Depression comorbidity in patients with chronic hepatitis C and its possible relation to treatment outcome

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Background
The highest number of hepatits C virus all over the world is in Egypt. Depression, which occurs during the course of illness, can affect the treatment response, compliance to therapy and hence, disease outcome.

Objectives
The objective of this study was to evaluate the presence of depression in patients with chronic hepatitis C (CHC) either using interferon therapy or not.

Method
A case–control study was carried out on 200 patients with CHC and 200 healthy controls. The patients were subdivided into two groups. Group 1 included patients who were treated with pegylated interferon and ribaverin, whereas group 2 included patients with CHC and not receiving interferon. The patients and controls were subjected to careful clinical assessment, laboratory investigation and assessment of depression through Mini-International Neuropsychiatric Interview schedule for psychiatric interview and Beck Depression Inventory.

Results
Depression was more prevalent in patients with CHC. The prevalence of depression in the interferon-receiving group (G1) was 42% (42 patients) and 30% (30 patients) in the noninterferon-receiving group (G2). Depression was correlated with decreased number ofred blood cells, decreased haemoglobin percentage, less sustained viral remission and treatment discontinuation.

Conclusion
Depression is prevalent in a considerable way in patients with CHC, and in a much greater and severe form in those on interferon therapy (G1). The presence of depression might be related to poor treatment outcome. Psychiatric assessment and early intervention is mandatory in this population.

Keywords:
chronic hepatitis C, depression, treatment outcome

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Introduction

The prevalence of hepatitis C virus (HCV) infection varies throughout the world with the highest number in Egypt [1]. The current standard treatment of HCV consists of combination therapy of pegylated interferon α (peg IFN-α) and ribaverin [2]. Treatment consideration for HCV is based on presentation of the disease (acute versus chronic), genotype, laboratory values, coinfection (HIV, hepatitis B) and comorbidities. Sustained viral response (SVR), which is undetectable HCV in the blood for 6 months at the end of treatment, occurs in 50% of the patients [3].

People with a diagnosis of HCV have to deal with special issues. HCV is a single-stranded RNA virus that mutates or replicates very rapidly, making this disease difficult to treat. Individuals face HCV as a chronic progressive disease that does not have a cure. The diagnosis of HCV can have harmful effects on psychological well being. The emotional challenge becomes great, a person deals with a chronic disease without letting it take over his or her life [4]. In addition, during the course of illness, symptoms related to treatment, such as acute confusional state, delirium, depression, irritability and even mania occur. In the absence of interferon therapy, comorbid depression, cognitive decline and fatigue are common [5]. Presence of depression, which occurs in 30–50% of patients during IFN-α treatment, can alter response to therapy and compliance on treatment [1].

Therefore, the aim of this study was to evaluate the presence of depression in patients with chronic hepatitis C (CHC), either using IFN therapy or not, and to find the possible effect on treatment outcome.

Materials and methods

Patients

A cross-sectional, case–control study was carried out on 200 patients with CHC. They were collected from the Tropical Medicine outpatient clinic, Ain Shams University, Cairo, Egypt. The study was carried out from the period March 2006 to July 2009. A comprehensive sample was taken. The patients were classified into two groups.

The first group (G1) included 100 patients receiving peg IFN-α and ribavirin. The second group (G2) included 100 patients who were not receiving interferon.

Inclusion criteria

All the patients were serum positive for anti-HCV and had circulating HCV RNA as confirmed by reverse-transcription PCR for G1. CHC is defined as the presence of antibody to HCV with intermittent or persistent abnormal liver function tests for more than 6 months (or presence of viremia for those with persistently normal liver function tests) [6]. Patients with earlier therapy attempts (i.e. not treatment naive) were included in the IFN-receiving group if they fulfilled all other criteria for study participation. The patients were aged between 18 and 65 years and completed at least 8 weeks of antiviral therapy.

Exclusion criteria

The patients were excluded from the study if they had advanced liver cirrhosis (child stages B or C), coinfections (hepatitis B virus or HIV), severe internal diseases (e.g. cancer, ischaemic heart disease or autoimmune disease), current pregnancy or the absence of reliable contraception in female patients, premorbid psychiatric illness or neurological disorder (severe depression or psychosis) and active intravenous drug use or alcohol abuse if there was any other contraindication to IFN-α in the IFN-receiving group.

Controls

Two hundred healthy controls were included in the study. They were relatives of the patients. They were age-matched and sex-matched with the patients.

