A longitudinal study of psychiatric consequences of hepatitis C virus patients receiving interferon therapy

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Objective
A growing body of evidence suggests that patients infected with hepatitis C virus (HCV) have a high prevalence of psychiatric disorders. Antiviral treatment, particularly interferon (IFN), may induce an increase in the incidence of psychiatric symptoms observed in HCV patients.

Aim
This study aimed to identify the possible psychiatric complications in patients infected chronically with HCV and follow up these complications on treatment with pegylated IFN plus ribavirin.

Patients and methods
This is a longitudinal follow-up, comparative (case–control) study conducted on 90 patients, all of whom were subjected to a semistructured interview, psychometric assessment by International Classification of Diseases-10 Symptom Checklist for Mental Disorder version 1.1 for psychiatric evaluation, laboratory investigations to exclude decompensate liver cases, liver biopsy, and abdominal ultrasonography.

Results
HCV prevalence was found to be significantly higher in the age group of 30–40 years. Results of the International Classification of Diseases-10 symptom checklist showed prevalence of psychiatric complications linked to HCV infection before therapy, which included generalized anxiety disorder; these complications increased after treatment, such as mixed anxiety and depression and moderate depression. HCV infection independent of IFN therapy and hepatitis B virus infection caused mild depression and mixed anxiety and depression.

Recommendations
HCV-related psychiatric consequences and HCV therapy-related psychiatric complications should be included in the differential diagnosis of patients, and patients should be assessed through consultation liaison psychiatry.

Keywords:
hepatitis C virus, interferon therapy, psychiatric consequences

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Introduction

The hepatitis C virus (HCV) epidemic in Egypt is unique and well documented in the international medical scientific literature. There are many estimates of the number of infected people in Egypt. Many publications suggest that over 15% of the people in Egypt are infected. This is 10 times greater than in any other country in the world. The prevalence of HCV in western countries is less than 2%. The prevalence of HCV varies throughout the country. The available data suggest that the northern Nile Delta has the highest prevalence, at ~28%. The much smaller population of Upper Egypt, in the south, has a slightly lower HCV prevalence of ~20%. The two major urban centers, Cairo and Alexandria, have the lowest prevalence of ~9 and ~6%, respectively. The incidence of HCV in rural women is 0.5% per year [1].

In addition to the physical problems associated with chronic HCV, there is a high rate of psychiatric comorbidity, with up to 40% of HCV-infected persons meeting diagnostic criteria for a concurrent, active psychiatric disorder [2].

Depression is the most common comorbid psychiatric disorder, with prevalence ranging from 28 to 50%; the prevalence of anxiety disorders ranges from 18 to 41% [3].

The prevalence of comorbid HCV and psychiatric disorders has been studied in veteran samples, revealing rates of 9–16% for bipolar disorder, 17–24% for psychotic disorders, and 30% for personality disorders, with antisocial disorder most common at 16% [4].

The causal relationship between interferon α (IFN-α) administration and occurrence of mood disorders has been tackled by various research works focusing on the importance of the immune system in the pathophysiology of depression [5].

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According to current pathophysiological theories, depression results from disorders of various central nervous system functions, mainly limbic, monoaminergic, and neuroendocrinal systems. However, exogenous IFN-α does not cross the blood–brain barrier when unscathed and an intermediary mechanism is necessary. The first to be addressed is the cytokine system itself as it is composed of numerous different molecules interacting in an infinite number of possible combinations. Some of these cytokines (e.g. some interleukins) are activated by IFN-α and can reach the central nervous system; they are good candidates for the role of second messenger mediating the induction of psychobehavioral disorders. Second, one should keep in mind that serotonin is a monoaminergic neurotransmitter classically involved in depression pathophysiology; studies have demonstrated that IFN-α modulates the peripheral activity of indoleamine-dioxygenase, a regulating enzyme of serotonin metabolism, possibly through T lymphocyte CD4 activation. Third, some authors have postulated an immune-induced vagal mechanism to explain depression caused by IFN-α [6].

Aim

This study aimed to identify the possible psychiatric complications in patients chronically infected with HCV and follow up these complications on treatment with pegylated IFN (peg-INF) plus ribavirin.

Patients and methods

Research design

The study is a longitudinal follow-up, comparative (case–control) study.

Site of research and selection of cases

This study was conducted on 90 patients selected at random from the hepatic virus treatment center in Benha Fever Hospital and from the National Committee for Control of Viral Hepatitis between October 2010 and June 2011.

Patients were diagnosed on clinical and laboratory basis. They comprised 29 (32.2%) women and 61 (67.8%) men and their ages ranged from 18 to 60 years.

