Evaluation of Depression in Hepatitis C or B Patients Under Antiviral Therapy

Antiviral Tedavi Altındaki Hepatit B ve C Hastalarında Depresyonun Değerlendirilmesi

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ABSTRACT Objective: Neuropsychiatric symptoms are widely reported in association with chronic hepatitis and interferon-alpha (IFN-α) treatment. We evaluated frequency and degree of depression in our patients who had used interferon-alpha and lamivudine. **Material and Methods:** One hundred and eighty patients followed up in Okmeydanı Education and Training Hospital, Hepatology Outpatient Clinic between August and December 2006 with a diagnosis of hepatitic B or C, were evaluated using the Structured Interview Guide and Hamilton Depression Rating Scale. The patients were under treatment with IFN-α or lamivudin. **Results:** In our patient population, 111 were males and 69 were females (mean age: 40.9 years). 104 had hepatitis B and 76 had hepatitis C. The mean duration of treatment was 44.18 months. The mean score of the The Hamilton Depression Rating Scale was 11.69. 30.6% of the patients were normal, 47.7% had minor depression and 21.7% had major depression. 30.6% of the patients using IFN were normal, 46.5% had minor and 22.9% had major depression. Among patients using lamivudin alone, 30% of them were normal, 70% had minor depression and none of them had major depression. There was no statistical significant difference between patients using IFN or lamivudin in terms of depression score and depression severity. **Conclusion:** Both hepatitis B and C patients experienced depression independent of their treatment regimen.

Anahtar Kelimeler: Hepatitis; depression; interferon-alpha

ÖZET Amaç: Kronik hepatit ve interferon-alfa (IFN-α) tedavisinde nöropsikiyatrik semptomlar çok sayıda bildirilmiştir. Biz IFN-α ve lamivudin kullanmış kendi hastalarımızda depresyon sıklığını ve derecesini araştırdık. **Gereç ve Yöntemler:** Okmeydanı Eğitim ve Araştırma Hastanesi hepatoloji polikliniğinden takipli hepatit B ve C tanılı 180 hasta yapılandırılmış görüşme klavuzu ve Hamilton depresyon skalası kullanılarak değerlendirildi. Hastalar IFN-α ve lamivudin tedavisi altında idiler. **Bulgular:** Hasta popülasyonumuz 111 erkek ve 69 kadın idi (ortalama yaş: 40.9 yıl). Yüz dört hasta hepatit B'li ve 76 hasta Hepatit C'li idi. Ortalama tedavi süresi 44.18 aydı. Ortalama Hamilton depresyon skala skoru 11.69'du. %30.6 hasta normal, %47.7'si minör depresyonlu ve %21.7'si majör depresyonluydu. IFN kullanan %30.6 hasta normal, %46.5 hasa minör ve %22.9 hasta majör depresyon sahibiydi. Sadece lamivudin kullanan hastaların %30'u normal, %70'i minör depresyon sahibi iken majör depresyonu olan yoktu. Depresyon ciddiyeti ve depresyon skorlamasına göre IFN veya lamivudin kullanan hastalar arasında istatistiksel olarak bir fark bulunmamaktaydı. **Sonuç:** Hepatit B ve C hastalarının her ikisinde de yaşanan depresyon tedavi rejimlerinden bağımsızdır.

Key Words: Hepatit; depresyon; interferon-alfa

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Neuropsychiatric symptoms are widely reported in association with both chronic hepatitis and interferon-alpha (IFN-α) treatment. During both acute and chronic stages of hepatitis C, slowness, severe

fatigue, hypersomnia, lethargy, irritability, emotional lability, social withdrawal, and lack of concentration are frequently reported. Among 309 drug users, depressive symptoms were reported in 57.2% of those with hepatitis C, compared to 48.2% in patients without hepatitis C virus, as determined with the Center of Epidemiologic Studies Depression Scale.[1] Malaguarnera et al.[2] found elevated mean scores representing mild depression on the Zung Self-Rating Depression Scale before IFN-α treatment.[2,3] In patients with and without hepatitis C who were awaiting liver transplantation, Singh et al. found significantly more mood disturbance, tension and anxiety, confusion and bewilderment, and pain and higher Beck Depression Inventory scores in patients with hepatitis C, none of whom had been treated with IFN.[4,5] Others have reported depression in 2%-30% of hepatitis C patients.[6-9] In a retrospective review, it has been reported that 24% of 359 untreated hepatitis C patients were depressed and that of those 24%, two-thirds required antidepressant treatment.[10]

IFN-α affects neuroendocrine, cytokine, and neurotransmitter pathways. It has been shown to increase plasma cortisol levels which may be one possible mechanism for induction of depression, since chronically increased hypotalamic-pituitary-adrenal activity is associated with depression.[11,12] IFN-α induces cytokines, such as interleukin-1 (IL-1), IL-2, IL-6, and tumor necrosis factor-alpha (TNF-α) all of which may also contribute to neuropsychiatric symptoms.[13,14] Alterations in the serotonin transporter may also play a role in IFN-α-associated depression since serotonin transporter plays a crucial role in the termination of serotonergic neurotransmission.[15,16] Recently, Morikawa et al. showed that IFN-α alters serotonin transporter mRNA, suggesting a possible mechanism of IFN-α-induced depression.[17]

In the light of the above-mentioned knowledge, this study was designed to assess prospectively the depression level in hepatitis C or B patients under antiviral therapy and to compare these two groups of patients in terms of depression severity.