Methods

Patients and healthy controls were subjected to the following:

1. Careful history taking including age and sex of patients, disease duration and medications received;
2. Thorough clinical examination with stress on BMI, splenomegaly and presence of ascitis;
3. Laboratory investigation including liver function tests, such as alanine aminotransferase, aspartate aminotransferase, bilirubin and albumin, and complete blood picture, namely Red Blood Cells (RBCs) count, white blood cells count and platelet count;
4. Abdominal ultrasound to confirm liver size and texture, portal vein dilation and the size of spleen;
5. Semistructured psychiatric interview, the Mini-International Neuropsychiatric Interview (MINI) schedule, using the Arabic version to screen patients for depression, which was done by an experienced psychiatrist [7];
6. Screening for depressive symptoms using Beck Depression Inventory (BDI): the BDI was used for those patients with depression. It is a 21-item questionnaire that assesses symptoms of depression. The BDI has been found to be sensitive and has been validated for rating the severity of depression. Items are rated on a 0–3 scale and added for a total score of 0–63, with higher scores indicating greater severity. A score of more than 9 indicates a depressive mood (10–18, mild; 19–29, moderate and 30–63, severe) [8].

Statistical analysis

The statistical package for the social sciences software (SPSS for Windows, English version 12.0. SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. *T*-tests for independent samples were carried out to test for differences in continuous variables between patient subgroups. Chi-square test was used to compare the frequencies of categorical variables between patient subgroups. Pearson's correlation coefficient was used to correlate variables. The value of *P* was considered as follows: *P* value less than 0.05 = significant, *P* value less than 0.01 = moderately significant and *P* value less than 0.001 = highly significant (SPSS, 2004).

Results

This case–control study was carried out on 200 patients with CHC. They were compared with age-matched and sex-matched healthy controls. The patients with CHC had higher prevalence of depression as reported by the MINI schedule of psychiatric disorders together with BDI scores (Table 1).

The first group, (G1, patients with CHC receiving peg IFN-α and ribaverin) and the second group, (G2, patients with CHC not receiving interferon) were age-matched and sex-matched. The mean age for the first group (G1) was 46.06 ± 6.6 years, whereas for the second group (G2) was 46.8 ± 5.46 years ($t = -0.62$ and $P = 0.53$). Sex distribution in the first group (G1) was 68 : 32 and in the second group was 76 : 24 (male : female), respectively ($\chi^2 = 0.7$ and $P = 0.17$). The two groups were age-matched and sex-matched.

Both G1 and G2 were matched with regard to the reported symptoms, associated conditions, disease duration, clinical examination findings and laboratory investigations (Table 2). Screening for depression using the

Table 1 Age, sex, body mass index, prevalence of depression and Beck Depression Inventory Scores in patients and controls

	Patients with chronic hepatitis C ($n=200$)	Healthy controls ($n=200$)	Statistical value	*P*
Age	46.42 ± 6.06	45.4 ± 4.06	$T=1.92$	0.06
Sex (male/female)	184/52	140/60	$R=3.599$	0.057
BMI	25.6 ± 2.9	23.2 ± 1.1	$T=1.98$	0.056
Depression	70	15	$T=10.94$	<0.001
BDI	13.73 ± 13	5 ± 5.4	$T=8.77$	<0.001

BDI, Beck Depression Inventory; BMI, body mass index.

Table 2 Comparison of clinical data between the studied groups showed no statistically significant difference between the first group (G1) and the second group (G2)

			Statistical values	
Clinical data and investigations	G1 ($n=100$, %)	G2 ($n=100$, %)	t	P
Accidental discovery	48 (58)	68 (68)	1.07	0.3
Easy fatigability	22 (22)	14 (14)	1.08	0.3
Right hypochondrial pain	20 (20)	18 (18)	0.065	0.8
DM	26 (26)	34 (34)	0.76	0.38
Hypertension	22 (22)	16 (16)	0.59	0.44
Disease duration (years)	6.46 ± 2.6	6.84 ± 2.07	−0.8	0.43
BMI (kg/m^2)	26.4 ± 4.02	27.8 ± 4.5	−1.6	0.11
Pallor	60 (60)	62 (62)	0.42	0.84
Clubbing	4 (4)	6 (6)	0.21	0.65
Hepatomegaly	10 (10)	22 (22)	2.68	0.1
Splenomegaly	12 (12)	18 (18)	0.71	0.4
Bilirubin	0.99 ± 0.31	0.92 ± 0.29	1.11	0.26
Albumin	3.97 ± 0.7	3.9 ± 0.67	0.55	0.58
ALT	115.5 ± 53.08	122.28 ± 54.28	−0.63	0.52
AST	88.4 ± 46.19	96.5 ± 48.57	−0.85	0.39
RBCs	4.26 ± 0.76	4.08 ± 0.85	1.06	0.28
Hb	11.4 ± 1.8	11.01 ± 2.09	1.02	0.3
Platelets	216.5 ± 42.2	203.56 ± 38.04	1.6	0.11
WBCs	5.27 ± 1.19	5.42 ± 1.31	−0.57	0.57

