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The Distribution Clinical and Demographic Features of HBsAg Positive Patients in Şanlıurfa Region

Şanlıurfa Yöresinde HBsAg Pozitif Hastaların Klinik Dağılımı ve Demografik Özellikleri

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ABSTRACT

Objective: The objective of this study was to investigate the distribution of the clinic and demographic characteristics of hepatitis b surface antigen (HBsAg) positive patients in Şanlıurfa region.
Materials and Methods: HBsAg seropositive patients admitted to the gastroenterology outpatient clinics were classified as inactive carriers, chronic hepatitis B (CHB), hepatitis B virus (HBV) cirrhosis, chronic hepatitis delta and cirrhosis. Demographic and clinical features of the patients and antiviral treatment they received were analyzed.
Results: HBsAg seropositivity was detected in 296 patients (mean age: 38.8±13.7 years, range: 15-74), 152 patients (51%) were male (mean age: 38.5±14.4 years, range: 15-73) and 144 (49%) were female (mean age: 39.1±13.7 years, range: 15-74). Two hundred five patients (69%) were detected to be inactive HBV carriers (mean age: 37.7±12.9 years, range: 15-74) and 91 (44.4%) of them were male. CHB was detected in 44(16%) patients (mean age: 36.7±13.4 years, range: 17-69) and 27 (60%) were male. Cirrhosis was detected in 30 (10%) patients (mean age: 49±15 years, range: 20-73) and 24 (83%) were male. Seventeen patients (5%) (mean age: 37.8±12.8 years, range: 16-60) were anti-hepatitis D virus (anti-HDV) positive, 11 (65%) were male, 5 of them were in the cirrhotic stage. Two patients (0.6%) had HBV/HCV co-infection, two patients (0.6%) had hepatocellular carcinoma (HCC). Seven patients were pregnant, three patients were given tenofovir in the 3rd trimester, due to high viral load. Seventy one of 73 (26%) patients who were identified to have cirrhosis or chronic hepatitis due to HBV or HDV, 71 of (those who received or completed interferon treatment) received antiviral therapy, most commonly tenofovir. Liver transplantation was performed in two patients (0.6%) due to HBV related liver cirrhosis.
Conclusion: Three-quarters HBsAg seropositive patients in Şanlıurfa region were inactive HBV carriers and one quarter were at the stage of chronic hepatitis or cirrhosis. Inactive carriers and chronic hepatitis patients are often in the 3rd decade and cirrhotic patients were in the 4th decade of life. Chronic HDV was observed in 5% of patients, HBV related HCC 0.6%, HBV/HCV co-infection was found in 0.6% of patients. Almost all patients with chronic hepatitis or cirrhosis were found to be received or/receiving antiviral treatment and the most commonly used medication was tenofovir.
Keywords: Inactive carriers, chronic hepatitis B, hepatitis D, cirrhosis, treatment