They were divided into three groups:

(1) *Group 1*: This group included 30 patients with chronic hepatitis C who received IFN therapy (HCV treatment).
(2) *Group 2*: This group included 30 patients with chronic hepatitis C who did not receive IFN therapy and served as the control group.
(3) *Group 3*: This group included 30 patients with other chronic liver disease (hepatitis B) who were matched for age, sex, and educational level to the patient groups and were included as a control group for the psychiatric evaluation of any differences between hepatitis B and hepatitis C regardless of the IFN therapy.

Patient selection

Inclusion criteria

(1) Age 18 years or older.
(2) HCV RNA positivity in serum.
(3) Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher).
(4) Compensated liver disease [total serum bilirubin <1.5 g/dl; international normalized ratio 1.5; serum albumin >3.4; platelet count 75 000 mm; and no evidence of hepatic decompensation (hepatic encephalopathy or ascities)] [7].
(5) Acceptable hematological and biochemical indices (hemoglobin 13 g/dl for men and 12 g/dl for women; neutrophil count 1500/mm^3; and serum creatinine <1.5 mg/dl) [7].

Exclusion criteria

(1) Presence of any psychiatric disorders.
(2) Currently using of illicit drugs or alcohol but willing to participate in a substance abuse program or alcohol support program. Candidates should be abstinent for a minimum period of 6 months.
(3) Coinfection with HIV.
(4) Solid organ transplant (renal, heart, or lung).
(5) Presence of autoimmune hepatitis or other autoimmune conditions known to be exacerbated by peg-IFN and ribavirin.
(6) Presence of untreated thyroid disease.
(7) Pregnant or unwilling to comply with adequate contraception.
(8) Presence of severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart diseases, poorly controlled diabetes, or chronic obstructive pulmonary disease.
(9) Known hypersensitivity to drugs used to treat HCV.

Methods

All presenting patients were interviewed and given a full explanation of the aim of the work and written informed consent was taken.

All patients were subjected to the following.

A semistructured interview that emphasized the following.

General medical examination

A full medical examination was carried out to assess any comorbid physical disease, with special emphasis on neurological assessment and hepatic function. Hepatic assessment was conducted by the hepatologist at the hepatic virus treatment center in Benha Fever Hospital and at the Benha University Hospital Tropical Department.

Thorough history taking

(1) Detailed history of the patients, all of whom were matched for age, sex, residence, level of education, occupation, social status, and source of infection.

(2) Current episode of psychiatric illness or history of any disorder.
(3) History of psychiatric hospitalization.
(4) History of substance abuse or dependence.
(5) Family history of affective disorder or suicide attempt or other psychiatric disorders.
(6) Number of dropout cases and the causes.
(7) Thorough mental state examination to assess the presence of any psychiatric disorders and their severity using International Classification of Diseases (ICD)-10 diagnostic criteria.

Psychometric assessment

Psychometric assessment was carried out using the ICD-10 Symptom Checklist for Mental Disorder version 1.1 for psychiatric evaluation [8], which is a semistructured instrument intended for clinicians' assessment of psychiatric symptoms and syndromes in the F0–F6 categories. It allows the quick determination of a preliminary diagnosis from an initial brief interview. The module comprises a symptom list and lists of states that, according to ICD-10 criteria, should be excluded or could be associated with the syndromes substance abuse or dependence. It was also used to code the severity of different psychiatric disorders. The ICD-10 criteria were applied in both the studied groups and the control group.

Laboratory investigations

Both the studied group and the control group were subjected to laboratory investigations to assess the suitability of the patients for IFN therapy and to exclude decompensated liver cases [7]. The investigations included the following:

(1) Complete blood count and international normalized ratio.
(2) Kidney functions.
(3) Liver function profile: aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, ammonia, and serum albumin.
(4) Hepatitis markers:
    (a) Hepatitis B virus (HBV): HBsAg, HBsAb, HBc (IgM), HBc (total), and HBeAg.
    (b) HCV: HCV Ab and HCV PCR.

Liver biopsy

Liver specimens from 60 HCV patients were examined for confirmation of diagnosis, exclusion of other causes, and determination of the stage of fibrosis and grade of inflammation using an algorithm for the grading of activity in chronic hepatitis C – the METAVIR [9].

Sixty HCV patients and 30 HBV patients underwent abdominal ultrasonography including the liver and the spleen.

Patient assessment timetable

We assessed all patients included in the study at different times:

(1) Immediately before beginning the course of IFN therapy.
(2) At 4, 12, and 24 weeks after beginning the course of IFN therapy.

Treatment regimen

Thirty patients were scheduled to receive combined peg-IFN-α2b (100 μg once weekly) with ribavirin (800–1000 mg/dl) based on body weight (<70 or >70 kg).

