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PREVALENCE OF OCCULT HEPATITIS B VIRUS INFECTION AMONG CHRONIC HEMODIALYSIS ADULT PATIENTS IN MINIA GOVERNORATE, EGYPT

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Background and aim: *Occult hepatitis B virus (HBV) infection (OBI) is viewed as a serious health hazard since it can lead to the advancement of acute hepatitis B virus infection, the emergence of cirrhosis, and the development of hepatocellular cancer (HCC). This study's goal was to find out how prevalent OBI was among hemodialysis (HD) patients in the Minia governorate of Upper Egypt.* ***Methods****: This study included 100 patients with end-stage renal disease getting regular hemodialysis and had negative HBV surface antigen (HBsAg) testing. ELISA was used to test sera for the presence of antibodies against HBsAg (anti-HBs) and antibodies against HBV core antigen (anti-HBc). Nested PCR with polymerase (pol) gene-specific primers and real-time PCR with surface (s) gene-specific primers were both used to detect HBV DNA.* ***Results****: Anti-HBs and anti-HBc antibodies were found in 41 and 48 % of total samples, respectively. In addition, 52.1% of anti-HBc positive patients, were positive for anti-HCV antibodies. Out of 48 anti-HBc positive samples, 33 (68.75%) samples were positive for HBV DNA. HBV DNA was shown to be significantly associated with anti-HCV antibody-positive samples (P = 0.043). Amongst samples that tested positive for anti-HBc with or without anti-HCV antibodies, there was no significant difference in ALT levels (P=0.604).* ***Conclusion****. The application of anti-HBc testing to identify OBI is a superior method to raise security in hemodialysis facilities. We recommend as well using molecular methods such as nested PCR and real-time PCR to detect HBV DNA among HD patients*

Keywords: *HBV DNA; Hemodialysis; Occult hepatitis B virus; pol gene, s gene; nested PCR*

INTRODUCTION

Even though vaccination is extensively utilized, there are over two billion HBV infections worldwide, making it a serious medical problem. Liver disease caused by HBV, which affects 350 million HBV carriers globally, results in almost a million deaths yearly[1,2]**.** The most important serological HBV marker, HBsAg, is typically used for diagnosis[3]. Advances in molecular techniques have made it possible to identify HBV in several ways[4]. These techniques showed that individuals without detectable HBsAg could

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nevertheless have HBV-DNA in their liver and/or serum, together with anti-HBc antibodies and anti-HBs. This condition is known as occult hepatitis B infection (OBI)[5].

OBI patients may be either seropositive or seronegative. Anti-HBc, with or without the presence of anti-HBs, is a marker for seropositive OBIs, whereas seronegative OBIs are those that are negative for both antibodies. Given the increased percentage of HBV infections that have been effectively treated, it is somewhat unsurprising that the vast majority of OBIs are seropositive[4].

Risk factors for OBI are persons who receive blood transfusions, sex workers, HD patients, liver transplant recipients, co-infection with the hepatitis C virus and the human immunodeficiency virus (HIV) and from an infected mother to her fetus. HD patients are at high threat of HBV and other blood-borne infections due to lengthened vascular access to shared dialysis machines, anemia from occasional blood transfusions, and invasive procedures for dialysis access. Moreover, the immunological suppression brought on by end-stage renal disease causes poorer responses to the HBV vaccine, which raises the likelihood of developing OBI[6,7].

The varying incidence of OBI in hemodialysis patients is affected by many factors, such as selection bias, sensitivity and specificity of the tests, medical therapies, and the segregation of HBV-positive patients from the hemodialysis machine[8]. The goal of this research was to study the prevalence of OBI among chronic hemodialysis adult patients in Minia governorate, Egypt.

METHODS

Patients

Ethics statement: The study protocol conformed to the ethical guidelines of the 1975, Declaration of Helsinki, as revealed in *a priori* approval (No. HV13/2020) by the commission of the Ethics of Scientific Research, Faculty of Pharmacy, Minia university.

One hundred blood samples were taken at random from patients with end-stage renal illness who were receiving regular hemodialysis and tested negative for HBsAg. At the Minia General Hospital in Minia, Egypt. All blood samples were taken between January 2019 and November 2019. The study was approved by faculty of Pharmacy, Minia university. Informed consent was taken from all participants.

