Comparison of the level of Depression and Anxiety in Inactive Hepatitis B Carriers and Chronic Hepatitis B Patients

Nazlım AKTUĞ DEMİR[1], Mustafa ÇELİK[2], Servet KÖLGELİER[3], Şua SÜMER[4], Selçuk AKSÖZ[5]
Lütfi Saltuk DEMİR[6], Ahmet Çağkan İNKAYA[7]

SUMMARY

Objective: The aim of this study was to evaluate the relative contribution of chronic illness and the physical effects such illness on the mental status of chronic hepatitis B patients by comparing them to inactive hepatitis B carriers, based on Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) scores.

Materials and Methods: The study included 444 participants: 249 HBsAg-positive inactive carriers (IC group) and 195 chronic hepatitis B patients (CH group) that were undergoing follow-up at Adiyaman University Research and Education Hospital, Department of Infectious Diseases Department. HBV carrier status and chronic hepatitis B were diagnosed based on European Association for the Study of Liver (EASL) guidelines. The HDRS and HARS were administered to all the participants via psychiatric interview.

Results: The overall mean HDRS score was 6.2 ± 8 and the overall mean HARS score was 6.0 ± 7.1. Mean HDRS score in the IC group was 7.5 ± 5.8, versus 8.8 ± 6.6 in the CH group; the difference was significant (P = 0.037). Mean HARS score were similar in both groups (P > 0.05). There wasn't a difference in anxiety or depression scores based on participants'gender or age (P > 0.05). Additionally, there wasn't a correlation between duration of illness, and family history of hepatitis or cirrhosis, or anxiety or depression scores (P > 0.05). Anxiety scores were higher among the participants with comorbidity, in both CHB and IC groups(P = 0.005 and P = 0.001, respectively). Depression scores were higher among the IC group participants with comorbidity (P = 0.003). that can occur during the treatment and follow-up of chronic hepatitis patients. The presence of comorbidity in chronic hepatitis patients increases the risk of psychiatric complications.

Conclusion: Psychiatric comorbidity, particularly anxiety and depression, are important problems

Keywords: Hepatitis B, chronic, complications, depression, anxiety

INTRODUCTION

It is estimated that more than 2 billion people worldwide are infected with hepatitis B virus (HBV) (Robinson 1995). Worldwide, HBV is among the most important causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Myers et al. 2003). Research has shown that the prevalence of psychiatric disorders in chronic hepatitis B patients is higher than that in the general population (Evon et al. 2007; Ozkan et al. 2006; El-Serag et al. 2002). Kunkel et al. (2000) reported that the prevalence of depressive symptoms in chronic hepatitis B patients was 46%. Overlooking accompanying psychiatric disorders in chronic hepatitis B (CHB) patients can result in a decrease in treatment compliance, and familial, vocational, and social functionality, and can adversely affect the disease course.

As compared to CHB patients, the literature contains fewer data on carriers of HBV that don't develop chronic hepatitis B. Lok et al. (1985) investigated the psychosocial effect of hepatitis B in 40 carriers in England. They reported that 90% of the participants had sexual, occupational, social,

Received: 24.01.2012 - **Accepted:** 15.11.2012

[1,5]Infecious Diseases Specialist, Infectious Diseases Clinic, Adiyaman State Hospital, Adiyaman, [2]Assis Prof., Psychiatry Department, Adiyaman University, Adiyaman, [3]Assis Prof., Infectious Diseases Department, Adiyaman University, Adiyaman, [4]Assis Prof., Infectious Diseases Department, Selcuk University, Konya, [6]Public Health Specialist, Adiyaman Provincial Health Directorate, Adiyaman, [7]Assis Prof., Infectious Diseases Department, Hacettepe University, Ankara, Turkey.

E-mail *mustacelik@yahoo.com*

familial, or physical problems, and that many of the observed problems were due to fear of transmitting HBV. Atesci et al. (2005) compared 43 asymptomatic hepatitis B carriers and 43 healthy controls, reporting that there was a higher incidence of psychiatric disorders in the carriers than in the controls (30.2% versus 11.6%). The researchers concluded that psychiatrists should be involved in the follow-up of asymptomatic HBV carriers.

Altindag et al. (2009) compared quality of life and the level of depression in 30 CHB patients, 30 hepatitis B carriers, and 30 healthy controls. They observed lower quality of life and higher levels of depression, based on the Beck Depression Inventory, in the chronic hepatitis B patients and asymptomatic carriers than in the controls; there wasn't a difference between the carriers and patients, which might have been due to the small study population—a limitation of the study highlighted by the researchers. Arslan et al. (2003) compared the level of anxiety and depression in 20 children with CHB, 20 asymptomatic carriers, and 43 controls. Anxiety was measured using the State-Trait Anxiety Inventory for Children and depression was measured using the Childhood Depression Inventory. The researchers did not observe a difference in anxiety or depression between the 3 groups, but the study was limited by a small study population. The present study aimed to compare the level of anxiety and depression in a population of CHB patients and hepatitis B carriers larger than that which has been previously studied.