ÖZ

Amaç: Şanlıurfa yöresinde hepatit B yüzey antijeni (HBsAg) pozitif hastaların klinik dağılımı ve demografik özelliklerinin araştırılması amaçlanmıştır.
Gereç ve Yöntemler: Aralık 2011-Nisan 2012 tarihleri arasında gastroenteroloji polikliniğine başvuran HBsAg seropozitif hastalar; inaktif taşıyıcı, kronik hepatit B (KHB), hepatit B virüs (HBV) sirozu, kronik delta hepatiti ve sirozu olarak sınıflandırıldı. Bu hastaların demografik, klinik özellikleri ve aldıkları antiviral tedaviler incelendi.
Bulgular: HBsAg pozitif saptanan 296 hastanın yaş ortalaması 38,8±13,7 yaş (dağılım 15-74), 152'si (%51) erkek, yaş ortalaması 38,5±14,4 yaş (dağılım 15-73), 144'ü (%49) kadın, yaş ortalaması 39,1±13 yaş (dağılım 15-74) idi. İnaktif HBV taşıyıcı teşhisi konulan 205 (%69) hastanın yaş ortalaması 37,7±12,9 yaş (dağılım 15-74) ve 91'i (%44,4) erkek idi. Kronik hepatit saptanan 44 (%16) hastanın yaş ortalaması 36,7±13,4 yaş (dağılım 17-69) ve 27'si (%60) erkek idi. HBV siroz saptanan 30 hastanın (%10) yaş ortalaması 49±15 yaş (dağılım 20-73) ve 24'ü (%83) erkek idi. Hastaların 17'sinde (%5) anti-hepatit D virüs (anti-HDV) pozitif saptanmış olup yaş ortalaması 37,8±12,8 yaş (dağılım 16-60), 11'i (%65) erkek ve 4 tanesi sirotik evrede idi. İki hasta (%0,6) hepatit HBV/HCV koenfeksiyonu idi. Hastalardan 7 tanesinde gebelik vardı, 3 tanesine yüksek viral yük nedeniyle 3. trimesterde tenofovir verilmişti. İki hastada (%0,6) hepatosellüler karsinom (HSK) saptandı. HBV veya delta hepatitine bağlı kronik hepatit veya siroz evresinde olan 73 (%26) hastadan 71 tanesi (interferon tedavisi almış, tedaviyi tamamlamış hastalar dahil) antiviral tedavi almış veya almakta olup en sık tenofovir kullanmakta idi. Hastalardan 2 tanesine (%0,6) HBV'ye bağlı karaciğer sirozu nedeniyle karaciğer nakli yapıldı.
Sonuç: Şanlıurfa yöresinde HBsAg (+) hastaların dörtte üçü inaktif HBV taşıyıcısı, dörtte biri kronik hepatit veya sirotik dönemdedir. İnaktif taşıyıcı ve kronik hepatit hastalar sıklıkla 3. dekadda, sirotik hastalar dördüncü dekattadır. Kronik delta hepatit sıklığı %5, HSK sıklığı %0,6, HBV/HCV koenfeksiyon sıklığı %0,6'dır. KHB veya siroz olan hastaların tamamına yakını antiviral tedavi almış/almakta olup en sık tenofovir kullanmaktadır.
Anahtar Kelimeler: İnaktif taşıyıcılık, kronik hepatit B, delta hepatit, siroz, tedavi

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Introduction

Worldwide, more than 400 million individuals are chronically infected by hepatitis B virus (HBV) who are at an increased risk for progressive hepatocellular cancer (HCC) and cirrhosis. Individuals with HBV infection should be followed up throughout their lives (1).

According to a nationwide study conducted in 2010 by Turkish Association for the Study of the Liver (TASL), it was estimated that 3 million individuals had hepatitis B in Turkey. It was determined that the rate of hepatitis b surface antigen (HBsAg) positivity indicating HBV carrier state was 4%, anti-HBs positivity indicating immunity against HBV was 32% and anti-hepatitis D virus (anti-HDV) positivity was 2.7%. When considering HBsAg positivity rates by regions, it was most commonly encountered in the Central and Southeastern Anatolian regions, whereas it was most rarely encountered in the Aegean and eastern part of the Central Anatolian regions.

It was estimated that 50 million new HBV infection cases were diagnosed annually, 5-10% of adults and 90% of pediatric patients became chronic and 75% of those, who progressed to chronic hepatitis B (CHB), cirrhosis and HCC, were living in Asia. The best strategy to decrease the incidence of HBV related cirrhosis and HCC was to prevent HBV infection (2). Death, hepatic decompensation and HCC risks are increased in CHB patients (3). CHB diagnosis is made by combination of serological, biochemical, virological and histological markers. Natural progression of HBV infection is divided into 4 phases: immune tolerance, immune clearance (HBeAg positive CHB), inactive HBsAg carrier state and reactivation (HBeAg negative CHB).

Antiviral treatment is essential for patients whose ALT and HBV DNA levels are high in immune clearance and reactivation phases. It seems that suppression of HBV DNA and suppression of its permanent replication by CHB treatment may decrease progression to cirrhosis and HCC (4).

It is not always easy to differentiate between inactive HBV carrier state and HBeAg negative CHB because of biochemical (normal ALT) and virological (HBeAg negativity and low HBV DNA levels) characteristics. In clinical practice, differentiation of inactive carrier state from temporary remission of CHB is very important (5). The steatosis incidence is increased in inactive HBV carrier state, increased ALT levels may be misleading. Abdominal ultrasonography (USG) should also be requested in the baseline evaluation of each HBsAg-positive patient in addition to serology and biochemistry (6).

According to recent data, HBsAg positivity rate is approximately 4% in Turkey and our country is in the moderate endemic region. The aim of this study was to investigate clinical distribution and demographic characteristics of HBsAg (+) patients living in Şanlıurfa, which is one of regions with the highest HBV seropositivity rate.