Patients have different ages, genders, past history of blood transfusions, previous surgeries, liver disease and durations on hemodialysis. Patients also have different causes of end-stage renal disease and have different co-morbidities as diabetes, hypertension, or both. Patients with positive hepatitis B surface antigen, malignancy, or under chemotherapy in addition to patients on antiviral therapy for HBV were excluded from the study.

Samples collection and processing

Ten milliliters of blood drawn from each patient in a plain vial for a liver function profile, serological testing, and PCR amplification of HBV DNA. For 10 minutes, the samples were centrifuged at 3000 rounds per minute (r.p.m). Separated serum was kept at a temperature of –20 °C until it was examined.

Serological tests

All serum samples underwent anti-HBs and anti-HBc testing utilizing a third-generation enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions and recommendations (Prechek Bio Inc., Taiwan). Screening of anti-HCV antibody for all samples was done as a routine work at the Minia General Hospital.

Biochemical analysis

Following the manufacturer's instructions, liver function tests (Alanine Amino Transferase [ALT]) were examined (Quimica Clinical Application, S.A Co., Ltd., Espana, Spain). Using the guidelines provided by the manufacturer, kidney function tests (urea and creatinine) were conducted (Chema Diagnostica Co., Ltd., Monsano, Italy).

DNA extraction

Separation of PBMCs from blood was done using Ficoll Hypaque (Lonza, Verviers, Belgium) according to the manufacturer’s instructions then lysed by lysis buffer provided

in the kits, then automated extraction of the total DNA from lysed PBMCs and plasma was performed using Favor prep Blood Genomic DNA Extraction Mini Kit (Artus™ GmbH, Hamburg Germany), according to the manufacturer's instructions.

Detection of HBV DNA

Detection of HBV DNA (pol gene) by nested PCR

To amplify the viral genome, the pol gene of the HBV was targeted in two consecutive PCR cycles using two pairs of internal and external primers, outer sense primer *HBPr134* (*5′*-TGCTGCTATGCCTCATCTTC-3′), outer antisense primer *HBPr135* (*5′*-CA(G/A)AGACAAAAGAAAATTGG-3′), inner sense primer *HBPr75* (*5′*-CAAGGTATGTTGCCCGTTTGTCC-3′) and inner antisense primer *HBPr94* (*5′*-GG(T/C)A(A/T)AAAGGGACTCA(A/C)GAT G-3′)**.** The thermocycling conditions and amplification protocol were done as previously described and the nested amplification products were 341 bp[9].

Detection of HBV DNA by Real-time PCR

The assay relies on the targeted amplification of HBV-DNA using primers that are specific to the s gene. The primers used were *s*-sense [5′-AGAACATCGCATCAGGACTC-3′ (159–178)] and *s*-antisense [5′-CATAGGTATCTTGCGAAAGC-3′ (642–623)]. The thermocycling protocol included a 10-min AmpliTaq activation step at 95 °C, 40 cycles of PCR amplification at the following temperatures: denaturation for 15 s at 95 °C, annealing for 30 s at 55 °C, and extension for 1 min at 72 °C. A melting curve analysis was performed to determine the purity and specificity of the amplification product. The melting curve analysis profile was 95 °C for 1 min, 50 °C for 30 s and 95 °C for 15 s.[10].

Statistical analysis

Version 16 of SPSS was used for the statistical analysis. Numbers and percentages were used to describe qualitative data. The Mann Whitney test was used for non-parametric quantitative data, the Fisher's exact test was used to compare groups, and the T-test of independent samples was used for parametric quantitative data. Significance level at P value < 0.05.

RESULTS AND DISCUSSION

Results

Anti-HBc and anti-HBs antibodies were found in 48% and 41% of the 100 samples analyzed in this study that were taken from HD patients, respectively. Serum ALT were found to be elevated in 58% of the individuals. In addition, HCV antibodies were present in 25/48 (52.1%) of the 48 anti-HBc positive patients.

Demographic information of positive and negative HBV DNA patients

Table 1 provides a summary of several characteristics of HD patients who tested positive for anti-HBc. Based on the results of the HBV PCR, patients were divided into groups: HBV DNA positive patients (33 patients) and HBV DNA negative patients (15 patients). The mean age of the patients was 48.3±12 and 48.4±14.2 years, respectively. HBV DNA was common among men (63.6%) (P=0.031). There is no statistically significant difference for liver and renal function tests between HBV DNA positive and HBV DNA negative patients' (ALT, Urea, Creatinine) (P=0.875, 0.178, and 0.392, respectively).