MATERIALS and METHODS

Sample

The study included 444 HBsAg-positive participants; 249 HBsAg-positive inactive carriers (ICs) (IC group) and 195 CHB patients (CHB group) that were undergoing follow-up at Adiyaman University Research and Education Hospital, Department of Infectious Diseases Department, Adiyaman, Turkey. Based on the 46% prevalence of depression in CHB patients reported by Kunkel et al. (2000), the present study's sample size was calculated to be 191, as follows: $\alpha = 0.05$, $\beta = 0.80$, P0 = 0.46, and P1 = 0.36.

HBV carrier status and CHB were diagnosed using European Association for the Study of Liver (EASL) guidelines. IC status was diagnosed in HBsAg-positive individuals without liver necrosis or inflammation and in whom viral replication was terminated or below certain levels [HBsAg (+) for ≥6 months, HBeAg (–)/anti-HBeAg (+), HBV DNA <2000 IU mL^{-1} (104 copies mL^{-1}), normal ALT and AST results ≥3 times during the previous year, and absence of hepatitis-specific liver biopsy findings]. Chronic hepatitis was defined as the presence of viral replication (HBeAg and/or HBV DNA positivity) and significant inflammatory activity in the liver. Standard interferon beta2a 180 μg was administered QWK; in order to ensure that the doses were standard patients with chronic renal failure were excluded. Written informed consent was obtained from all the participants.

Scales

A sociodemographic data form was completed by all the participants. All the participants were interviewed by the same psychiatrist, and the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) were administered.

Hamilton Depression Rating Scale (HDRS)

HDRS was developed by Hamilton (1960) to measure the severity of depression. The 17-item scale has a maximum score of 53. Scores ≥14 are indicative of depression. The Turkish version of the scale was reported to be valid and reliable for use in Turkey (Akdemir et al. 1996).

Hamilton Anxiety Rating Scale (HARS)

HARS was developed by Hamilton (1959) to determine the level of anxiety and distribution of symptoms, and to measure change in symptom severity. It consists of 14 items that assess both mental and somatic symptoms. The presence and severity of symptoms are rated by an interviewer. The Turkish version of the scale was reported to be valid and reliable for use in Turkey by Yazici et al. (1998).

Data were analyzed using SPSS v.16.0 for Windows. Categorical variables were analyzed using the chi-square test and continuous variables were analyzed via the t test. Pearson's correlation analysis was used to measure correlations between HDRS and HARS scores, and certain variables.

FINDINGS

The study included 267 males and 177 females. A positive family history of HBV infection was observed in 252 of the participants and 48 of the participants had a first- or second-degree relative with cirrhosis associated with HBsAg positivity. In all, 65 articipants had a comorbid illness—the most common of which were diabetes mellitus, asthma, hypertension, and osteoporosis (Table 1). In all, 56 of the participants had a history of psychiatric treatment. There wasn't a difference in the level of depression or anxiety in the participants according to sex or age ($P > 0.05$). Additionally, there wasn't a difference in depression or anxiety levels according to disease duration, family history of HBV infection, or family history of cirrhosis ($P > 0.05$). Mean HARS score was significantly higher in those in both groups that had comorbid illnesses ($P = 0.005$ and $P = 0.001$, respectively). Mean HDRS score was significantly higher among those in the IC group that had a comorbid illnesses ($P = 0.003$).

Among the study participants, 249 were in the IC group and 195 were in the CHB group. The overall mean HDRS score was 6.2 ± 8 and the overall mean HARS score was 6.0 ± 7.1. Mean HDRS score in the IC group was 7.5 ± 5.8, versus 8.8 ± 6.6 in the CHB group. Mean HDRS score in the CHB group was significantly higher than that in the IC group (P = 0.037). Mean HARS score in both groups were similar (P > 0.05). Mean HDRS and HARS scores in both groups are shown in Table 2. There wasn't a difference between ALT levels or HBsAg titers, or HDRS or HARS scores in the entire study population (P > 0.05), but HBsAg titers were positively correlated with HDRS scores in the IC group (P = 0.001)

In all, 36 of those in the CHB group had previously undergone interferon treatment, but had stopped before this study began, whereas 44 were receiving weekly interferon treatment and 115 were using oral antivirals. There wasn't a significant difference in HDRS or HARS scores based on history of interferon use, or based on current interferon or oral antiviral treatment (P > 0.05).

