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Assessment of Fatigue and Psychologic Disturbances in Patients with Hepatitis C Virus Infection

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Abstract

Background: It is a common clinical impression that fatigue is a frequent, and often debilitating, symptom in patients with chronic hepatitis C virus (HCV) infection. However, despite its obvious clinical importance, several aspects of fatigue, including its relationship with the underlying liver disease and the presence of psychologic disturbances, have not been well examined. **Goals:** The current study was carried out to assess these issues. **Study:** A total of 149 subjects were included in the study and were assigned to one of the following study groups: healthy controls (31), chronic HCV infection (24), combined HCV infection and chronic alcohol abuse (32), alcoholic liver disease (22), and chronic non-liver diseases (40). All subjects were administered investigator-assisted questionnaires designed to analyze the presence and severity of fatigue and psychologic abnormalities. **Results:** The mean (±SD) fatigue scores in patients with chronic HCV infection (140 ± 22.9; $p = 0.002$), alcoholic liver disease (127 ± 31.4; $p < 0.001$), mixed (HCV/alcoholic) liver disease (131 ± 29.0; $p < 0.001$), and chronic non-liver diseases (128 ± 35.9; $p = 0.004$) were significantly greater compared to with healthy subjects (101 ± 31.8). The total fatigue scores were higher in HCV-infected subjects compared with the other patient groups, but the differences failed to reach statistical significance. Moreover, the fatigue experienced by patients with HCV did not improve with rest as effectively as in the other study groups. All patient groups had higher scores for psychologic disturbances compared with healthy subjects. **Conclusions:** The current study shows that fatigue and psychologic disturbances occur frequently in chronic diseases. The fatigue experienced by patients with HCV infection is more severe and intransigent and responds poorly to relieving factors. Moreover, patients with HCV infection are more depressed and harbor greater feelings of anger and hostility compared with those with non-liver chronic diseases. These observations are important because proper management of the psychologic symptoms may have a favorable impact on the quality of life of patients with HCV infection.

Key Words: Hepatitis C—Alcoholic liver disease—Fatigue.

Hepatitis C virus (HCV) infection is one of the major causes of liver disease in the United States and around the world. A population-based serologic study suggested that 1.8% of the general population in the United States has antibodies to HCV.[1] Acute infection with HCV is generally a mild illness compared with other viral causes of hepatitis; however, unlike other viral hepatititides, the infection usually fails to resolve spontaneously and the majority of individuals (approximately 80%) become chronically infected.[2] Liver disease in subjects with chronic infection is of variable severity. It usually runs a protracted and often an insignificant course for prolonged periods, but about 20% of individuals experience a progressive illness with the development of cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[2,3] In addition, HCV infection is associated with a variety of extrahepatic syndromes, including essential mixed cryoglobulinemia and membranoproliferative glomerulonephritis.[4–6] With nearly 4 million Americans and 100 million individuals worldwide currently infected, HCV infection is likely to become an even greater global public health and economic problem in the future.

Patients with chronic HCV infection typically have few symptoms, and most of these are mild and nonspecific. The most frequent symptom is fatigue, which is commonly described by the patient as malaise, lethargy, or poor energy level. In some patients, fatigue becomes all-pervasive and has an important impact on the quality of life. Despite its obvious clinical importance, several aspects of fatigue in hepatitis C remain controversial. Although some studies have shown that patients with hepatitis C have higher fatigue scores and reduced health-related quality of life compared with healthy controls,[7–10] other studies did not find many differences between patients with hepatitis C and other subjects, including healthy blood donors who served as controls.[2,3] Treatment with interferon either has been shown to have no effect on the health status measures[11] or has resulted in significant improvement in the health-related quality of life.[10,12,13] Moreover, the influence of psychologic disturbances on the fatigue experienced by patients with HCV has not been clearly examined. Thus, it is a real clinical challenge to not only characterize the presence and intensity of fatigue but also determine the association of fatigue with the comorbidities that are present in most chronic illnesses, such as the fear and anxiety of illness, tensions about transmitting infection to others and the possibility of future complications, and death.