Materials and Methods

All HBsAg pozitive patients, who applied to gastroenterology outpatient clinic at Harran University Medical School between December 2011 and April 2012, were differentially diagnosed as inactive carriers, CHB, HBV related cirrhosis, chronic hepatitis deltaand cirrhosis after detailed biochemical, virological, radiogical and pathological investigations.

HBsAg positive patients with HBV DNA value below 2000 IU/mL and who were negative for anti-HDV and anti-HCV were accepted as carriers, whereas biopsy was performed in patients with high ALT and HBV DNA value over 2000 IU/mL. If Ishak fibrosis stage was ≥2 and Histology activity index (HAI) was >6, the patient was accepted as CHB.

Patients diagnosed with cirrhosis histologically or clinically with acids and who developed encephalopathy were accepted to have decompensated cirrhosis. Demographic and clinical characteristics of these patients and their antiviral treatmentswere investigated.

SPSS program was used for statistical analysis.

Results

Demographic Characteristics

HBsAg seropositivity was detected in 296 patients (mean age: 38.8±13.7 years, range: 15-74), 152 patients (51%) were male (mean age: 38.5±14.4 years, range: 15-73) and 144 (49%) were female (mean age: 39.1±13.7 years, range: 15-74). Two hundred and five patients (69%) were detected to be inactive HBV carriers (mean age: 37.7±12.9 years, range: 15-74) and 91 (44.4%) of them were male. CHB was detected in 44 (16%) patients (mean age: 36.7±13.4 years, range: 17-69) and 27 (60%) were male. Cirrhosis was detected in 30 (10%) patients (mean age: 49±15 years, range: 20-73) and 24 (83%) were male. Seventeen patients (5%) (mean age: 37.8±12.8 years, range: 16-60) were anti-HDV positive, 11 (65%) were male, 5 of them were in the cirrhotic stage (Table 1).

Clinical Characteristics

Of patients, 205 (69%) were inactive HBV carriers, 44 (16%) were with CHB, 30 (10%) were with cirrhosis related to HBV and 17 (5%) were with hepatitisdelta. Two patients (0.6%) had HBV/HCV co-infection and two patients (0.6%) had HCC. Five of deltahepatitis patients were at cirrhotic stage (Table 1). Seven patients were pregnant. Seventy one of 73 (26%) patients who were identified to have cirrhosis or CHB or HDV, 71 (who received or completed interferon treatment) received antiviral therapy, most commonly tenofovir. Liver transplantation was performed in two patients (0.6%) due to HBV related liver cirrhosis. Lamivudine

Table 1. Clinical and sex distribution and age means of HBsAg (+) patients

Diagnosis	Number	Percentage	Age
Inactive HBVcarrier	205	69%	37.7±12.9 years (15-74)
Chronic hepatitis B	44	16%	36.7±13.4 years (17-69)
Cirrhosis due to HBV	30	10%	49±15 years (20-73)
HDV hepatitis/ cirrhosis	17	5%	37.8±12.8 years (16-60)
Total	296		38.8±13.7 years (15-74)
Male	152	51%	38.5±14.4 years (15-73)
Female	144	49%	39.1±13 years (15-74)

HDV: Hepatitis D virus, HBV: Hepatitis B virus

prophylaxis was given in two patients, who were receiving chemotherapy, one with lymphoma and the other with gastric cancer. As the patient with gastric cancer did not use the drug for 2 months, acute hepatitis developed and the patient died because of hepatic failure.

Hepatocellular Cancer

HCC was diagnosed in two of patients with cirrhosis; one of them had cirrhosis due to hepatitis delta and chemoembolization was performed, and the patient was on the transplantation list in another center. The other patientpresented with rupture of exophytic HCC on the basis of HBV cirrhosis, and the patient was referred to a transplantation center, but the patient was reported died duringfollow up.

Treatment

Antiviral treatment was given to 71 (including patients received but did not complete interferon treatment) out of 73 (26%) patients with chronic hepatitis or cirrhosis stage related to HBV or hepatitis delta. Antiviral treatment drugs and the number of the patients were tenofovir, entecavir, lamivudine, pegylated interferon and 39 (55%), 12 (17%), 7 (10%), 13 (18%), respectively. Both transplanted patients (0.6%) were receiving tenofovir and tenofovir was given in the 3rd trimester in 3 out of 7 pregnant women because of high viral load.

