

Hepatitis C and Poor Quality of Life: Is it the Virus or the Patient?

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ABSTRACT

Hepatitis C is a systemic disease that has many extrahepatic manifestations in addition to hepatic inflammation and fibrosis, some of which may result in a poor health-related quality of life (HRQOL). Fatigue is perhaps the most frequent and disabling extrahepatic symptom of hepatitis C virus (HCV), reported in almost one-half of all chronically infected individuals. Many other factors are associated with a poor quality of life in patients with HCV, including a number of physical and psychological factors. The objective of this article is to review the association between HCV and impaired HRQOL due to fatigue and psychological disturbances.

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Hepatitis C virus (HCV) is the major cause of end-stage liver disease in many countries of the world with more than 170 million people found to be infected.^[1]

Typically, HCV is a silent infection with symptoms and signs appearing only in those with severe and advanced disease. However, there is now a growing awareness that hepatitis C is a systemic disease that has many extrahepatic manifestations in addition to liver inflammation and fibrosis.^[2] Some of these extrahepatic manifestations result in a poor health-related quality of life (HRQOL). These symptoms include fatigue, anorexia, myalgia, arthralgia, irritability, and headaches. Fatigue is perhaps the most frequent and disabling extrahepatic symptom of HCV, reported in almost one-half of all infected individuals.^[2] Although vastly variable in intensity and expression, its presence often compromises the patient's quality of life. In addition to fatigue, many other factors are associated with a poor quality of life in patients with HCV, including a number of physical and psychological factors. The objective of this article is to review the association between HCV and impaired quality of life due to fatigue and psychological disturbances.

HCV AND POOR QUALITY OF LIFE

The effect of HCV on the quality of life in chronically infected patients has been the subject of many studies, some of which were summarized recently in a review.^[3] Chronic HCV appears to directly compromise HRQOL. One of the largest studies conducted to date reported the results

of interferon-based antiviral therapy in 642 HCV-infected patients, before and after treatment.^[4] At presentation, there was a significant reduction in HRQOL in patients with HCV as compared to well-norms in the presence or absence of cirrhosis. In another study by the International Hepatitis Interventional therapy group, Ware *et al.* reported that five out of eight short-form 36 questionnaire (SF-36) (a special questionnaire designed to evaluate HRQOL) concepts: physical functioning, role-physical, general health, vitality, and social functioning, were significantly reduced in patients with HCV compared with matched population norms.^[5] In another study from Britain, 72 unselected, sequential patients with chronic HCV were compared with 30 sequential patients with chronic hepatitis B (HBV) infection and HBsAg positivity.^[6] Patients with evidence of cirrhosis were excluded. All of the SF-36 scores were markedly reduced in patients with chronic HCV infection, indicating that these patients perceived themselves to be unwell and reported significant reduction in their quality of life. In contrast, chronic HBV patients exhibited no significant reductions in their SF-36 scores, except in the variables of "mental health" and "general health perception," and only minimal effects on the SF-36 scores that assess an individual's capacity for physical activities. When the two groups (HCV and HBV) were compared directly, HCV patients showed greater impairment in social functioning, physical limitations, energy, and fatigue parameters compared to HBV patients.

On the other hand, other studies in different populations of patients showed different results. A Japanese group applied

the Todai Health Index (a checklist for a self-administered scoring system covering a variety of physical and psychological symptoms) to examine the potential symptoms in 60 patients with chronic HCV in comparison with normal controls.^[7] They found no characteristic subjective symptoms in patients with HCV compared to healthy controls, except for a lower aggression score. In another Japanese study, Fukuhara *et al.* used the SF-36 questionnaire to test a group of Japanese patients with HCV. No significant differences between patients and controls were found.^[8] In addition, two studies from North America also showed no difference in HRQOL. The first study by Davis *et al.* used the sickness impact profile.^[9] This study was criticized because of the low sensitivity of this instrument to detect clinically relevant changes. In the second study, American blood donors who were found by chance to have HCV (who seemed to have a high incidence of fatigue [61%] and headache [54%] in a previous study),^[10] were re-examined in comparison to normal healthy blood donors without HCV. The fatigue rate in the non-HCV group was as high as 70%, suggesting no difference between the two groups.^[3] The importance of this study is paramount in that it studied a random sample from a random population in which symptoms and HCV status were assessed entirely independently, unlike most other studies which involved patients referred to tertiary care centers.^[11]

HEPATITIS C AND FATIGUE

Many uncontrolled studies suggest that a significant proportion of HCV patients suffer from fatigue. For example, Tong *et al.* found that 67% of patients with posttransfusion HCV reported fatigue^[12] while Kenny-Walsh *et al.* reported fatigue in at least 81% of Irish women with HCV due to HCV-contaminated anti-D immune globulin.^[13] Similarly, Barkhuizen *et al.* reported that in hepatology outpatients, fatigue was found in a significant (67%) proportion of HCV-positive patients compared to 44% of HCV-negative patients.^[14] In one of the largest studies of its kind, Poynard *et al.* reported that among 1614 patients with HCV from France, 53% reported fatigue at their initial visit and the fatigue was severe in 17% of these patients.^[15] This study also found that fatigue was associated independently with the female gender; age > 50 years, cirrhosis, depression, and purpura. Nevertheless, it is essential to note that there are hardly any studies investigating fatigue in HCV patients in comparison to a control group.