Serological tests

One hundred samples obtained from HD patients (HBsAg negative) were tested for HBV markers showing that anti-HBs and anti-HBc antibodies each alone were identified in 11 and 18 samples, respectively, while thirty samples were positive for both anti-HBs and anti-HBc antibodies **(Table, 2)**.

The anti-HBc positive samples were tested for HBV DNA. It was found that 33 samples were positive for HBV DNA.

Biochemical tests

ALT levels were measured in dialysis patients with various HCV and anti-HBc antibody serological profiles. **Table 3** shows that out of 46 HCV positive patients, 26 (56.5%) patients had normal ALT levels. No significant difference was observed in ALT levels among HCV negative patients and HCV positive patients with or without anti-HBc antibody (P=0.604) **(Table, 3)**.

Table 1: Demographic information of positive and negative HBV patients.

Variables		Anti-HBc positive N=48		P value
		HBV DNA Negative	HBV DNA Positive	
		N=15	N=33	
Age	Mean ± SD	48.4±14.2	48.3±12	0.975
Sex	Male Female	١٤(٩٣.٣%) ١(٦.٧%)	٢١(٦٣.٦%) ١٢(٣٦.٤%)	0.031*
Alt	Normal Up Normal	6(40%) 9(60%)	14(42.4%) 19(57.6%)	0.875
Urea	Mean ± SD	146.9±31.7	166.1±49.9	0.178
Creatinine	Mean ± SD	8.9±2.6	9.5±2.5	0.392

Mann-Whitney test for non-parametric quantitative data (represented by median); Independent Samples (T) test for parametric quantitative data (expressed by mean); Fisher's exact test for qualitative data between the two groups. Significance level at P value < 0.05.

Table 2: HBV markers among hemodialysis patients.

Viral marker	No	%
	N=100	
Negative samples	41	41
Anti-HBs alone	11	11
Anti-HBc alone	18	18
Anti-HBs + Anti-HBc	30	30
Anti-HBc positive samples (N=48)		
Anti–HBc with DNA	33	68.8
Anti–HBc without DNA	15	31.3

Table 3: ALT levels in dialysis patients with various HCV and anti-HBc antibody serological profiles.

ALT	HCV negative				HCV positive			
	anti-HBc negative		anti-HBc positive		anti-HBc negative		anti-HBc positive	
	N	%	N	%	N	%	N	%
Normal	12	36.7	10	43.5	10	47.6	10	40
Up Normal	19	63.3	13	56.5	11	52.4	15	60
Total	31	100	23	100	21	100	25	100
P value	0.615				0.604			

significant level at P value < 0.05.

Table 4: HBV DNA positivity in hemodialysis patients with and without anti-HCV.

HBV-DNA	Anti-HCV negative		Anti-HCV positive		P value
	NO	%	NO	%	
Positive	13	56.5	20	80	0.043*
Negative	10	43.5	5	20	
Total	23	100	25	100	

significance level at P value < 0.05.

Detection of HBV DNA

A total of 33 occult HBV infections were discovered in the 100 chronic HD patients, and they were all anti-HBc positive. Of the 48 dialysis patients who tested positive for anti-HBc, 33 (68.8%) had the pol gene amplified using conventional PCR (**Fig. 1)**. Using the real time PCR technique to amplify the (s) gene, HBV DNA was found in 24/48 (50.0%) of the patients.

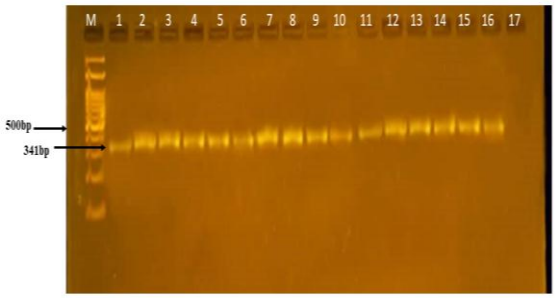

Fig. 1: Electrophoresis of pol gene nested PCR products (341bp) extracted from serum samples of hemodialysis patients. M: 100-bp DNA ladder; 1 – 16 are amplified products.