Discussion

Despite widespread vaccination programs, CHB is still one of the most important health problems in the world and 350-400 million individuals are infected by HBV. On the contrary to expectations, the study indicated that the prevalence of hepatitis B was at moderate endemic level in Turkey; its prevalence (2.7%) was similar to that observed in Western populations among young adults (aged between 18 and 30 years) (7,8,9). According to the study of TASL in 2010, it was estimated that there were 3 million individuals infected by HBV in Turkey. Positivity rates of HBsAg and anti-HDV were determined to be 4% and 2.7%, respectively. HBsAg positivity rates were determined in neighboring regions of Şanlıurfa as 2.5% in Diyarbakır and 9.9% in Gaziantep (8). Değertekin et al. (10) reported that anti-HDV positivity rates reported by majority of investigators in Turkey varied between 0.94% and 5.5% and anti-HDV positivity rate was high as 20-25% among acute viral hepatitis cases in the Southeast Anatolia Region. While HBsAg seroprevalence was determined approximately at 1% among blood donors in the province of Erzurum (9), HBsAg positivity rate was reported at 3.6% among women of childbearing age and pregnant women in Şanlıurfa (11). It was expected that disease related to HBV and HDV would be encountered frequently in the province of Şanlıurfa and our annual series of nearly 300 patients was also confirming that. In line with expectations, anti-HDV frequency in our series was determined as 5%, which was approximately twice the mean of Turkey.

Knodell's modified histological activity index score and Ishak fibrosis score are being used commonly in liver biopsy evaluations (12). In our patients, biopsy was performed for the diagnosis of CHB in patients considered for the treatment and evaluations were performed by using Ishak scoring.

Among 2870 patients followed in the department of gastroenterology at İstanbul University Medical School between years 1997 and 2010, 52 (2%) symptomatic patients were diagnosed with extrahepatic involvement retrospectively (13). Extrahepatic involvement was not determined in our patient group, but detailed investigations were not performed for this aspect.

HBsAg carrier rate among Asian originated Americans was reported to be 7-16% and HBV was reported as the most important cause for chronic hepatitis, cirrhosis and HCC in these patients (14). Risks of death, hepatic decompensation and HCC are increased in CHB patients (3). The diagnosis of CHB is made by combination of serological, virological, biochemical and histological markers (4). In a study evaluating cirrhotic patients in Şanlıurfa region, HBV was the most common cause of cirrhosis and it was encountered in approximately half of the patients. Among our cirrhotic patients, the etiological cause was HBV in 39% and HDV in 6% of cases (15). In our HBsAg-positive patient series, 69% were inactive HBV carriers, 16% had CHB and 10% had cirrhosis related to HBV. CHB diagnosis was made in patients with high HBV DNA and AL levels by performing liver biopsy. The diagnosis of cirrhosis was made depending on thrombocytopenia, hepatic atrophy, splenomegaly, ascites, signs of esophageal varices by performing biopsy or clinical examination. HCC diagnosis was made depending on AFP, USG and dynamic magnetic resonance imaging.

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV (REVEAL-HBV) study reported from Taiwan indicated the strong correlation between HBV DNA and HCC. The population-based cohort study indicated that independent risk factors were male gender, advanced age, high ALT, HBeAg positivity, high HBV DNA level, genotype C and core promoter mutation. It was also reported that HBsAg level might predict HCC risk in HVB carriers with low viral load and individualize treatment should be considered in high-risk carriers according to HCC risk rate (16,17,18). In our patient group, HCC was also diagnosed in 2 patients (0.6%); one of them had HBV and the other had HDV backgrounds. Both patients had cirrhosis backgrounds and they were males. The patient, who developed HCC related to HBV, died.

Patients with high ALT and HBV DNA levels during HBV infection, immune clearance and reactivation phases are candidates for antiviral treatment. Pegylated interferon alpha-2b, pegylated interferon alpha-2a, lamivudine, adefovir, entecavir, telbivudin and tenofovir are the available treatment options in CHB. Patients starting treatment should be followed up every 3-6 months (4). Entecavir and tenofovir are recommended as the first line treatment for CHB. The primary aims of treatment are to suppress viral replication permanently so that clinical remission can be provided to reverse fibrosis and to decrease and to prevent late-stage hepatic failure and progression to HCC. If the patient has cirrhosis and HBV DNA values are at detectable levels, then antiviral treatment should be given (14). In our patient group, treatment was started in patients who were diagnosed with CHB by biopsy and cirrhosis by positive HBV DNA. Distribution of patient number to tenofovir, entecavir, lamivudine, and pegylated interferon was 39 (55%), 12 (17%), 7 (10%) and 13 (18%), respectively. Both transplanted patients (0.6%) received tenofovir. All patients are still attending outpatient visits every 3 months regularly.