At the 24th week, if HCV RNA was undetected, treatment was continued for 48 weeks; otherwise the medications were stopped.

The dose of the IFN or the ribavirin was modified or discontinued if adverse effects developed. Adverse effects were either hematological or biochemical or nonhematological and nonbiochemical and were graded according to severity (mild, moderate, severe, and life threatening) with special algorithm for modification and discontinuation.

Statistical analysis

The collected data were tabulated and analyzed using SPSS (version 16; SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages, whereas quantitative data were expressed as mean and SD. The χ^2-test, McNemer's test, paired '*t*-test', the Student '*t*-test', analysis of variance (F), and Pearson's product correlation coefficient (r) were used as tests of significance. P values less than 0.05 were considered significant.

Results

Demographic results

The demographic results of the HCV patients (before therapy and including those excluded from therapy) and HBV patients were as follows:

As regards age distribution, the proportion of both HCV and HBV patients was found to be significantly higher in the age group 30–40 years (38.9%) ($\chi^2 = 15.7$ and $P = 0.015$) compared with other age groups (30% in 18–30-year-olds, 24.4% in 40–50-year-olds, and 6.7% in 50–60-year-olds).

With regard to residence, HCV and HBV were insignificantly more prevalent in rural areas [59 (65.6%) patients] compared with urban areas [31 (34.4%) patients] ($\chi^2 = 3.6$ and $P = 0.16$).

With regard to sex distribution, 61 (67.8%) patients were male and 29 (32.2%) were female. There was no statistically significant difference as regards sex ($\chi^2 = 1.9$ and $P = 0.38$).

As regards educational level, 22 (24.4%) patients were illiterate, seven (7.8%) had primary level education, three (3.3%) had preparatory level, 36 (40%) had secondary level education, and 22 (24.4%) had higher level education. This result showed that there was no statistically significant difference as regards educational level ($\chi^2 = 5.9$ and $P = 0.66$).

As regards occupation the results showed no statistically significant difference between the groups: 16 (17.8%)

patients were government employees; 18 (20%) were nongovernmental employees; and 56 (62.2%) were housewives or laborers ($\chi^2 = 6.8$ and $P = 0.15$).

The marital status showed that there was no statistically significant difference as regards marital status: 75 (83.3%) patients were married, eight (8.9%) were single, three (3.3%) were engaged, three (3.3%) were divorced, and one (1.1%) patient was widowed ($\chi^2 = 7.1$ and $P = 0.53$).

Other results from the semistructured interview

Results of the HCV patients (before therapy and including those excluded from therapy) and HBV patients also showed the following:

Source of infection

The source of infection was insignificant: 55 (61.1%) patients had unknown source of infection, nine (10%) were infected through blood transfusions, 11 (12.2%) were infected during dental treatment, seven (7.8%) were infected sexually, and eight (8.9%) were infected during operations ($\chi^2 = 13.8$ and $P = 0.086$).

Physical comorbidity

Physical comorbidity was statistically insignificant. Associated physical illnesses reported in our patients included Bilharziasis (29 patients, 32.2%), diabetes mellitus (nine patients, 10%), diabetes mellitus along with hypertension (one patient, 1.1%), cardiac disease (one patient, 1.1%), and hypertension (four patients, 4.4%) ($\chi^2 = 11.8$ and $P = 0.29$).

Past history of previous psychiatric disorders

Past history of previous psychiatric disorders revealed no statistically significant difference regarding its presence among 51 (56.7%) patients ($\chi^2 = 31.5$ and $P = 0.025$).

Family history of psychiatric disorders

There was a statistically insignificant prevalence of negative family history among 85 (94.4%) patients in the studied groups, showing that the studied groups were matched as regards the family history of psychiatric disorders ($\chi^2 = 0.42$ and $P = 0.81$).

Causes of exclusion of or delay in hepatitis C virus therapy in hepatitis C virus-infected patients

The causes of exclusion of or delay in HCV therapy in HCV-infected patients were as follows: obesity with body weight more than 100 kg in 20% of cases; F4 degree of fibrosis in 20% of cases; negative PCR in 20% of cases; improper laboratory results in 13.3% of cases; addiction in 13.3% of cases; pregnancy in 6.7% of cases; and depression with suicidal ideation in 6.7% of cases.

International Classification of Diseases-10 symptom checklist

Clinical psychiatric results

Table 1 shows the results of the ICD-10 checklist of HCV patients (before therapy and including those excluded from therapy) and HBV patients. On comparison, a highly statistically significant difference ($P<0.001$) was found as regards prevalence of psychiatric complications linked to HCV infection, including generalized anxiety disorder (10%) among HCV patients before starting therapy, and mild depression and mixed anxiety and depression (20%) among HCV patients excluded from therapy and among HBV patients (13.3%).