HEPATITIS C AND PSYCHIATRIC DISORDERS

Many studies have reported a high incidence of depression in chronic HCV-infected patients. For example, Dwight *et al.* report that 28% of their HCV patients fulfil the criteria for major depression.^[16] In an effort to determine the incidence of psychiatric co-morbidities among veterans in the US with HCV, Lehman *et al.* used well-established scoring criteria in

various questionnaires to study 120 consecutive patients with chronic HCV.^[17] Almost half of the patients had a history of nonsubstance abuse-related psychiatric disorders and about a third of the patients were receiving psychotropic medications at the time of the evaluation. Depression was found in 44%, anxiety in 38%, post-traumatic stress disorder in 20%, and alcohol-related problems in 26% of patients with HCV. However, this study may have overestimated the true prevalence of psychiatric disorders in the HCV population as it was performed in veterans who typically have a high level of alcohol consumption. Similar results of clinically significant emotional distress in 35% of HCV patients were reported by Fontana *et al.* in 220 unselected patients with compensated chronic HCV.^[18] It is worth noting that in most of the above studies, there was no control group for comparison. On the other hand, in a large, controlled Italian study, a higher prevalence of lifetime major depression was observed among HCV patients than in HBV patients and controls.^[19]

IS THE VIRUS THE CULPRIT?

From the above discussion, it seems reasonable to conclude that patients with HCV have a decreased HRQOL that is associated with fatigue and many psychiatric co-morbidities. However, the question that remains unanswered is whether this poor quality of life is directly related to the virus and its interaction with the body or alternatively, related to the patient in terms of co-morbidities, reaction to the illness, reporting of symptoms, and other multiple factors? In the remainder of this review, the most important issues related to the interaction between viral, medical, social, and ethnic factors in relation to HRQOL in HCV-infected patients, will be summarized as follows:

Fatigue is common

Fatigue is a common phenomenon within the general population. For instance, in a study by Shakil *et al.*, fatigue was found in about 61% of American blood donors who were found to have HCV.^[10] However, when the same investigators studied the healthy blood donors without HCV, they found that the incidence of fatigue was 70% in this group.^[2] In another study dealing with a different infectious disease, Fukuda *et al.* found that >40% of people who had experienced an acute infection with Q fever fulfilled the criteria for chronic fatigue syndrome.^[20] Of note, as mentioned before, many studies reporting decreased HRQOL in HCV patients did not include a control group. This makes it extremely difficult to isolate the effect of the virus on the development of fatigue in the background of these high rates of fatigue in the general population.

HCV is associated with other psychiatric disorders

As discussed above, HCV has been shown to be associated with many psychiatric disorders that may, by themselves, contribute to the reduced HRQOL. These include depression, anxiety, post-traumatic stress disorder, and alcohol-related

problems.^[16] These psychiatric symptoms have been shown to be associated with fatigue, functional disability, and somatization in HCV patients.

The effect of knowledge of the diagnosis

The patient's awareness that he/she has a disease with potentially serious consequences can in itself lead to alterations in the quality of life. It is important to distinguish between psychological reactions to the knowledge that one has been infected with HCV and the direct effects of the virus itself. Previous studies have aimed to define the role that awareness of the diagnosis can play in altering the quality of life. In a study from Australia by Rogers, patients who were previously admitted to hospitals with acute hepatitis between 1971 and 1975 were traced and their stored serum was tested for hepatitis C markers.^[21] Available patients (some aware and some unaware of their diagnosis) were interviewed and given the SF-36 questionnaire. Interestingly, individuals who were aware of their diagnosis ($n = 15$) rated significantly worse on seven of the eight standard SF-36 scales compared to the normal Australian population. On the other hand, individuals who were unaware of their serostatus ($n = 19$) scored significantly worse on only three scales. There were no other epidemiological, physical, or biochemical differences between the two groups. Similarly, 1286 rural Egyptian patients who were unaware of their hepatitis C status were prospectively interviewed by blinded investigators using the SF-12 QOL questionnaire. It was found that the 146 individuals who turned out to be infected, scored similar results compared to the 1140 individuals who were negative.^[22]

Two interesting studies looked at patients presenting with chronic fatigue syndrome and assessed their HCV status retrospectively to avoid the psychological effects of knowing about the HCV infection.^[23,24] Neither study reported any association between the quality of life and the HCV status. On the other hand, patients with HCV were found to have a more significant reduction in their quality of life than did patients with chronic hepatitis B in a study by Foster *et al.* This suggested that prior knowledge of the diagnosis of the viral infection was not important.^[3]

