant differences during the natural course of chronic HBV infection and, isolated HBsAg positivity without anti-HBc can be seen in acute infection (1,3). However, during chronic HBV infection, the absence of anti-HBc with the persistent positivity for HBsAg and detectable HBV DNA comprises an atypical serological profile (1,3).

Case

A 21-year-old male patient was positive for HBsAg. HBsAg positivity was identified approximately one year ago. He had no history of liver biopsy or treatment for HBV infection when he was referred to our outpatient clinic. He had no active complaint. There was not any remarkable feature (e.g., chronic disease, immunosuppressive status or continuous drug use) on admission. The patient's mother and sister had a history of HBV infection. No pathological finding was detected during physical examination.

Laboratory examination showed that serum glucose, urea, creatinine, lipids, electrolytes, bilirubins, alkaline phosphatase, gammaglutamyl transaminase and blood cell count were all within

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the normal limits. Aspartate aminotransferase (AST) was 26 U/l, alanine aminotransferase (ALT) was 58 U/l.

As a result of serological assays, HBsAg and hepatitis B envelope antigen (HBeAg) were positive; anti-HBc total, anti-HBs, anti-HBe, anti-HBc IgM, anti-HAV IgG, anti-HCV, and anti-HIV were negative. Since he was positive for HBsAg but negative for anti-HBc total, we repeated the serology tests and the same results were obtained. The results of the repeated tests with Abbott Axsym Core^{TM} were negative for anti-HBc. Then, anti-HBc negativity was also obtained by Abbott Architect Anti-HBc II.

HBV DNA level was high (2.050.201.984 IU/mL) by Taqman Real Time polymerase chain reaction assay, Fluorion HBV QNP 2.0 (İstanbul, Turkey). Abdominal ultrasound results were normal. Liver biopsy results indicated chronic hepatitis B with a mild necroinflammatory activity and mild fibrosis (Knodell's score: Grade; 3/18, stage; 2/6).

Discussion

The rate of chronic HBV infection with antiHBc negativity ranged from 0.05% to 1.79% in different studies (1,3,4). Anti-HBc negativity during HBV infection has been observed in a few different circumstances, such as false negativity, sample contamination, HBV variants with especially deletions in the core gene, immune tolerance to HBcAg, infants born to HBeAg-positive carrier mothers, immunocompromised patients or patients with circulating immune complexes composed of anti-HBc and HBcAg (1,3).

The diagnostic tests have continuously improved over the last few decades. Sensitivity and specificity differences exist between assays and may sometimes explain the discrepant results in some patients. Positive results detected by repeated tests with different kits in anti-HBc-negative individuals have been reported (3,4,5,6). In our patient, the results of repeated tests with Abbott Axsym CoreTM were negative. Then, anti-HBc negativity was also obtained by Abbott Architect Anti-HBc II. While different data have been reported for specificity of Abbott anti-HBc assays, high values for sensitivity (99.1%, 98%) and negative predictive value (99.6%) have been reported for Abbott Architect Anti-HBc II and it has been assessed as reliable (3,5,6,7). In addition,, nonspecificity problem observed in old Abbott anti-HBc assays, including Abbott Axsym CoreTM, has been reported to be solved with Abbott Architect Anti-HBc II (3,7).

The immune tolerance to HBcAg is known by the incapacity of the individual to produce anti-HBc or to produce it in undetectable levels (1). The immune tolerance can be caused by T-cell anergy, a small number of specific peripheral T lymphocytes, an inefficient antigen presentation or an inefficient lymphokine production by the antigen-presenting cell (1). Therefore, a selective immune system defect could lead the immune tolerance to HBcAg and, consequently, lack of production of anti-HBc and existence of this atypical serological profile (1,3). In anti-HBc-negative patients with chronic HBV infection, a relative immunosupression due to coinfection with human immunodeficiency virus (HIV), history of transplantation (kidney, heart or bone marrow), history of chemotherapy, leukemia, end-stage renal failure and systemic inflammatory diseases, such as histiocytosis x and sarcoidosis, have been reported (1,3,8). It is emphasized that the absence of anti-HBc was concomitant with a more severe immunosuppression like a CD4-cell count of less than 50/mm^3 and HIV plasma volume above 100.000 copies per ml, while anti-HBc was detectable when the level of immunosuppression was less significant (3). In our patient, he was negative for anti-HIV and there was no immunosuppressive status which could lead to anti-HBc negativity induced by reduction of antibody production.

