Original Article

Comparison of the Prevalence of Psychiatric Co-Morbidities in Hepatitis C Patients and Hepatitis B Patients in Saudi Arabia

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ABSTRACT

Background/Aim: Hepatitis C is a major health concern world-wide and is frequently associated with psychiatric co-morbidity. The most common genotype in Saudi Arabia differs from genotypes prevalent elsewhere and thus we aimed to determine if psychiatric disturbances occur in Saudi patients infected with hepatitis C and whether these symptoms extend to those infected with hepatitis B. **Materials and Methods:** Data were collected from hepatitis C and hepatitis B patients using the general health questionnaire (GHQ-28) and The Short Form Health Survey (SF-36) questionnaires. Tinnitus patients served as control subjects. The Chi-square test was used to examine the relationship between categorical variables. Continuous variables were compared using the Student's *t*-test or the Wilcoxon-Mann-Whitney test for skewed data, and correlations were evaluated by calculating Spearman's rho. The odds ratio was used to determine the association between variables and the likelihood of being a psychiatric case. **Results:** Hepatitis C patients were twice as likely to be labeled as a psychiatric case compared with hepatitis B patients ($P = 0.01$). Age and gender were not predictive factors though there was a non-significant tendency toward a higher prevalence of psychiatric cases among females. Hepatitis C patients also scored lower than hepatitis B patients in 3 domains of the SF-36 questionnaire, indicating a greater reduction in quality of life (QoL). **Conclusion:** We demonstrate an increased incidence of psychiatric symptoms in Saudi Arabian hepatitis C patients compared to hepatitis B patients and controls. This highlights the importance of collaboration between hepatologists and psychiatrists in order to improve the QoL in this patient group.

Key Words: Depression, general health questionnaire, hepatitis B, hepatitis C, psychiatric, Saudi Arabia, SF-36

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The World Health Organization currently estimates that 3% of the world's population is infected with the hepatitis C virus (HCV).[1] In the past decade, it has been the leading cause of end-stage liver disease and the leading indication for liver transplantation in the developed world.[2] By 2007, HCV had superseded Human Immunodeficiency Virus as a cause of death,[3] accounting for 8,000-10,000 deaths per year in the US alone.[4] Although the incidence of HCV has declined since its peak in 1989, there is still a large asymptomatic population who are likely to develop clinical symptoms,[5] and HCV-related mortality is predicted to continue to increase until around the year 2015.[6]

Prevalence varies world-wide from around 1% to 2% in developed countries, up to around 9.6-13.6% in North Africa.[7] In Saudi Arabia, the Ministry of Health reports a prevalence of 1.7% for the years 1995-2006[8] with an average of 3.5% for the Arab world.[9] However, figures as high as 7.3% have been quoted for the period 2008-2011[10] though this was data was from only one location.

Although it is estimated that 6% of the world's population are carriers of the hepatitis B virus (HBV),[11] which is a major risk factor for hepatocellular carcinoma, incidence will continue to decline due to vaccination programs. Global vaccination coverage is now estimated to be 69%[12] and was implemented in Saudi Arabia in 1989.[13]

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The occurrence of psychiatric disturbances has been widely reported in both hepatitis C patients treated with Interferon-α (IFN-α), and those who are untreated[5,14] with an incidence of around 22.4-28%.[15,16]

In contrast, there are few reports of similar psychiatric disturbances in HBV-infected patients. One study investigating the incidence of psychiatric illness in patients infected with either HCV or HBV reported a higher incidence of major depressive disorder in hepatitis C patients than in controls or those infected with hepatitis B.[17] Moreover, health-related quality of life (HRQoL) has been shown to be unrelated to severity of liver disease in HCV infection,[18] suggesting a pathophysiological link between HCV and depression.

In view of the differing genetics in our population, this study aimed to determine whether psychiatric comorbidities were present in Saudi Arabian patients infected with HCV, and whether these symptoms also extended to HBV patients. Neuropsychiatric side-effects resulting from the treatment of HCV with IFN-α and their management have been previously reviewed in detail,[19] and this work focuses on the prevalence of psychiatric symptoms in untreated patients with hepatitis with the aim of improving quality of care in these individuals.