HBV DNA positivity according to HCV status

For both anti-HCV-positive and anti-HCV-negative HD patients, HBV DNA positivity is displayed in Table 4. HBV DNA was found in 13/23 and 20/25 of the individuals who tested negative for anti-HCV and positive for anti-HCV, respectively. Our results showed that HBV DNA was common among anti-HCV positive patients (P = 0.043).

Discussion

The presence of OBV infection with undetectable HBsAg is a risk factor for the onset of hepatic disease. HBV infection is a significant co-morbid disease that, regardless of location, can lead to outbreaks of hepatitis B within the HD group despite the deployment of several approaches to reduce new infection[11].

Increased HBV transmission among HD patients was linked to using the same machines for HBV infected and uninfected patients, the presence of undiagnosed hepatitis B among HBV negative groups, and the preparation of injectable medicines in the dialysis treatment room[12].

HD patients were examined for hepatitis B surface and core antibodies in the current study. Thirty-three patients out of 100 getting regular hemodialysis therapy had OBI, and they were all tested positive for anti-HBc. The frequency of OBI among the tested HD individuals was in agreement with previous findings[13,14]. Although a lower prevalence was previously reported[15,16] indicating that OBI was absent in their HD patients.

According to previous reports, the prevalence of OBI in people on renal dialysis ranges from 0% to 58%[15,17]. Interpretation is challenging due to significant discrepancies in the populations of the studies and the sensitivity of the HBV-DNA assay. According to Cabrerizo *et al*[18]**,** 57.6% of HD patients experienced OBI. A sizable cohort (585) of Italians undergoing chronic dialysis was studied by Fabrizi *et al*[17]**,** they stated that OBI wasn't present in their study group and that 20.8% of HD patients had anti-HBc. Beykaso *et al* (2022) found that out of 115 anti-HBc positive samples, 21 (18.3%) samples had HBV DNA signifying OBI.

The incidence of HBsAg in Egypt is of moderate endemicity (2–8%). Nevertheless, no accurate estimation of the prevalence of OBI in Egypt's major population groups, such as HD patients or blood donors, is available. Data from earlier studies conducted in Egyptian dialysis facilities indicate that between 4% and 26% of patients had OBI[19,20]. These variations in OBI rates in HD patients between different studies, as well as our study, could be brought on by a number of factors, including epidemiology of HBV, and burden of the infection in different regions, differences in sociodemographic characteristics of the participants, hemodialysis unit health policies, variances in the sensitivity of the technologies used to detect the viral genome, as well as differences in the size of the study groups[21-23]**.**

It is believed that mutant HBV infections prevent the detection of OBI using currently available commercial molecular techniques. These mutations may make the virus more persistent, slow down its rate of replication, or decrease its ability to create an antigen. Despite the fact that anti-HBc is a marker for prior viral exposure, there are no recommendations for anti-HBc screening in hemodialysis facilities[24].

Given that HBsAg-negative HD patients may have HBV DNA with anti-HBc positive antibodies. The current study highlights the importance of anti-HBc as a good marker for detecting OBI. Results revealed 48 individuals who tested positive for an anti-HBc marker but who would not have been consistently identified in hemodialysis facilities. Of these patients, 33 patients (68.75%) were found to have OBI by nested PCR while Real-time PCR showed that 24 samples were positive for HBV DNA. The low viral load of the samples could be the cause of the discrepancy between the results of the nested PCR and real-time PCR. The nonhomogeneous distribution of the target DNA in the sample volume may have caused certain aliquots to possess a viral load close to the real-time PCR assay's lower limit of detection[25]**.** Anti-HBc positive individuals may have a hidden infection, according to prior studies[15,24].

Our results highlight the importance of testing OBI. As patients undergoing dialysis use the same dialysis equipment, is it possible for others to obtain OBI from them? This is an essential question related to our findings. Consequently, nosocomial transmission could not be ruled out. As a result, it is crucial to identify these individuals in hemodialysis clinics to prevent the spread of the virus among patients.

Twenty-six cases in the current study demonstrated elevated liver transaminase activity; however, elevated aminotransferase levels were not correlated with anti-HBc or OBI. Another study found that people with OBI rarely have abnormal liver enzymes[24]. Additionally, we did not report a relation between OBI in our study population and biochemical liver testing.