G1, patients with hepatitis C receiving pegylated interferon-α and ribavirin; G2, patients with hepatitis C who were not receiving interferon. BMI, body mass index; DM, diabetes mellitus; Hb, haemoglobin; NS, nonsignificant; RBCs, red blood cells; WBCs, white blood cells. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

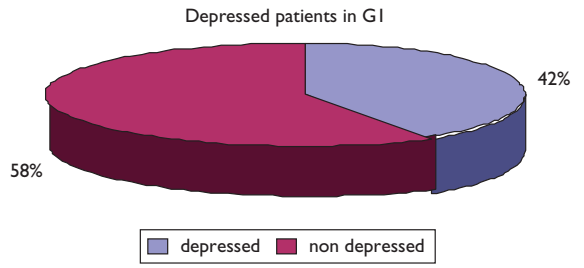
MINI schedule for psychiatric disorder showed that 42 (42%) and 30 (30%) patients were depressed in both G1 and G2, respectively. Although depression was more prevalent in G2, it did not reach statistically significant levels ($\chi^2 = 1.56$ and $P = 0.21$). This is further illustrated in Figure 1.

Depression was further confirmed by BDI. In G1, 42 patients were depressed versus 15 depressed patients in G2. Moreover, the depressive scores were highly significantly elevated in the IFN-receiving group, being 17.62 ± standard deviation (17.4) in G1 and 9.84 ± standard deviation (8.78) in G2, respectively ($t = -2.88$ and $P = 0.006$). Comparision of the severity of depression using the BDI showed that the first group (G1) expressed higher frequency of severe depression, whereas the second group (G2) expressed higher frequency of mild depression, to a statistically significant level ($\chi^2 = 6.04$ and $P = 0.049$). This is further described in Figure 2.

Evaluation of the effect of depression on treatment outcome was done through the assessment of effect of depression on laboratory data, achieving SVR and compliance on treatment. In the IFN-receiving group (G1), depressed patients showed lower RBC count and haemoglobin level than nondepressed patients as illustrated in Table 3.

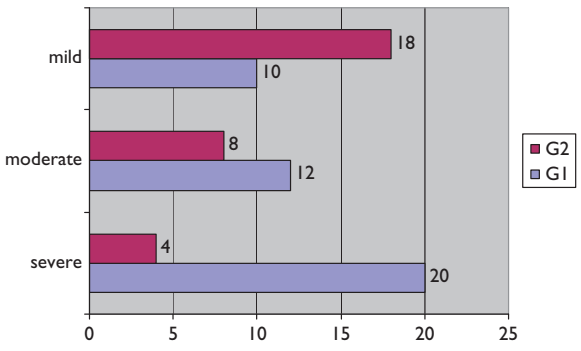
Moreover, there was an inverse correlation between BDI scores and both RBC count ($R = -0.3$ and $P = 0.029$) and haemoglobin percentage ($R = 0.26$ and $P = 0.04$) in G1. In G1, nondepressed patients ($n = 58$) achieved SVR nearly two times than nondepressed ($n = 42$) with regard to the percentage. This difference reached a significant statistical level ($\chi^2 = 4.02$ and $P = 0.045$). Moreover, noncompliance on treatment in depressed patients in G1 was two times more than nondepressed patients, but did not reach a statistically significant level ($\chi^2 = 1.64$ and $P = 0.2$). This is further illustrated in Figure 3.

Figure 1



Shows the percentage of depressed patients in group 1 (G1) and group 2 (G2), respectively. G1: patients with hepatitis C receiving pegylated interferon-α (peg IFN-α) and ribavirin. G2: patients with hepatitis C who were not receiving interferon. NS, not significant.