The objectives of our study were 2-fold. One, we wanted to determine whether the fatigue experienced by patients infected with hepatitis C is truly more severe than that in patients with liver diseases not related to HCV infection and non-hepatic chronic systemic illnesses. Second, we wanted

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to assess the association of fatigue with psychologic disturbances, which occur frequently in this group of patients, given their past or current history of alcohol and substance abuse.

MATERIALS AND METHODS

Diagnostic Instruments

The study was conducted on a predominantly male population of 149 patients at the Houston Veterans Administration Medical Center (Houston, TX, U.S.A.). The patients were administered interviewer-assisted questionnaires: one to quantify and characterize fatigue and another to assess the impact of fatigue on the quality of life. The 29-item Fatigue Assessment Instrument provided a global severity scale, as well as information regarding the triggers and pacifiers of fatigue.[14] The Fatigue Assessment Instrument measured the current symptom profile of each subject; the sensitivity and specificity of this survey is more than 80% in assessing clinically relevant fatigue.[14] The 65-item Sickness Impact Profile assessed the impact of fatigue on a subject's daily functioning, with particular emphasis on psychologic parameters such as anxiety and depression. During the administration of the questionnaires, medically trained interviewers were blinded with regard to the patient's diagnosis. Detailed clinical evaluations and laboratory studies were performed on all patients to allow comparison of hepatic dysfunction with symptom severity.

Study Subjects

Five groups of subjects were included in the study. The chronic hepatitis C group consisted of 24 patients, all of whom had anti-HCV antibodies detected by the second generation recombinant immunoblot assay test (RIBA-II). All of these subjects completely abstained from alcohol use and had serum transaminase levels elevated above the upper limit of normal. The alcoholic liver disease group consisted of 22 patients who had a history of chronic alcohol abuse, defined as consumption of six drinks a day or more (≥80 g of ethanol/d) for more than 5 years, and in whom serum antibodies to HCV were negative by the RIBA-II test. Patients with dual liver disease consisted of 32 patients with a history of chronic alcohol use (≥80 g of ethanol/d for more than 5 years), detectable serum antibodies to HCV by the RIBA-II test, and elevated serum transaminase levels. All of the patients in the HCV-infected group, alcoholic liver disease group, and dual liver diseases group were negative for other causes of chronic liver disease and for the presence of serum hepatitis B virus surface antigen. None of the HCV-infected patients were receiving interferon therapy at the time of assessment.

Two control groups were included in the study. One group consisted of 40 patients with at least one chronic systemic illness (such as diabetes mellitus, hypertension, coronary artery disease). All such "non-liver controls" had normal liver tests. The second control group consisted of 31 healthy veterans who were selected during a routine health screening fair and served as normal controls.

Statistical Analysis

Descriptive statistical analyses were prepared from the study sample; the results are presented as mean ± SD. Nonpaired Student *t* test, and one-way or two-way analysis of variance were used to compare quantitative data grouped by one or more factors, with a 95% CI for the difference of the means. All analyses were performed with SigmaStat (SPSS Inc.) statistical software.

RESULTS

The mean (±SD) age of all of the patient populations included in the study was 51.9 ± 11.6 years. Healthy subjects were age-matched with HCV-infected patients and with those with dual HCV and alcoholic liver disease. The mean age of patients with non-liver systemic diseases was higher compared with the other study groups: healthy subjects (46 ± 12.8 years; $p < 0.001$), HCV-infected group (51.3 ± 10.7 years; $p = 0.07$), and patients with dual liver disease (45.8 ± 4.9 years; $p = 0.03$). There were no significant differences in the gender or racial compositions of the study groups.

Laboratory Tests

The results of laboratory tests in the four patient groups are shown in Table 1. There was no difference in the serum hemoglobin values in the different study groups. However,