MATERIALS AND METHODS

Consecutive patients attending the Hepatology Clinic at King Khalid University Hospital in Riyadh between February 2006 and July 2008 with a confirmed diagnosis of hepatitis C or hepatitis B were approached for participation in this study. Inclusion criteria were age above 18 years and positive anti-HCV antibody test with confirmation by HCV RNA polymerase chain reaction or positive test for hepatitis B surface antigen (HBsAg). Exclusion criteria were inability to give informed consent, clinical evidence of decompensated liver cirrhosis (ascites, history of hepatic encephalopathy or history of variceal bleeding), history of intravenous drug use, current alcohol or drug abuse, concomitant significant medical illness (such as chronic renal failure, heart failure, or chronic lung disease), well-known diagnosed significant psychiatric illness, and the current use of antiviral therapy. For the control group, patients attending the Neurotology Clinic at King Abdulaziz University Hospital, diagnosed with tinnitus and no history of either HCV or HBV, were asked to participate. The study was explained to all patients and each signed an informed consent form. The general health questionnaire (GHQ) 28 and SF-36 questionnaires were fully explained to each patient, and then the forms were filled out by patients themselves. Previously, validated Arabic versions of the GHQ[20] and SF-36[21] questionnaires were used. Patients were also asked to fill out a questionnaire that contained additional personal information on marital status, number of family members, educational level, average income, and living conditions. The patients' charts were accessed and other general medical information was recorded.

General health questionnaire

The GHQ is designed to assess the presence of mental illness related to general medical conditions. The focus is on the emergence of new psychological disorders and the GHQ thus evaluates recent symptoms rather than being designed to assess lifelong personality traits.

The GHQ 28 used in our study is a scaled version of the original GHQ 60 and is divided into the following sections: Somatic, anxiety/insomnia, severe depression, and social dysfunction.[22] In terms of validity of the GHQ as a screening device of psychiatric distress, each test item discriminates between respondents who are psychologically distressed and those who are not, and all versions of the test demonstrate adequate sensitivity and specificity consistent across language. Alhamad and Al-Faris[20] have previously validated an Arabic version for use in the Saudi Arabian population.

A number of scoring methods can be applied. Modified Likert scoring (0, 0, 1, 2) is simpler than Likert, the rational being that little is gained by discriminating between the first 2 columns where the responses are "less than usual" and "no more than usual"). The modified Likert method was used for this study. A higher score indicates a higher probability of mental disorder and an individual is considered to have a psychiatric disorder when their score reaches 5 or more.

SF-36

SF-36 is a general survey of health, which does not target a specific disease state, so it is useful for a wide variety of purposes. It was designed for use in population surveys and health policy evaluations,[23] and is valuable for assessing the benefit of different treatments or the impact of disease, comparing general and specific populations, and for evaluating individual patients.

Eight health concepts found to be the most frequently measured in health surveys were selected to form the SF-36,[24] and have been shown to be those most affected by disease and treatment.[25,26] Scores for each range from 0 to 100, with a higher score indicating a better health status, except for bodily pain where a lower score equates to less pain and thus a higher HRQoL.

The SF-36 is a practical alternative to longer measures of general and mental health such as the medical outcomes study[27] that it was designed to reproduce and has been widely used because of its generic nature. Depression is one of the most frequently studied conditions,[28] with a number

of studies finding the SF-36 scale to be predictive of the course of clinical depression.[29,30]

Data analysis

Data were entered into an MS Excel spreadsheet. Individual HRQoL items were recoded, summed and transformed according to standardized formula. Descriptive statistics were summarized as mean score and standard deviation and median (range) as appropriate. The Chi-square test was used to examine relations between categorical variables. Comparison of continuous variables was carried out using the Student's *t*-test or the Wilcoxon-Mann-Whitney test for skewed data. Correlation between continuous variables was evaluated by calculating Spearman's rho. The odds ratio (OR) was used to determine the association between different variables and likelihood of being a psychiatric case. A *P* value of 0.05 was considered as statistically significant. All analyses were performed with Stata Version 10 (Stata Corporation, College Station, TX, USA).

RESULTS

A total of 372 patients participated in the study. There were 150 patients in the tinnitus group, 110 in the HBV group and 112 in the HCV group. The HCV group was significantly older than the other groups ($P < 0.01$). There was a statistically significant association between gender and disease ($P < 0.01$). The HCV group was more likely to have females compared to the HBV and tinnitus groups. There was borderline significance in GHQ scores across the three groups, with the HCV group having the highest median score (4.0 [0-31]). There was also a borderline significant difference in patients being labeled as a psychiatric case ($P = 0.05$).

There was no strong evidence to show the relationship between hepatitis patients and tinnitus patients. However, logistic regression showed that the odds of being defined as a psychiatric case was 1.37 higher in HCV patients compared to tinnitus patients (OR = 1.37, 95% confidence interval [CI: 0.84-2.24]). The odds of being grouped as a psychiatric case was 0.69 in HBV patients compared to tinnitus patients (OR = 0.69, 95% CI: 0.41-1.15). On the other hand, compared to HBV patients, HCV patients were twice as likely to be labeled as a psychiatric case (OR = 1.98, 95% CI: 1.15-3.42) and this finding was significant ($P = 0.01$) [Figure 1].