This effect of knowledge of the diagnosis on the HRQOL has been reported with many other chronic diseases. For example, normotensive subjects who had been misdiagnosed with hypertension were substantially more likely (30 vs 8%) to have symptoms of depression compared to matched, unlabeled normotensive controls.^[25]

The relation to the viral load

In the previously mentioned study on Irish women,^[13] although fatigue was significantly increased in patients with HCV compared to controls, there was no difference between those who were HCV RNA-positive and those who were HCV RNA-negative, i.e., whether they were viremic

or not. Moreover, in another study in hemophiliac patients, there was again no difference in the mean levels of fatigue in patients who were free of the virus (antibody-positive, but HCV RNA-negative) and those who were HCV RNA-positive.^[26] If there was a true pathophysiological effect of the virus resulting in poor HRQOL, one would assume that this effect would only be present in viremic patients; but the evidence suggests otherwise.

The effect of liver disease

HCV is a major cause of chronic liver disease and most chronic liver diseases have been consistently reported to cause fatigue. In a study by Obhrai *et al.*, special questionnaires were used to assess fatigue and psychological disturbances in patients with various forms of chronic liver diseases, including HCV.^[27] They found that total fatigue scores were significantly higher in all patient groups than in healthy subjects, although there were no significant differences in the total fatigue scores of patients with different liver diseases (chronic HCV, alcoholic liver disease, and dual HCV infection and alcohol). Interestingly, 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 compared to other groups. This suggests that there was no increase in the actual fatigue scores in patients infected with HCV compared to other diseases, but that there may be a maladaptation with this symptom in HCV patients. In another study in which 239 patients with various causes of liver disease (including HCV) were examined in an outpatient setting, 70% had some form of musculoskeletal pain, and 54% had fatigue.^[14] In this study, there was a significant association between HCV and pain, and between HCV and fatigue, but the overall prevalence of pain and fatigue in the study population was also high.

Effect of intravenous drug use

Intravenous drug use (IVDU) which is common in patients with HCV (especially in the west) is certainly an important factor that can contribute to poor HRQOL. Two studies have suggested that although IVDU is associated with a more marked reduction in the quality of life in HCV-infected patients, even patients without a prior history of IVDU have a reduced quality of life. Johnson *et al.* reported depression in drug users with or without HCV infection, and found a statistically insignificant trend toward increased depression in the HCV-positive patients.^[28] These results were substantiated by Foster *et al.*^[6] To investigate the effect of nonviral factors on the reduction in the quality of life, the investigators studied the effect of IVDU. When patients with no past history of IVDU were examined, they were found to have a small improvement in the overall quality-of-life scores compared to those with a prior history of IVDU. However, when compared with normal controls, patients with no history of IVDU had a significant reduction in the quality of life, suggesting that although the history of IVDU is associated with an inferior quality-of-life score, HCV

patients without this background still had a compromised quality of life. In this study, there was no correlation between the quality-of-life scores and liver disease severity parameters such as liver enzymes or stage of disease as seen in liver histology.

Other factors

Finally, if perception of the disease is indeed an important factor in reporting fatigue and other symptoms in patients with HCV, then many known and unknown factors will probably affect the response of the patients and their reporting of these symptoms. Such factors may include ethnic background, income, employment, education, etc. This may explain the differences seen between the rates of compromise in the quality of life seen in studies done in North America (reporting high incidence) and studies done in Japan (where two studies showed no significant reduction in the quality of life).^[7,8] It may also partially explain the differences in the quality of life noticed between HCV- and HBV-infected patients. Although various factors may be responsible for such a disparity in study outcomes, the impact of ethnicity needs to be studied further before any further conclusions can be reached.^[29]

EFFECT OF ANTIVIRAL TREATMENT ON QUALITY OF LIFE

Many studies have reported a reduction in fatigue after eradication of HCV.^[4,5,30] In a large study by Cacoub *et al.* conducted on 431 patients, fatigue decreased in 35% of responders to antiviral therapy *vs* 22% in patients who had detectable HCV at the end of treatment—a difference that was statistically significant.^[31] In another study, all patients who had fatigue prior to therapy were reported to have complete disappearance of this symptom after eradication of the virus.^[32] On the other hand, other studies showed no improvement in the quality of life after treatment.^[9] Although a positive effect of treatment on fatigue does suggest that the virus itself may have a role in the pathogenesis of fatigue in these patients, this again does not rule out the effect of psychological factors in decreasing the fatigue. It is noteworthy that in only one study^[4] were the patients blinded to the results of the HCV RNA status, a fact that can clearly introduce bias in the interpretation of such studies.

CONCLUSION

It is evident that patients with chronic HCV have a compromised quality of life, a higher prevalence of fatigue, and psychiatric disorders. These effects do not seem to be related to the severity of liver inflammation or fibrosis. What remains unclear is the exact role of the HCV virus in impairing the quality of life. It is likely that other related and seemingly unrelated factors such as psychological status and ethnic background, may also play a role in the subjective

reporting of quality-of-life parameters.

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