TABLE 1. *Results of blood tests in the different study groups§*

	Non-liver controls (n = 40)	HCV alone (n = 24)	HCV + alcohol (n = 32)	Alcohol alone (n = 22)
Hemoglobin (g/dL)	14.4 (1.9)	14.6 (1.4)	14.6 (1.5)	13.1 (2.1)
WBC (mm^3)	7.5 (2.2)	6.1 (2.0)‡	5.7 (2.1)‡	7.0 (2.7)
Platelets (mm^3)	235.5 (76.2)	184.5 (69.8)‡	182.2 (81.6)‡	199.7 (118.3)
Bilirubin (mg/dL)	0.7 (0.4)	0.8 (0.5)	1.1 (0.7)	1.3 (1.1)*
Albumin (g/dL)	4.1 (0.6)	3.9 (0.6)‡	3.8 (0.6)‡	3.5 (0.7)*
ALT (U/L)	30.2 (19.0)	83.8 (50.6)†	84.8 (59.5)†	35.3 (16.5)
AST (U/L)	29.6 (14.3)	77.3 (46.5)*	85.9 (53.3)*	58.7 (46.7)*
ALP (U/L)	76.8 (19.0)	95.6 (48.9)	114.6 (123.0)	125.8 (53.6)*
PT (s)	12.7 (1.9)	12.6 (1.5)	12.4 (1.2)	13.2 (1.4)

*$p < 0.001$ compared with non-liver control population.
†$p < 0.001$ compared with alcoholic liver disease (alone) population.
‡$p < 0.05$ compared with non-liver control population.
§Values depict mean (SD).
ALP indicates alkaline phosphatase; PT, prothrombin time; ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cell.

compared with the non-liver control group, patients with HCV infection had significantly lower total white cell and platelet counts whether or not they had history of alcohol abuse. No such abnormalities were seen in patients with alcoholic liver disease.

As expected, liver tests showed greater derangement in all of the three patient groups with liver disease compared with non-liver controls. Serum aminotransferase (alanine transaminase and aspartate transaminase) values were significantly higher in chronic HCV infection with or without chronic alcohol abuse compared with non-liver controls. In patients with alcoholic liver disease, serum aspartate transaminase values were higher than alanine transaminase levels, and these were significantly greater than non-liver controls. Similarly, serum albumin was significantly lower in all patient groups with liver disease compared with non-liver controls. However, the prothrombin time showed no significant difference between patients with liver disease and the non-liver controls.

Fatigue Assessment Instrument

The results of the 29-item Fatigue Assessment Instrument are shown in Table 2. The total fatigue scores were significantly higher in all patient groups compared with healthy subjects ($p < 0.005$). However, there was no significant difference in the total fatigue scores between patients with different liver diseases (chronic HCV infection, dual HCV and alcoholic liver disease, and alcoholic liver disease alone) and subjects with non-liver systemic disorders. Similarly, there were no significant differences in the total fatigue scores among the various liver diseases.

Analysis of different aspects of fatigue provided interesting results. The impact of fatigue on the individual in the form of interference with physical activity or mental concentration was significantly greater in patients with HCV infection compared with the other study groups; the difference reached statistical significance when compared with patients with non-liver disorders and healthy individuals ($p < 0.05$). Moreover, the physical and mental effects of fatigue, such as worsening lethargy and reduction in motivation, were also increased in HCV-infected individuals; the difference was statistically significant when compared with healthy subjects ($p < 0.005$), but not with the other study groups. Relief from fatigue (after rest and sleep) was less effective in the HCV-infected patients; the difference was statistically significant when compared with healthy subjects and the non-liver control group, but not with other liver diseases.

Sickness Impact Profile

The results of the 65-item Sickness Impact Profile are shown in Table 3. All parameters of the Sickness Impact Profile were worse in the four patient groups compared with healthy subjects. In general, patients with liver disease showed greater abnormalities compared with the patients with non-liver systemic disorders. The most significant difference was observed with respect to depression, in which the scores were significantly greater in patients with chronic HCV infection (19.5 ± 12.0; $p = 0.004$), dual liver disease (20.9 ± 13.1; $p < 0.001$), and alcoholic liver disease (19.2 ± 16.1; $p = 0.017$) than in the non-liver controls (10.8 ± 11.0). However, there was no significant difference in the depression scores among the three chronic liver disease groups.