DISCUSSION

Psychiatric symptoms are frequently observed during the course and/or treatment of chronic viral hepatitis (Altindag et al. 2009; Ozkan et al. 2006; Atesci et al. 2005 Kunkel et al. 2000; Lok et al. 1985,). A review of the literature showed that more studies have examined chronic hepatitis C (CHC) patients, as compared to CHB patients (usually with comparatively smaller samples). Strengths of the present study are that the targeted sample size based on power analysis was achieved and that CHB patients and ICs were compared.

Among CHB patients, many factors, including age at which the disease was acquired, family history of the disease, and difficulty performing daily activities, negatively affect patient mood. Those that acquire the disease early in life are usually better able to cope with the disease (Ferenci et al. 2008). Leutscher et al. (2010) reported a higher rate of depression in female CHC patients taking interferon and ribavirin treatments than patients who weren't taking these treatments. In the present study there wasn't a relationship between sex, age, duration of illness, family history of HBV infection, or family history of cirrhosis, and HDRS or HARS scores in the CHB group.

In patients with chronic hepatitis the presence of comorbid disease adversely affects quality of life and increases the likelihood of psychopathology. Evon et al. (2007) reported an increased risk for the development of depression in CHC patients with comorbid illness. Hussain et al. (2001) reported a significantly higher risk for psychopathology in CHC patients with underlying diseases. In the present study HARS scores were significantly higher in both groups (P = 0.005 and P = 0.001, respectively), and HDRS scores were significantly higher among those in the IC group with comorbid illnesses (P = 0.003) than participants without comorbid illnesses. To the best of our knowledge the literature does not include any large-scale studies comparing psychopathology in HBsAg-positive patients and ICs. Altindag et al. (2009) observed lower quality of life and higher depression scores in CHB patients and carriers than in controls, but there wasn't a difference between the CHB patients and ICs. In the present study the mean HDRS score was significantly higher in the CFB group than in the IC group (P = 0.037), which might have been be due to somatic illness caused by the disease, psychiatric side effects of drugs used to treat exacerbation of infection, and the psychological effect of a chronic illness. To differentiate between these factors Carta et al. (2007) compared healthy controls with CHB and CHC patients that didn't take interferon. They observed a higher incidence of depression in the CHC patients than in the CHB patients and controls, which indicates that hepatitis increases the tendency for depression independent of interferon treatment. In order to identify other differences between patients and carriers inflammatory markers, such as TNF-α, interleukin-8, and CRF should be examined.

Markers of acute stress reaction, such as steroids, interferon, and inflammatory markers, are thought to play a role in the development of depression. Evaluating the association between inflammatory markers, such as elevated liver function test results and elevated HBsAg titers, and depression scores is therefore very important. Krueger et al. (2011) evaluated depression in CHC patients, but didn't observe a significant difference between viral load, liver function test results, or genotype, and the development of depression during treatment. In the present study there wasn't an association between ALT levels or HBsAg titers, and HDRS or HADS scores, which might have been due to the low sensitivity of HBsAg level measurement to detect inflammation. HARS scores in the present study were similar in both groups (P > 0.05).

Interferons—a treatment option for CHB—are associated with significant psychiatric side effects, which frequently lead to cessation of treatment. Interferon treatment can cause cognitive, behavioral, and affective disturbances, and may lead to major depressive disorder, cognitive impairment, difficulty concentrating, and anxiety (Yumru et al. 2006; Golden et al. 2005; Hussain et al. 2001). Antiviral agents are another treatment option for CHB, and are associated with a lower frequency of psychiatric side effects (Raison et al. 2005; Fried et al. 2002). A comparative study on CHC and CHB patients using interferons observed a lower rate of psychiatric side effects in the CHB patients, even those that were receiving interferon treatment (Marcellin et al. 2008). Evon et al. (2007) evaluated 215 CHC patients and noted varying degrees of depressive symptoms in 98 (46%) and symptoms

of anxiety symptoms in 40 (19%). One study performed in Turkey compared the level of anxiety and depression in CHC patients that did and did not receive interferon treatment (interferon treatment: n = 40; no interferon treatment: n = 15). The CHC patients in the interferon treatment group had significantly higher rates of anxiety and depressive disorders (Yumru et al. 2006). In the present study the 249 participants in the IC group were not receiving interferon treatment, 36 of those in the CHB group had previously been treated with interferon, 44 in the CHB group were receiving weekly interferon treatment, and 115 in the CHB were using oral antiviral treatment, but there wasn't a significant difference in HDRS or HARS scores based on history of interferon use, or based on current interferon or oral antiviral treatment ($P > 0.05$). In the present study treatment duration in the CHB group was not standardized and as such interferon-associated effects may not have begun in some patients and may have resolved in others. Low HDRS and HARS scores in both groups may be another factor that might have masked any interferon-related effect.