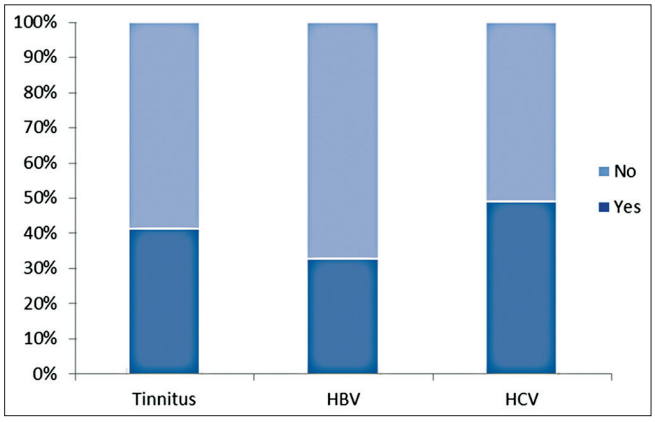

Figure 1: Percentage of each group labeled as a psychiatric case or not. hepatitis C virus patients were twice as likely to be labeled as a psychiatric case compared with hepatitis B virus patients (odds ratio = 1.98, 95%, confidence interval: 1.15-3.42, $P = 0.01$)

Age was not a significant factor in predicting whether a patient would be labeled as a psychiatric case. Compared to males, females were more likely to be labeled as a psychiatric case (OR = 1.66, 95% CI: 1.06-2.61). There were no significant relationships between gender and being labeled as having a psychiatric disorder across the disease groups. However, the OR of females being labeled as a psychiatric case compared to males were: OR = 1.95, 95% CI: 0.87-4.33; OR = 1.18, 95% CI: 0.53-2.62; OR = 1.65, 95%: 0.71-3.87 for tinnitus, HBV, and HCV patients respectively.

When we compared SF-36 scores between the hepatitis patients, there was a significantly lower score for the physical functioning ($P < 0.01$), role limitations due to physical functioning ($P = 0.01$), social functioning ($P = 0.02$) and bodily pain ($P < 0.01$) domains in the HCV patients compared to HBV patients [Table 1, Figure 2]. We also looked at the relationship between GHQ scores and SF-36 scores. There was a negative correlation between GHQ scores and SF-36 scores in all domains [Table 2]. Comparisons of SF-36 scores among those classified as psychiatric cases or not yielded statistically significant differences [Table 3].

DISCUSSION

The identification of psychiatric disorders in HCV patients is of particular importance not only in improving their quality of

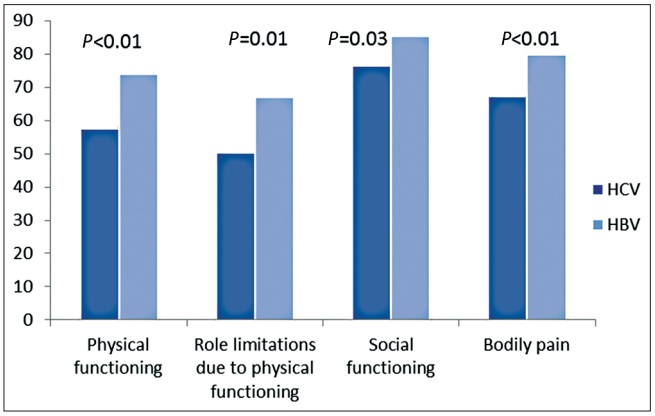

Figure 2: SF-36 scores differed significantly in a number of domains when comparing hepatitis C virus and hepatitis B virus patients

Table 1: General characteristics of study population with GHQ and SF-36 scores

Variable	Overall (*N*=372)	Tinnitus (*n*=150)	HBV (*n*=110)	HCV (*n*=112)	*P* value
Age (years)	40.8±13.0	36.3±10.1	37.5±12.0	48.4±13.2	<0.01*
Gender					
Male	145 (39.0)	60 (58.3)	55 (50.0)	30 (26.8)	<0.01*
Female	180 (48.4)	43 (41.8)	55 (50.0)	82 (73.2)	
GHQ score	3.0 (0-41)	3.0 (0-34)	2.0 (0-41)	4.0 (0-31)	0.05*
Psychiatric case					
No	219 (58.9)	88 (58.7)	74 (67.3)	57 (50.9)	0.05*
Yes	153 (41.1)	62 (41.3)	36 (32.7)	55 (49.1)	
SF-36 score#					
Physical functioning	65.4±28.8		74.0±26.1	57.5±29.1	<0.01*
Role limitations due to physical functioning	58.3±40.9		66.9±40.6	50.3±39.7	0.01*
Role limitations due to emotional problems	61. 9±42.1		58.4±43.3	65.0±41.0	0.32
Energy/fatigue	55.5±20.7		57.6±19.0	53.6±22.1	0.23
Emotional wellbeing	67.6±19.7		65.8±19.1	69.3±20.2	0.26
Social functioning	80.8±25.8		85.4±22.3	76.5±28.1	0.03*
Bodily pain	73.2±29.2		79.6±26.3	67.2±30.6	<0.01*
General health	63.2±19.7		65.0±19.0	61.6±20.4	0.28