Feelings of anger and hostility were significantly greater in patients with chronic HCV infection, whether they were completely abstinent (17.0 ± 10.0; $p = 0.007$) or indulging in heavy alcohol use (17.1 ± 9.8; $p < 0.001$), compared with patients with non-liver chronic systemic illnesses (10.0 ± 9.5). Patients with alcoholic liver disease had scores for anger and hostility that were similar to non-liver controls, which were lower than scores in patients with HCV infection, but the difference failed to reach statistical significance. Poor energy level and fatigue were higher in HCV-infected subjects compared with the other liver disease groups; this difference was statistically significant compared with patients with non-liver systemic diseases ($p < 0.01$). Thus, the total of the negative Sickness Impact Profile parameters (depression, tension, anger, and fatigue) were significantly greater in the HCV-infected groups (both abstinent and current alcohol users) than in the other study groups. By contrast, positive parameters, such as vigor and vitality, were significantly reduced in all patient groups compared with healthy subjects, but there was no difference between the patients groups.

TABLE 2. *Fatigue Assessment Instrument scores in different study groups‡*

Parameter	Healthy subjects ($n = 31$)	Non-liver ($n = 40$)	HCV alone (N 24)	HCV + alcohol ($n = 32$)	Alcohol alone ($n = 22$)
Impact	29.2 (17.7)	46.6 (23.8)*	59.9 (12.7)†	51.5 (18.5)*	51.9 (19.8)*
Effect	16.5 (6.5)	20.0 (6.2)	22.5 (4.6)*	20.2 (5.0)	20.2 (5.2)
Relief	24.0 (4.0)	21.9 (4.6)*	18.9 (5.7)†	20.0 (5.5)*	19.5 (6.4)*
Trigger	31.6 (11.2)	39.9 (10.9)	39.1 (9.4)	39.5 (8.8)*	35.7 (9.8)
Total fatigue	101.3 (31.8)	127.5 (35.9)*	140.4 (22.9)*	131.2 (29.0)*	127.3 (31.4)*

*$p < 0.005$ compared with healthy control population
†$p < 0.05$ compared with non-liver control population.
‡The values depict mean (SD).

TABLE 3. *Results of the Sickness Impact Profile scores in the different study groups§*

Parameters	Healthy subjects (n = 31)	Patient groups: Non-liver (n = 40)	HCV alone (n = 24)	HCV + alcohol (n = 32)	Alcohol alone (n = 22)
Negative parameters					
Depression	6.7 (7.0)	10.8 (11.0)†	19.5 (12.0)‡	20.9 (13.1)‡	19.2 (16.1)*‡
Tension	6.2 (7.0)	9.4 (7.8)†	12.5 (7.4)*	11.6 (6.8)*	11.0 (8.3)†
Anger	6.7 (6.8)	10.0 (9.5)†	17.0 (10.0)*‡	17.1 (9.8)*‡	12.6 (9.4)*
Fatigue	5.6 (5.2)	10.9 (7.7)*	16.2 (5.8)*‡	13.5 (6.7)*	12.9 (7.2)*
Total -ve scores	25.2 (21.7)	41.1 (31.3)†	65.2 (30.9)*‡	63.1 (31.1)*‡	55.7 (38.4)*
Positive parameters					
Vigor	23.6 (4.9)	18.5 (35.9)*	15.8 (5.3)*	16.7 (6.1)*	19.1 (6.7)*

*$p < 0.01$ compared with healthy control population.
†$p < 0.05$ compared with healthy control population.
‡$p < 0.01$ compared with non-liver control population.
§Results are expressed as mean (SD).

DISCUSSION

Assessment of fatigue and its impact on the quality of life in HCV infection has produced conflicting results. In a study on asymptomatic blood donors, HCV-infected individuals had a benign infection and most did not suffer any serious consequences as a result of this illness.[15] In another study, conducted at the National Institutes of Health, 108 patients with HCV-related liver disease were given a self-administered questionnaire to assess the degree of disease-related symptoms.[3] The results were compared with a similarly tested control group of 100 healthy blood donors without antibody to HCV. There was no difference between the two groups with regard to the symptoms of hepatitis, and a similar proportion of healthy subjects and patients with HCV reported fatigue (70% and 62%, respectively). However, using specifically designed and validated instruments, several workers have found significantly greater disability in the quality of life in patients with chronic HCV compared with uninfected individuals.[7–10,12,13]

An important aspect of assessing the impact of chronic HCV infection is determining whether the reduction in the patient's quality of life is caused by the HCV or the comorbidities associated with the illness. For example, patients with HCV frequently have history of alcohol and drug abuse and may be coinfected with hepatitis B virus. In one study, the investigators adjusted for some of these comorbidities,[8] whereas another study excluded patients with a history of drug abuse from analysis.[9] The results showed that despite exclusion of such confounding factors, patients with HCV infection had a greater reduction in their quality of life scores.