Lack of anti-HBc production also has been reported in infants born to HBeAg-positive carrier mothers due to helper T-cell tolerance to HBcAg and HBeAg induced by transplacental maternal HBeAg (1,3,9). The mother and sister of our patient had a history of HBV infection and since immunoprophylaxis was not routine in our country during the period our patient was born, it can be considered that the risk of perinatal transmission was higher.

HBV variants with core mutations could cause infections with a low level of production or a lack of detection of anti-HBc (1,10). Variant core HBV strains are expected to be defective for B-cell epitopes and T-helper cell epitopes, which are mainly between 80 and 140 amino acids of the core protein. This may explain the low level production of anti-HBc which was detectable only with a very sensitive assay as demonstrated in mice experiments (10). Although the absence of anti-HBc has also been attributed to a new virus termed HBV2, discrepant data have been produced since this first report without further characterization of this virus (3,4,11). At the same time, there are studies that have not detected any mutation which could lead to anti-HBc negativity (3,4,8,9). In our patient, HBV DNA sequence analysis was not performed.

There is an opinion that the presence or absence of HBeAg in this atypical serological profile may be associated with the mechanism that justifies the profile (1). For example, in the case of immune tolerance to HBcAg or vertical transmission, the presence of HBeAg in the profile seems likely, since precore/core regions remain unchanged and normal synthesis of viral antigen goes on. On the other hand, following the occurrence of core gene deletions, depending on the region involved, the absence of HBeAg may occur, since both antigens are encoded by the same gene (1). Our patient was positive for HBeAg.

HBcAg can be secreted rarely from infected hepatocytes after liver necrosis during the phase of active replication of infection in a state of immunosuppression, such as coinfection with HIV, transplantation and chemotherapy (1,8). Immune complex formation of anti-HBc with HBcAg can occur because of the excessive presence of HBcAg in the bloodstream and, thus, anti-HBc can become undetectable. Our patient had mild necroinflammatory activity, he was negative for anti-HIV, and there was no immunosuppressive status which could lead to anti-HBc negativity induced by immune complexes occurrence.

Considering our patient and the available data in the literature, although there is an important shortcoming like not performed HBV DNA sequence analysis, since there was no serious immunosuppressive status, which could lead to anti-HBc negativity induced by immune complexes occurrence or by reduction of antibody production, his mother and sister had a history of HBV infection, there was high risk of perinatal transmission in our country during the period the patient was born and he was negative for anti-HIV and positive for HBeAg, and he had mild necroinflammatory activity, we thought that immune tolerance by perinatal transmission could be probable cause of chronic HBV infection in our anti-HBc-negative patient,

A minimal ALT elevation, mild fibrosis and mild necroinflammatory activity was detected in our patient. The relationship between anti-HBc negativity and liver damage remains unclear. There are studies showing increased liver damage in anti-HBc-negative patients with chronic HBV infection, or no relationship between them (3,10).

Conclusion

As a conclusion, anti-HBc levels can show significant differences during the natural course of chronic HBV infection and isolated HBsAg positivity without anti-HBc can be seen in acute infection. However, during chronic HBV infection, an atypical serological profile characterized by the presence of HBsAg without anti-HBc can be seen in infections with HBV variants, in infants born to HBeAg positive carrier mothers and immunocompromised patients. The effect of anti-HBc negativity on prognosis remains unclear.

Ethics

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Afyon, Berksan Şimşek, Ayper Kaya, Concept: Murat Afyon, Design: Murat Afyon, Data Collection or Processing: Murat Afyon, Berksan Şimşek, Ayper Kaya, Analysis or Interpretation: Murat Afyon, Berksan Şimşek, Ayper Kaya, Literature Search: Murat Afyon, Berksan Şimşek, Ayper Kaya, Writing: Murat Afyon.

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Telbivudine-Related Myopathy: A Case Report

Telbivudin İlişkili Miyopati: Bir Olgu Sunumu

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ABSTRACT

Telbivudine has potent antiviral activity against hepatitis B virus. Although there are several reports concerning the safety profile of telbivudine, most adverse events are described as mild and transient in nature. In this paper, we report a case of reversible telbivudine-induced myopathy. To detect this adverse event, monitoring of serum creatine kinase level and recognition of myopathic signs and symptoms are necessary.
Keywords: Telbivudine, myophathy, case report

ÖZ

Telbivudin hepatit B virüsüne karşı güçlü bir antiviral etkinliğe sahiptir. Telbivudinin güvenlik profili ile ilgili birçok rapor olmasına rağmen, çoğu yan etkinin ılımlı ve geçici özellikleri tanımlanmıştır. Bu yazıda telbivudine bağlı geri dönüşümlü bir miyopati olgusu bildirilmiştir. Bu yan etkiyi saptamak için, serum kreatin kinaz düzeyinin izlenmesi ve miyopatik belirti ve bulguların tanınması gereklidir.
Anahtar Kelimeler: Telbivudin, miyopati, olgu sunumu