GHQ: General health questionnaire, SF-36: The short form health survey, HBV: Hepatitis B virus, HCV: Hepatitis C virus, #Overall scores of HBV and HCV groups only

Table 2: Association between GHQ and SF-36 scores

Variable	Overall		HBV		HCV	
	Spearman's rho	*P* value	Spearman's rho	*P* value	Spearman's rho	*P* value
Physical functioning	−0.41	<0.01	−0.41	<0.01	−0.34	<0.01
Role limitations due to physical functioning	−0.38	<0.01	−0.36	<0.01	−0.36	<0.01
Role limitations due to emotional problems	−0.43	<0.01	−0.46	<0. 01	−0.42	<0.01
Energy/fatigue	−0.58	<0.01	−0.47	<0. 01	−0.67	<0.01
Emotional well-being	−0.52	<0.01	−0.54	<0. 01	−0.50	<0.01
Social functioning	−0.43	<0.01	−0.47	<0.01	−0.36	<0.01
Bodily pain	−0.47	<0.01	−0.51	<0.01	−0.46	<0.01
General health	−0.45	<0.01	−0.44	0.01	−0.42	<0.01

GHQ: General health questionnaire, SF-36: The short form health survey, HBV: Hepatitis B virus, HCV: Hepatitis C virus

Table 3: SF-36 scores among the psychiatric and non-psychiatric cases

Variable	Non-psychiatric case	Psychiatric case	*P* value
Physical functioning	71.2±27.3	56.2±28.9	<0.01
Role limitations due to physical functioning	67.3±40.0	44.0±38.3	<0.01
Role limitations due to emotional problems	73.5±37.4	43.5±42.9	<0.01
Energy/fatigue	63.7±16.8	42.5±19.8	<0.01
Emotional well-being	73.7±17.0	57.9±19.9	<0.01
Social functioning	88.1±18.7	69.2±30.8	<0.01
Bodily pain	82.8±22.0	58.0±32.7	<0.01
General health	69.5±16.2	53.4±21.0	<0.01

SF-36: The short form health survey

life (QoL), but also in optimizing compliance and treatment outcome in those undergoing therapy. Psychiatric disorders occur in both treated and untreated HCV patients and may influence the course and treatment of hepatitis C due to the requirement for dose reduction or termination of drug therapy. Patients with pre-existing psychiatric disorders are considered to be at higher risk of developing neuropsychiatric complications such as depression and suicidal ideation during IFN therapy,[31,32] though there are some observations, which report conflicting data.[33,34] Furthermore, individuals who experience increases in depressive symptoms during treatment may be less likely to clear the virus.[35]

Results of our GHQ questionnaire showed a significant difference between HCV and HBV patients in terms of whether they were labeled as a psychiatric case. This was unrelated to the age or gender of the patient. However, we observed no statistically significant difference between the control group and either the HCV or the HBV group. As expected, patients in the HCV group were more likely to be classified as a psychiatric case, but in fact the HBV patients were less likely to be classified in this way than the control group. The reason for this may be an increased tendency for tinnitus patients to exhibit

psychiatric symptoms compared to the general population. This is apparent from the number of these patients who were labeled a psychiatric case [Table 1], and could be confirmed by comparison with a group of healthy controls.

Our SF-36 data yielded lower scores for HCV than for HBV in the physical functioning, role limitations owing to physical functioning, social functioning, and bodily pain. Lower scores correspond to a lower HRQoL except for bodily pain, indicating a poorer outcome for HCV than for HBV patients. A lower score for bodily pain means less pain; therefore, a higher QoL which suggests that HBV patients experience more physical pain than HCV patients. Comparisons of SF-36 scores between those labeled as psychiatric cases and those who were not, yielded significant differences, confirming the value of the questionnaire in these patients. In addition, we confirmed an association between data collated from the two types of questionnaire by the observation of a negative correlation as would be anticipated. To the best of our knowledge, a correlation between GHQ and SF-36 data in hepatitis patients has not been previously investigated.