MATERIAL AND METHODS

The study included 180 patients who were followed up in Okmeydanı Education and Training Hospital, Hepatology Outpatient Clinic between August and December 2006 with a diagnosis of Hepatitic B or C. The patients were interviewed face-to-face. After collection of informed consent, the patients were evaluated using the Structured Interview Guide and Hamilton Depression Rating Scale (HAM-D). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1), which was validated by Corapcioglu et al. for sensitivity and selectivity for Turkish population was a semi-structured interview.[18] The Hamilton Depression Rating Scale was a 17-item scale. The questionnaire rated the severity of symptoms observed in depression such as low mood, imsomnia, agitation, anxiety and weight loss. Each question had between 3-5 possible responses which increase in severity. Scores of 0-7 were accepted as normal, 8-15 minor depression and 16 or high major depression.

The patients were under treatment with lamivudin (100 mg/kg; orally), peg IFN-α-2a (180 pg/week; subcutaneously), ribavirin (1000 mg for patients weighing ≤75 kg, and 1200 mg for patients weighing >75 kg), IFN-α-2a (9 MIU/week; subcutaneously), adefovir (10 mg/day orally), IFN-α-2b (10 MIU/3 days a week; subcutaneously) alone or in combination. Ten patients were using lamivudin alone at a dose of 100 mg/day orally.

The patients were evaluated in terms of body mass index (BMI). Hepatitis B virus DNA and hepatitis C virus RNA expression were evaluated using real time PCR (ABI Prism 7700 Cobas taqMan). The dynamic assay range of the technique was 30-2.109 IU/mL.

The statistical analysis was performed using SPSS Version 13.0 software package. The quantitative data were compared using Student's t test or Mann Whitney U test. Categorical data were analyzed using Chi-square test or Fisher's test. The statistical significance was accepted if $p<0.05$.

RESULTS

In a total of 180 patients, 111 were males and 69 were females. The mean age was 40.95 ± 11.67 years (range: 15-72 years). The mean duration of treatment was 44.18 ± 28.03 months (range: 1-113 months). The mean BMI of the patients was 24.63 ± 3.98 kg/m^2. The mean score of the The Hamilton Depression Rating Scale was 11.69 ± 6.45 (10.25 ± 5.61 of males and 14.00 ± 6.78 of females; p<0.001). The analysis of the depression score of the study population revelated that patients with hepatitis C had significantly higher scores compared to hepatitis B patients (p= 0.005). In the study population 30.6% (n= 55) were normal, 47.7% had minor depression (n= 86), and 21.7% had major depression (n= 39).

Table 1 summarizes the demographic characteristics of the study population.

Table 2 demonstrates the mean depression scores and depression severity of the patients with hepatitis B or C. In our study 104 patients had hepatitis B and 76 had hepatitis C. Among 76 patients with hepatitis C, 21.1% were normal, 51.3% had minor depression and 27.6% had major depression. In a total of 104 patients with hepatitis B, 37.5% were normal, 45.2% had minor depression and 17.3% had major depression. Two patient groups did not differ in terms of depression severity (p= 0.41).

TABLE 1: Patient demographics.

	Patient characteristics
Age (year)	40.95 ± 11.67
Gender (M:F)	111: 69
BMI (kg/m^2)	24.63 ± 3.98
Duration of treatment	44.18 ± 28.03
Depression score	11.69 ± 6.34
Depression severity	
Normal	55 (30.6)
Minor depression	86 (47.7)
Major depression	39 (21.7)

The values are given mean ± SD or n (%).

TABLE 2: Depression scores of the study patients.

	Hepatitis B (n= 104)	Hepatitis C (n= 76)	P value
Depression score	10.57 ± 6.26	13.22 ± 6.16	0.005
Depression severity			0.41
Normal	39 (37.5)	16 (21.1)	
Minor depression	47 (45.2)	39 (51.3)	
Major depression	18 (17.3)	21 (27.6)	

The values are given as mean ± SD or n (%). The depression score and depression severity were analyzed using Student's t test and Chi-square test, respectively.

TABLE 3: Depression scores of the study patients treated with interferon or lamivudin.