Introduction

Hepatitis B is a viral infection that affects the liver and can cause chronic liver disease. An estimated 240 million people have chronic hepatitis B (CHB) infection. More than 780.000 people die every year due to cirrhosis and liver cancer associated with CHB infection (1). Nucleos(t)ide analogues have an important role in the treatment of CHB. Telbivudine is a new nucleoside analogue (2,3). Transient creatine kinase (CK) elevation and rarely myopathy have been reported in a few number of patients who were treated with telbivudine (3). However, we observed proximal myopathy and elevated serum CK level, which thought to be associated with telbivudine in a CHB patient. To our knowledge, this is the first reported case of telbivudine-related proximal myopathy confirmed by electromyography in Turkey.

Case

A 30-year-old man was admitted to our outpatient clinic. He was diagnosed with CHB 10 years ago. Three months before being admitted to our clinic, his serum viral DNA level, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were 213.200 IU/mL, 231 (normal: Up to 41 U/L) and 115 IU/mL (normal: Up to 41 U/L), respectively. Liver needle biopsy was performed. Knodell histology activity index and İshak fibrosis score were 4/18 and 3/6, respectively. Telbivudine treatment (600 mg once daily) was started and the serum viral DNA level gradually decreased to 25 IU/mL after three months. However, he had pain in his arms and legs. Neurological examination was normal. His family history was negative for neuromuscular disorder. He had not taken any other medications that would be regarded as a cause of his symptoms while taking telbivudine. Laboratory examinations were as the following: AST: 25 IU/L, ALT: 24IU/L, total bilirubin: 0.9 mg/dL, blood urea nitrogen (BUN): 31 mg/dL, and serum creatinine: 0.9 mg/dL. His serum CK level was elevated from 187 to 234 IU/L (normal range: 0-200 IU/L). At the 19 month of telbivudine treatment, he had fatigue and could not lift his arms and legs. The serum CK level was 1068 IU/L. Electromyography (EMG) was performed and showed frequent positive sharp waves with myogenic motor unit action potentials in the iliopsoas muscles and a few positive sharp waves in the deltoid muscle. EMG findings showed proximal myopathy. Muscle biopsy was planned for confirmation, but the patient refused muscle biopsy. The antiviral agent was changed to 100 mg

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lamivudine once. He revisited our clinic one month after telbivudine withdrawal and his clinical symptoms improved. The serum CK level was also decreased to 157 IU/L.

Discussion

Telbivudine is a nucleoside analogue which is used in the treatment of CHB (4,5). Nucleoside analogues inhibit polymerase-gamma, which is responsible for mitochondrial DNA replication. This mechanism is thought to be associated with myopathy and lactic acidosis (5). Wang et al. (4) have reported the results of 655 patients treated with telbivudin and they observed myophaty and myositis in 0.6% of patients. Serum CK elevation was developed in 15.9% of patients over 4 years. They reported that serum CK elevation was transient and improved after discontinuing telbivudine treatment (4). Zou et al. (6) have reported an incidence of serum CK elevations and myopathy during telbivudine treatment of 84.3% and 5%, respectively. CK elevations were observed more frequently in men than in women, in patients aged ≤45 years and those with negative hepatitis B e antigen. They have reported that CK elevations healed spontaneously without discontinuing telbivudine in most of patients.

In the literature, there are a few case reports of telbivudine-induced myopathy (3,6). To our knowledge, this is the first report in Turkey regarding telbivudine-related myopathy confirmed by EMG. We could not confirm telbivudine-related myopathy by muscle biopsy. Our patient was not treated with interferon or other nucleoside analogues previously. He had not taken any other medications that would be regarded as a cause of his symptoms. Myopathy occurred after taking telbivudine and improved after discontinuing the treatment.

Conclusion

We thought further closer monitoring is necessary for the evaluation of CK elevation or myopathy in patients treated with telbivudine. In this way, telbivudine can be used safely and effectively in clinical practice.

Ethics

Ethics Committee Approval: The study were approved by the İzmır Bozyaka Training and Research Hospital of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

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Authorship Contributions

Surgical and Medical Practices: Bengisu Ay, Concept: Şebnem Çalık, Design: Banu Karaca, Data Collection or Processing: Erman Özdemir, Analysis or Interpretation: Nalan Ünel, Literature Search: Banu Karaca, Writing: Bengisu Ay, Şebnem Çalık.

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