Figure 2



Comparison of the severity of depression between groups according to Beck Depression Inventory (BDI), showed higher frequency of severe depression in group 1 (G1). G1: patients with hepatitis C receiving pegylated interferon-α (peg IFN-α) and ribavirin. G2, patients with hepatitis C who were not receiving interferon.

Table 3 Comparison of laboratory parameters between depressed and nondepressed patients in G1

	Depressed ($n=42$)	Nondepressed ($n=58$)	Student's *t*-test *t*	*P*
Bilirubin	0.86 ± 0.31	0.97 ± 0.28	−0.24	0.80
Albumin	3.97 ± 0.63	3.84 ± 0.72	0.65	0.51
ALT	129.48 ± 57.38	116.57 ± 53.22	0.81	0.42
AST	104.38 ± 51.19	90.68 ± 47.51	0.96	0.33
RBCs	3.81 ± 0.92	4.32 ± 0.76	−2.12	0.039*
Hb	10.3 ± 2.24	11.55 ± 1.88	−2.13	0.038*
Platelets	208.24 ± 45.02	200.18 ± 33.1	0.72	0.47
WBCs	5.41 ± 1.41	5.43 ± 1.27	−0.20	0.84

Hb, haemoglobin; RBCs, red blood cells; WBCs, white blood cells.
*Significant.

Discussion

Hepatitis B and C are, and will remain for some time, major health problems in Egypt and the entire continent of Africa. Both infections can lead to an acute or silent course of liver disease, progressing from liver impairment to cirrhosis and decompensated liver failure or hepatocellular carcinoma in a 20–30-year period [9].

Besides the late clinical sequelae of chronic liver disease, such as cirrhosis and hepatocellular carcinoma, a high prevalence of depressive and anxiety symptoms has been reported [10,11]. Surprisingly, the number of people with comorbid HVC and depressive disorder (including minor depression) increased significantly between 1995 and 2005 from 18% to over 35% of all people with diagnosed HVC [12].

In this study, depression is reported in 30% of patients in G2 with the absence of treatment with IFN. Earlier researches showed a range between 28 and 35% [12–14]. This proves the impact of CHC as a potent trigger for depression, irrespective of IFN-α treatment, presence of alcohol or substance abuse [15].

Etiopathogenic factors in this group are multiple. Ambiguity, complexity, inconsistency and unpredictability of the course of illness [16], alterations in brain metabolites as evident by magnetic resonance imaging spectroscopy [17] and emotional volatility and perception of stigma [18] are among the causes of depression in this population. Nevertheless, dealing with a chronic illness [4] and perceived indicators of changes of normal functioning [19] are one of the triggers of depression.

In the IFN-receiving group (G1), 42 patients (42%) suffered from depression. Despite comparable medical conditions between G1 and G2, the prevalence of depression in G1 is more. This goes with the agreement of reported depression with IFN therapy ranging from 3 to 45%, depending on the instrument used, age group, time from start of therapy and sex [12,20]. Few reports demonstrated a possible increase of depressive symptoms up to 77% after IFN-α treatment [21].

Many postulated theories have described the mechanism of IFN-induced depression. Among them are alteration of tryptophan metabolism into quinolinic acid [22], activation of the hypothalamic pituitary adrenal axis resulting in increase of stress peptides [23], increase in interleukin 6 [24], alteration of blood–brain barrier permeability through intercellular adhesion molecules-1 and activation of cells at blood–brain barrier [25]. Furthermore, IFN-α might affect the frontal lobe and anterior cingulated function [26], dopaminergic level and apoptotic system.

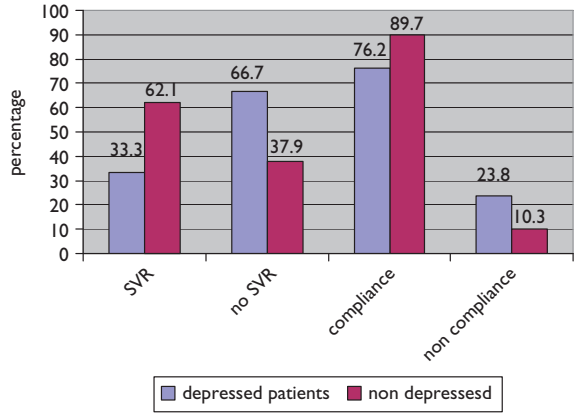
Although increased depression is more prevalent with increased duration of illness and male sex matching earlier results [27]. In the current, this result did not reach a statistical significant difference which might be related to the need to increase the sample size.