In conclusion, comorbid illness increases the risk of psychiatric illness in patients with chronic hepatitis; therefore, psychiatrists should be involved in the treatment of CHB patients. Although depression was observed more frequently in the CHB group, social isolation due to illness and the fear of infection exacerbation in the future may also increase the risk of psychopathology in ICs. Given the high incidence of hepatitis B in Turkey, involvement of psychiatrists in the follow-up of these patients might have a powerfully positive effect on public health.

REFERENCES

Akdemir A, Örsel S, Dağ İ et al (1996) Hamilton depresyon derecelendirme ölçeği (HDDÖ)'nin geçerliliği, güvenilirliği ve klinikte kullanımı. Psikiyatri Psikoloji Psikofarmakoloji Dergisi 4:251-9.

Altindag A, Cadirci D, Sirmatel F (2009) Depression and health related quality of life in non-cirrhotic chronic hepatitis B patients and hepatitis B carriers. Neurosciences (Riyadh) 14:56-9.

Arslan N, Buyukgebiz B, Ozturk Y et al (2003) Depression and anxiety in chronic hepatitis B: effect of hepatitis B virus infection on psychological state in childhood. Turk J Pediatr 45:26–8

Atesci FC, Cetin BC, Oguzhanoglu NK et al (2005) Psychiatric disorders and functioning in hepatitis B virus carriers. Psychosomatics 46: 142-7.

Carta MG, Hardoy MC, Garofalo A et al (2007) Association of chronic hepatitis C with major depressive disorders: irrespective of interferon-alpha therapy. Clin Pract Epidemiol Ment Health Oct 23;3:22

El-Serag HB, Kunik M, Richardson P et al (2002) Psychiatric disorders among veterans with hepatitis C infection. Gastroenterology 123:476-82.

Evon DM, Verma A, Dougherty KA et al (2007) High deferral rates and poorer treatment outcomes for HCV patients with psychiatric and substance use comorbidities. Dig Dis Sci 52:3251-8.

Ferenci P, Staufer K (2008) Depression in chronic hepatitis: the virus, the drug, or the ethnic background? Liver Int 28:429-31.

Fried MW, Shiffman ML, Reddy KR et al (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347:975-82.

Golden J, O'Dwyer AM, Conroy RM (2005) Depression and anxiety in patients with hepatitis C: prevalence, detection rates and risk factors. Gen Hosp Psychiatry 27:431-8.

Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50-5

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23: 56-62.

Hussain KB, Fontana RJ, Moyer CA et al (2001) Comorbid illness is an important determinant of health-related quality of life in patients with chronic hepatitis C. Am J Gastroenterol 96:2737-44.

Krueger C, Hawkins K, Wong S et al (2011) Persistent pro-inflammatory cytokines following the initiation of pegylated IFN therapy in hepatitis C infection is associated with treatment-induced depression. J Viral Hepat 18:e284-91.

Kunkel EJ, Kim JS, Hann HW et al (2000) Depression in Korean immigrants with hepatitis B and related liver diseases. Psychosomatics. Nov-Dec;41:472-80.

Leutscher PD, Lagging M, Buhl MR et al (2010) Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C. Hepatology 52:430-5.

Lok AS, van Leeuwen DJ, Thomas HC et al (1985) Psychosocial impact of chronic infection with hepatitis B virus on British patients. Genitourin Med 61: 279-82.

Marcellin P, Lau GK, Zeuzem S et al (2008) Comparing the safety, tolerability and quality of life in patients with chronic hepatitis B vs chronic hepatitis C treated with peginterferon alpha-2a. Liver Int 28:477-85.

Myers RP, Tainturier MH, Ratziu V et al (2003) Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. J Hepatol 39:222-30.

Ozkan M, Corapçioglu A, Balcioglu I et al (2006) Psychiatric morbidity and its effect on the quality of life of patients with chronic hepatitis B and hepatitis C. Int J Psychiatry Med 36:283-97.

Raison CL, Borisov AS, Broadwell SD et al (2005) Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 66:41-8.

Robinson WS (1995) Hepatitis B virus and hepatitis D virus. İçinde: Mandell GL, Bennett JE, Dolin R, editörler. Principles and Practice of Infectious Diseases, 4. baskı. New York, Churchill Livingstone 1406-39.

Yazıcı MK, Demir B, Tanrıverdi N et al (1998) Hamilton Anksiyete Değerlendirme Ölçeği, değerlendiriciler arası güvenirlik ve geçerlilik çalışması. Turk Psikiyatri Derg 9:114-7.

Yumru M, Sırmatel F, Vırıt O et al (2006) İnterferon Tedavisi Alan ve Almayan Hepatit C Hastalarında Anksiyete ve Depresyon Düzeyleri. Klinik Psikofarmakoloji Bült 16:155-9.