	Interferon (n= 170)	Lamivudin (n= 10)	P value
Depression score	11.82 ± 6.41	9.50 ± 4.55	0.421
Depression severity			0.184
Normal	52 (30.6)	3 (30.0)	
Minor depression	79 (46.5)	7 (70.0)	
Major depression	39 (22.9)	0 (0)	

The values are given as mean ± SD or n (%).The depression score and depression severity were analyzed using Mann Whitney U test and Chi-square test, respectively.

Among study population, 170 patients (94.4%) were under IFN therapy and 10 (5.6%) were using lamivudin. As demonstrated in Table 3, 30.6% of the patients using IFN were normal, 46.5% had minor and 22.9% had major depression. On the other hand, of patients using lamivudin alone 30% were normal, 70% had minor depression and none of them had major depression. There was no statistical significant difference between patients using IFN or lamivudin in terms of depression scores (p= 0.421) and depression severity (p= 0.184).

The values are given as mean ± SD or n (%).The depression score and depression severity were analyzed using Mann Whitney U test and Chi-square test, respectively.

DISCUSSION

The results of this study which aimed to evaluate depression status in chronic hepatitis patients un-

der treatment with IFN-α revealed that both hepatitis B and C patients experienced depression independent of their treatment regimen.

Four prospective studies have evaluated mood symptoms in hepatitis C patients treated wit IFN-α. Renaut et al. found that 3 of 58 patients with chronic viral hepatitis developed on "organic affective syndrome" marked by depression, hopelessness, emotional lability, and tearfulness.[19] In a prospective placebo-controlled study comparing the effects of four different types of IFN on the rate of depression in patients with chronic hepatitis C, a sudden increase in the mean scores on the Zung-Self-Rating Depression Scale for all IFN-treated groups was found. These scores increased from mild to moderate depression at 1 month for all groups and returned to baseline by 3 months of treatment. In a prospective study by Otsubo et al. 37.3% of 83 patients were diagnosed as having a major depressive episode, according to DSM-III-R criteria, at least once during a 24-week course of IFN therapy for hepatitis C.[8] The mean score on the Hamilton Depression Rating Scale was also higher compared to baseline. Pariante et al. followed 50 patients with hepatitis B and/or C, and found that 22% developed psychiatric diagnosis during treatment; 5 patients developed major depression, 3 developed depressive disorder, 2 developed severe dysphoria, and 1 developed anxiety disorder.[9]

In our study, we evaluated 180 patients with chronic hepatitis B or C and observed that 45.2% of hepatitis B patients and 51.3% of hepatitis C patients had minor depression according to the Structured Interview Guide and Hamilton Depression Rating Scale. Analysis of the depression scores of the two patient groups demonstrated that hepatitis C patients had significantly higher scores than hepatitis B patients. In our patient population, 94.4% were currently using IFN-α. Among patients using IFN-α, 46.5% had minor and 22.9% had major depression. However, there was no statistical difference between patients using IFN-α or lamivudin in terms of depression score and depression severity. Thus, the reported cases of depression among chronic hepatitis patients vary widely. The rates seem to be higher in studies which used a specific tool to assess depression and in prospective studies. The term "depression" has several meanings, ranging from transient sadness to the syndrome of major depression, thus, patients experiencing fatigue, malaise, or cognitive changes may also complain of being depressed. Suicidal ideation has also been reported, and completed suicide has occurred during the course of IFN-α therapy.[20,21]

In fact, the results of previous studies have shown that a variety of psychiatric disorders are common in patients with untreated chronic hepatitis. In studies using DSM-III-R criteria the prevalence of depressive disorders in patients with hepatitis C was reported to be 22.4%-28%.[22] These prevalence rates are substantially higher than the lifetime prevalence rates for the same disorders in the general population. Although the association between hepatitis C infection and psychiatric disorders has not been fully elucidated, it is possible that patients with psychiatric disorders are at increased risk for hepatitis C because they engage in high-risk behaviors more often than the general population. This notion is in accordance with the findings of a study which demonstrated that over 95% of the patients were diagnosed with psychiatric disorders long before hepatitis C infection was discovered.[23] Another explanation may be that hepatitis C infection remains asymptomatic for many years; thus, the patients may have undiagnosed hepatitis infection prior to the development of any psychiatric disorder. The specific impact of chronic hepatitis on central nervous system or psychological state prior to development of hepatic dysfunction needs to be clarified.

Another important finding of our study was that the percentage of female patients experiencing depression was higher than that of males. Although the depression scores of two genders did not differ significantly, the percentage of female patients without having depression was 21.7% whereas it was 36.0% in males. This finding is in accordance with previous observations showing that IFN-induced depression occurs more frequently in women than men, as assessed by Zung's self-rating depression scale.[24]

As a conclusion, the results of the present study indicate that approximately 70% of patients with chronic hepatitis experience depression independent of the type of treatment. Thus, this patient population should be monitored with caution during the follow-up since such psychiatric disorders negatively affect the patients' overall functioning and quality of life.

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