This poorer outcome with HCV compared to HBV is consistent with previous studies,[17,18,36] though Weinstein *et al*.,[36] found one of the independent predictors of depression to be female gender, in contrast to our observations. That HRQoL scores previously observed in an SF-36 questionnaire were reduced in HCV, but not HBV infection,[37] signifies that HCV infection *per se* reduces HRQoL rather than producing a non-specific awareness of having a viral infection. Moreover, reductions in HRQoL have been found even in patients who were unaware that they were HCV carriers.[38] Comparing depression and anxiety has revealed that depression but not anxiety may be increased in HCV, and that panic disorder may be higher in both HCV and HBV.[17] Similarly, Golden *et al*.,[2] found that depression, but not anxiety was associated with other adverse experiences of HCV infection. Thus, it may be that depression is a direct consequence of HCV infection, and that anxiety is a non-specific reflection of the patient's knowledge that they have a medical condition. Strong evidence for a direct pathological link between HCV infection and depression arises from a higher prevalence of depression in drug addicts infected with HCV than in those who are not infected.[39]

There are numerous studies relating to potential mechanisms for this link, which lends further support to our results. These studies have provided evidence for the involvement of elevated levels of pro-inflammatory cytokines,[40] HCV replication in the central nervous system (CNS),[41] the presence of an independent viral compartment in the CNS,[42] transport of the HCV virus into the CNS by leucocytes,[42] and induction of indolamine 2,3-dioxygenase.[43]

The most recent evidence suggests that the development of depression is associated with a selective hyper-responsiveness of the IFN system.[44] That this mechanistic evidence links HCV, but not HBV, with depression corroborates our findings.

In contrast to our data; however, results produced by several groups suggest a little difference between HCV and HBV patients in terms of psychiatric symptoms.

One group[45] who compared psychiatric co-morbidity in untreated HCV and HBV patients using the Structured Clinical Interview for DSM-IV Axis I Disorders and the SF-36 for measuring HRQoL, found no significant difference between the two hepatitis groups in terms of the rate of psychiatric diagnosis. Both groups showed statistically significant reductions in all subcategories of HRQoL criteria with psychiatric disorders (mainly depression) being the major contributors to reduced QoL.

Comparison of psychiatric disturbances in asymptomatic HBV carriers and healthy subjects using self-report questionnaires, structure clinical interviews, and the global assessment of functioning scale, revealed significantly higher rates of depression and anxiety in HBV carriers.[46] However, these psychiatric symptoms were associated specifically with concerns about contamination and future illness.

Another study, which measured physical and mental function using the SF-36 and the beck depression inventory (BDI), found a reduced HRQoL in both patients with chronic HBV and asymptomatic carriers[47] compared to control subjects.

The reason for this disparity in the results remains, though there are a number of feasible explanations. It is possible that there is a direct pathophysiological relationship between HCV and depression, whereas psychiatric symptoms associated with HBV may be a consequence of concerns about contamination, illness or stigma. It is unlikely that health questionnaires are able to distinguish between psychiatric effects caused by a direct viral action and those arising from the anxiety of being infected with hepatitis. The situation is perhaps further complicated by the fact that assessment methods vary between groups. For example, Patterson *et al*.,[48] have suggested that the use of BDI to screen patients results in an overestimation of the frequency of depressive symptoms in medical populations because the somatic symptoms of depression are also common symptoms of physical illness such as hepatitis, and leading to false positives.

Other factors that are likely to influence results include disease stage, additional co-morbidities, and whether the psychiatric symptoms were pre-existing or assumed to be a result of viral infection as a high proportion of people at risk

of psychiatric illness are infected with HCV. This may apply to a number of studies, including that discussed above.[46]

Moreover, it is possible that differences in the genetic profile of hepatitis patients may contribute to the variation in results observed. Six HCV and eight HBV genotypes exist (as well as several sub-genotypes) and their distribution world-wide varies with geographic location. Further, work would be required to discover whether patients expressing certain genotypes are more susceptible to psychiatric symptoms than others. Nevertheless, substantial evidence exists in support of identifying hepatitis patients suffering with concurrent psychiatric complications.

CONCLUSION

This study provides further evidence of the increased incidence of co-morbid psychiatric symptoms in patients infected with hepatitis C. We have shown a lower incidence of psychiatric complication in hepatitis B patients, which is in agreement with the majority of previous literature reports. This emphasizes the importance of collaboration between hepatologists and psychiatrists to promote the screening of HCV patients for depression prior to anti-viral treatment or to improve QoL by instigation of corrective therapy.

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