Regarding the relation between OBI and HCV, some research revealed relationships between the two[17,26]. In our study, a significant correlation between anti-HCV positivity and HBV DNA was observed. Another study conducted by Aghakhani *et al*[24], did not find a correlation between the presence of HCV and HBV DNA, although this was likely owing to the overall low prevalence of HCV infection in their study population. According to our findings, anti-HCV antibodies were present in 52.1% of anti-HBc positive samples. Other studies by Jilg *et al*[27] and Coppola *et al*[28], revealed a high correlation between anti-HCV and anti-HBc antibodies. Low levels of HBV viremia are caused by HCV molecules interfering with HBV replication because both the HBV and HCV genomes are present in a single hepatocyte. As a result of HCV treatment, chronic HBV patients are at high risk of HBV reactivation while the risk in those with OBI is low[29]

Conclusion

In conclusion, examining anti-HBc antibodies in dialysis patients may reveal latent HBV. Serological markers are frequently employed to diagnose HBV infection, however, to rule out potential occult infections, these markers must always be supported by molecular assays. Additional studies will improve our understanding of the clinical, laboratory, and epidemiological aspects of occult infections. Further multi-center longitudinal studies with larger patient populations are needed to determine the impact of occult hepatitis B in the spread of HBV infection in hemodialysis facilities.

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نشرة العلوم الصيدلية
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انتشار عدوى فيروس التهاب الكبد B الخفي بين مرضى غسيل الكلى المزمن البالغين في محافظة المنيا ، مصر

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على الرغم من أن عدوى فيروس التهاب الكبد B الخفي (HBV) تشكل تهديدًا عالميًا وتتزايد بشكل كبير، إلا أنه لم يتم إيلاء اهتمام كبير لها. تتميز عدوى فيروس التهاب الكبد B الخفي (OBI) بانخفاض مستويات الحمض النووي لفيروس التهاب الكبد B في الكبد و / أو البلازما، ومستضد التهاب الكبد B السطحي (HBsAg)، ووجود أو عدم وجود الأجسام المضادة السطحية لالتهاب الكبد B (مضادات HBs) أو الأجسام المضادة لمستضد التهاب الكبد B الأساسي (مضاد لـ HBc). يُنظر إلى OBI على أنه خطر صحي خطير لأنه يمكن أن يؤدي إلى تقدم عدوى HBV الحادة، وظهور تليف الكبد، وتطور سرطان الخلايا الكبدية (HCC). كان هدف هذه الدراسة هو معرفة مدى انتشار OBI بين مرضى غسيل الكلى (HD) في محافظة المنيا بصعيد مصر. تضمنت هذه الدراسة ١٠٠ مريض يعانون من مرض كلوي في نهاية المرحلة يخضعون لغسيل الكلى بانتظام وكان اختبار HBsAg سلبيًا. تم استخدام ELISA لاختبار المصل لوجود مضادات HBs وHBc. تم استخدام كل من PCR المتداخلة مع البادئات الخاصة بالجينات (polymerase) وPCR في الوقت الفعلي مع البادئات الخاصة بالسطح (الأسطح) الخاصة بالجينات للكشف عن HBV DNA. تم العثور على الأجسام المضادة لـ HBs والأجسام المضادة لـ HBc في ٤١ و ٤ ٪ من إجمالي العينات، على التوالي. بالإضافة إلى ذلك، كان ٥٢.١٪ من المرضى الموجودين ضد HBc إيجابيين للأجسام المضادة لـ HCV. من بين ٤٨ عينة موجبة ضد HBc، كانت ٣٣ (٦٨.٧٥٪) عينة موجبة لـ HBV DNA. أظهر HBV DNA أنه مرتبط بشكل كبير مع عينات إيجابية الأجسام المضادة لـ HCV (P = 0.043). من بين العينات التي تم اختبارها إيجابية لمضادات HBc مع أو بدون الأجسام المضادة لـ HCV، لم يكن هناك فرق كبير في مستويات
(ALT P = 0.604). يعد تطبيق الاختبار المضاد لـ HBc لتحديد OBI طريقة ممتازة لزيادة الأمان في مرافق غسيل الكلى. نوصي أيضًا باستخدام الطرق الجزيئية مثل تفاعل البوليميراز المتسلسل المتداخل وتفاعل البوليميراز المتسلسل في الوقت الحقيقي للكشف عن HBV DNA بين مرضى HD.