Another potential source of conflict is the issue of whether the reduction in the quality of life is related to liver disease or to HCV infection. To assess this issue, some studies excluded patients with cirrhosis and still found a reduction in the quality of life scores.[9,10] The direct effect of HCV infection can be tested by assessing patients before and after antiviral therapy. Recent studies have shown that successful elimination of the virus is accompanied with improvement in quality of life scores; the extent of improvement was directly related to sustained virologic and biochemical responses to treatment.[10,13] Conversely, nonresponders showed either a less-pronounced benefit[10] or had a significant decline in quality of life.[13]

In the current study, we went a step further. We compared fatigue scores in patients with HCV infection, alcoholic liver disease, and dual alcohol and HCV infection, which allowed us to determine the impact of different liver diseases that were clinically and biochemically well-compensated. We also included two control groups: patients with non-liver chronic systemic disorders (such as diabetes mellitus and coronary artery disease) and healthy veterans. The healthy controls were age-matched with patients with liver disease but were otherwise selected at random. Assessment of this group permitted us to compare patients with liver disease with a healthy population of veterans who had a similar service background and who had been exposed to similar combat experiences.

Patients with HCV infection had greater total fatigue scores than all the other study groups, although the differences reached statistical significance only against the healthy control subjects. Fatigue scores were higher in HCV infection than in alcoholic liver disease and in patients with dual alcohol and HCV infection. Subgroup analysis showed that all aspects of fatigue, such as the impact and consequence of fatigue on the individuals' general health, the response to relieving factors (such as rest and sleep), and the effect of triggering influences (such as stress and work), were worse in patients with HCV than in the other patient groups. These findings indicate that HCV infection is associated with greater fatigue despite a similar severity in the underlying liver disease. Patients with non-liver systemic

disorders also had significantly higher fatigue scores than healthy subjects, but in general these were lower than those seen in the three liver disease groups.

The pathogenesis of fatigue is unclear, and several factors have been incriminated. Excessive production of cytokines such as interferon, interleukin-1β, and tumor necrosis factor-α may be involved in the development of chronic fatigue syndromes.[16–18] Some studies have noted elevated cytokine levels in patients with chronic liver disease,[19] whereas others have found no causal link between cytokines and fatigue.[20–22] The most common risk factor for HCV infection worldwide is injected drug use; in this population, the seropositivity rate of HCV is nearly 80% in the United States.[23,24] Patients with chronic alcoholism also have a high prevalence of HCV infection, with rates varying from 15% to over 50%.[25–29] It has been suggested that the reduction in quality of life scores found in HCV infection may be attributable to factors such as psychiatric disturbances associated with previous or current substance abuse.[30] To examine this issue, we used the Sickness Impact Profile, an instrument that assesses both negative psychologic attributes, such as depression, tension, anxiety, and anger, as well as positive ones, such as vigor. All of the patient groups had higher total negative scores and lower scores for vigor than the healthy subjects. In general, most of the individual components of the Sickness Impact Profile showed greater derangement in liver disease compared with non-liver systemic disorders, with HCV-infected patients showing the highest negative scores compared with all other study subjects (Table 3). These observations suggest that psychologic abnormalities may have a direct role in the pathogenesis of fatigue in HCV infection.

In summary, the current study has shown that compared with healthy individuals, both fatigue and psychologic disturbances are more severe in patients with chronic illnesses and that the most severe abnormalities occur in HCV infection. We believe the lack of statistical significance in some of the observations is related to the relatively small number of individuals included in the different groups, a defect that can be remedied by performing large, multicenter studies. Our results show that the fatigue experienced by HCV-infected patients is not only more severe but also is more intransigent, responding less well to relieving factors such as rest and sleep. Moreover, patients with HCV infection appear more depressed and exhibit greater feelings of anger and hostility. Our findings have important therapeutic implications because effective treatment of the psychologic disturbances may improve patients' fatigue and, thus, may have a beneficial impact on the quality of life of patients with HCV.

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