In a trial to study the impact of depression on treatment outcome in G1 the relationship between depression and laboratory data, attainment of SVR and compliance of treatment have been investigated. There is an evident inverse correlation between RBC count, percentage of haemoglobin and depression in the IFN-receiving G1. IFN and ribaverin causes anaemia [28]. Further studies are needed to determine whether there is a relationship between depression and RBCs and percentage of haemoglobin. Actually in postpartum depression, the level of haemoglobin at day 7 postpartum was significantly correlated with postpartum depression [29].

Depression does affect treatment response in those patients. The rate of nonadherence to antiviral treatment was more in depressed patients. This could be related to the loss of interest and diminished quality of life, which make it difficult to maintain the treatment schedule for those patients [30]. In this study, depression diminishes response to treatment, evident by low viral clearance in depressed patients. This is in agreement with the studies carried out by El-Zayadi [1] and Raison *et al.* [5], which might be related to the impaired level and activity of B cells, T cells and NK cells [31].

In conclusion, depression is more prevalent in patients with CHC either receiving IFN therapy or not. However, the prevalence is more in those receiving peg IFN-α and ribaverin (G1). The severity of depressive symptoms was

Figure 3



The effect of depression on achieving sustained viral remission (SVR) and compliance on treatment. Number of depressed patients = 42, number of nondepressed patients = 58.

more evident in G1 as well. In this study, depression might be related to treatment outcome as it is related to decreased RBC count, decreased percentage of haemoglobin, noncompliance on treatment and less SVR.

There are some limitations for this study. There is an obvious need for prospective studies specially to determine the effects of different phases of treatment on depression and treatment outcome as depression affects treatment outcome in this study. Therefore, it is important to assess predictors of depression, such as poor sleep quality at baseline of therapy [32], S/S genotype of serotonin reuptake transporter promoter (5-HTTLPR) [33], measurements of tumour necrosis factor α and interleukin 1-β levels, [34] which are all predictive of later development of depression.

It is recommended to start psychiatric assessment at the beginning of therapy, to search for early predictors of depression. Patients with mild-to-moderate depression at the baseline are considered as a high-risk group for developing severe depression and treatment discontinuation [31,35]. Early treatment of depression does affect response and adherence to treatment [1]. The most studied antidepressants are citalopram [36] and paroxetin as they have strong anxiolytic effects. All selective serotonin reuptake inhibitors are proved to be safe in the treatment of depression after IFN-α treatment [37]. Associative neurovegetative symptoms, such as fatigue, anorexia, pain and psychomotor slowing show better response on serotonin–noradrenalin antidepressants (bupropion, psychostimulant or modafinil) [5]. Importantly, all patients who received antidepressants in other studies were able to complete the full course of IFN-α therapy. Hepatotoxicity has been rarely seen during selective serotonin reuptake inhibitor treatment [38,39]. A multidisciplinary team should be consulted to develop complex physical and psychological treatments for patients with CHC [18].

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الملخص العربى

دراسة معدل انتشار الاكتئاب فى المرضى المصابون بالالتهاب الكبدى الوبائى Cالمزمن

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***قسم الطب النفسى- كلية الطب- جامعة عين شمس**

****قسم طب المناطق الحارة- كلية الطب- جامعة عين شمس**

ينتشر التهاب الكبد الوبائى المزمن (c) في مصر أكثر من غيرها في مناطق العالم . يهدف البحث الحالي إلى دراسة معدل انتشار الاكتئاب في مئتي مريض مصري يعانون من التهاب الكبد الوبائي (c) سواء يتعاطون عقار الانتيرفيرون أو لا يتعاطونه مقارنة بمجموعة ضابطة من الأصحاء. تم فحص الاكتئاب بالمقياس المصغر للفحص النفسي و مقياس بيك للاكتئاب. كثر معدل الاكتئاب بدلالة إحصائية في مرضى التهاب الكبد الوبائي المزمن (c) عن المجموعة الضابطة .كانت نسب الاكتئاب بالمرضى كالأتي: 42% في المرضى المتعاطين عقار الانتيرفيرون و 30% في المرضي الذين لا يتعاطونه .ووجد أن هناك علاقة بين الاكتئاب و نقص عدد كرات الدم الحمراء و نقص نسبة الهيموجلوبين وقلة نسبة ثبات الشفاء من الفيروس وعدم الالتزام بالبرنامج العلاجي. وبالتالي تشير الدراسة إلى وجود علاقة بين الاكتئاب و مآل التهاب الكبد الوبائي المزمن(c) .