The long-term use of tenofovir and entecavir is both effective and safe in patients with compensated and decompensated cirrhosis. Potent antiviral agents are medicines which may provide

long-term HBV DNA suppression and improvement of cirrhosis with quite low resistance rates. Additionally, their long-term use may decrease the risk of HCC development (19). The most commonly given drugs in our patient group were tenofovir and entecavir. Two third of our patients on treatment have received these two potent drugs.

If there is a family history of HCC, then HCC risk is increased at every stage of HBV infection; these patients should be followed up more closely. If the HBsAg-positive patient carries the risk factor, the patient should be followed up for the entire life for HCC by AFP and abdominal USG every 6 months (14,16,20). For the risk of HCC, these patients attend outpatient visits every 3 months regularly and they have AFP and USG controls done in every 6 months.

When cancer chemotherapy or immunosuppressive treatment is started, all patients should be examined for HBsAg and if they are positive for HBV, they should receive antiviral prophylaxis. Reactivation of HBV infection is commonly encountered during immunosuppressive treatment or chemotherapy in patients with positive HBsAg. However, it may be encountered in HBsAg-negative, anti-HB core-positive patients. Clinical presentation may vary from asymptomatic state to severe hepatitis, hepatic failure or death (1,21). Two of our patients received lamivudine for prophylaxis, but as one of them discontinued the drug for 2 months, hedied due to hepatic failure.

Treatment should be considered in high viremia during pregnancy, co-infection, and if the patient receives immunosuppressive treatment (14). Anti-HCV treatment is successful in HBV/HCV co-infection, but HBV DNA should be monitored because of the risk for HBV exacerbation (22). There were 7 pregnant patients in our patient group and 3 of them received tenofovir in the last trimester because of high viral load. Treatment was not considered in the patient with HBV/HCV co-infection, because the patient was in thecirrhotic period.

In a study reported from Greece, Manesis et al. (23) reported that anti-HDV was examined in one third of patients with positive HBsAg and it was reported that 4.7% of them were positive. Since HDV infection is a rapidly progressing disease, interferon-based treatments may change its progression. It was determined that HBV DNA was prominently suppressed only by pegylated interferon treatment inchronic HDV patients. Therefore, it was reported that addition of oral nucleotide treatment to pegylated interferon was not required at treatment initiation in this group of patients, but if required during follow up, it might be suitable to add nucleotides to the ongoing treatment (24). Anti-HDV was positive in 17 (5%) of our patients and 5 of them were at cirrhotic stage. These patients received or continued pegylated interferon treatment. Our patient, who was transplanted due tohepatitis delta, was receiving tenofovir.

Conclusion

Among HBsAg(+) patients in Şanlıurfa region, 69% are inactive HBV carriers, 31% have CHB or cirrhotic stage. Inactive carrier CHB patients are generally in the 3rd decade, whereas cirrhotic patients are in the 4th decade of life. Among HBsAg(+) patients, the prevalence of chronic delta hepatitis is 5% HBV/HCV co-infection is 0.6% and the prevalence of HCC related to HBV is 0.6%. Nearly all patients with chronic hepatitis or cirrhosis have received/are receiving antiviral treatment and tenofovir is the most commonly used agent. Hepatitis B is still one of the most important health problems in the world, in the Turkey and in our region.

Authorship Contributions

Ethics Committee Approval: The study were retrospective, Informed Consent: Consent form was filled out by all participants, Concept: Ahmet Uyanıkoğlu, Design: Ahmet Uyanıkoğlu, Data Collection or Processing: Ahmet Uyanıkoğlu, Umut Sert, Burcu Çetin, Analysis or Interpretation: Ahmet Uyanıkoğlu, Literature Search: Ahmet Uyanıkoğlu, Writing: Ahmet Uyanıkoğlu, Peer-rewiev:External and Internal peer-reviewed, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared that this study has received no financial support.

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