Correlative results

With regard to the relation between liver function test and ICD-10 symptom checklist among HBV patients, a highly statistically significant relation ($P<0.001$) was found between the mean values of AST enzymes and severe depression without psychotic symptoms (65.0000 with SD 0.00000 and $F = 18.5$). There was also a highly statistically significant relation ($P<0.001$) between the mean values of AST enzymes and other mixed anxiety and depression (64.0000 with SD 0.00000 and $F = 18.5$). A highly statistically significant relation ($P<0.001$) was also found between the mean values of ALT enzymes and dysthymia (80.0000 with SD 0.00000 and $F = 30.5$). There was also a highly statistically significant relation ($P<0.001$) between the mean values of AST enzymes and other mixed anxiety and depression (75.0000 with SD 0.00000 and $F = 30.5$).

The following are the results of the relation between the abdominal ultrasound (liver and spleen) and ICD-10 symptom

Table 1 Results of International Classification of Diseases-10 checklist among hepatitis C virus patients (before therapy and including those excluded from therapy) and hepatitis B virus patients

	Groups [*n* (%)]			
ICD-10 checklist	HCV group before HCV therapy	HCV group excluded from HCV therapy	HBV group (control group)	Total [*N* (%)]
No disorder	25 (83.3)	8 (26.7)	10 (33.3)	43 (47.8)
GAD	3 (10.0)	0 (0.0)	0 (0.0)	3 (3.3)
Mild depression	1 (3.3)	6 (20.0)	4 (13.3)	11 (12.2)
Mixed anxiety and depression	1 (3.3)	6 (20.0)	4 (13.3)	11 (12.2)
Other mixed anxiety and depression	0 (0.0)	2 (6.7)	2 (6.7)	4 (4.4)
Somatoform disorder	0 (0.0)	4 (13.3)	0 (0.0)	4 (4.4)
Moderate depression	0 (0.0)	4 (13.3)	2 (6.7)	6 (6.7)
Schizotypal disorder	0 (0.0)	0 (0.0)	2 (6.7)	2 (2.2)
Dysthymia	0 (0.0)	0 (0.0)	2 (6.7)	2 (2.2)
Severe depression without psychotic symptom	0 (0.0)	0 (0.0)	2 (6.7)	2 (2.2)
Panic disorder	0 (0.0)	0 (0.0)	2 (6.7)	2 (2.2)
Total	30 (100.0)	30 (100.0)	30 (100.0)	90 (100.0)

$\chi^2 = 54.9$.
GAD, generalized anxiety disorder; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD, International Classification of Diseases.
$^{**}P<0.001$.

checklist in the HBV group (control group): A highly statistically significant relation was found between the abdominal ultrasound including the liver ($P<0.001$ and $\chi^2=52.4$) and the spleen ($P<0.006$ and $\chi^2=21.3$) and psychiatric disorders according to the ICD-10 symptom checklist among HBV patients, as 100% of patients with mild depression had normal liver and spleen, 50% of patients with mixed anxiety and depression had enlarged liver and spleen, and 100% of patients with severe depression without psychotic symptoms had portal tract thickening and enlarged spleen.

Effect of the duration of treatment among hepatitis C virus patients who received pegylated interferon/ribavirin treatment (30 patients)

Table 2 summarizes the effect of HCV treatment on psychiatric disorders according to the ICD-10 symptom checklist at 4 weeks after starting treatment. It shows that psychiatric disorders increased highly significantly after starting HCV treatment by 4 weeks. The most frequently seen were mild depression (10%) and other mixed anxiety and depression and moderate depression (6.7%), followed by panic disorder (3.3%).

Table 3 summarizes the effect of HCV treatment on psychiatric disorders according to the ICD-10 symptom checklist at 12 weeks after starting HCV treatment. It shows that psychiatric disorders increased highly significantly after HCV treatment by 12 weeks. The most frequent were mixed anxiety and depression (16.7%), moderate depression and severe depression without psychotic features (13.3%).

Table 4 summarizes the effect of HCV treatment on psychiatric disorders according to the ICD-10 checklist at 24 weeks after HCV treatment. It shows that psychiatric disorders highly significantly differ after HCV treatment by 24 weeks. An increase in mild depression (17.2%) and a decrease in severe depression without psychotic features (3.4%) were seen.

Effect of treatment dosage among hepatitis C virus patients who received pegylated interferon/ribavirin treatment (30 patients)

Table 5 shows the correlation between the mean values of ribavirin and IFN doses and ICD-10 symptom checklist in the HCV group 4 weeks after treatment. It shows statistically insignificant correlation between the mean values of ribavirin and IFN doses and psychiatric sequences according to the ICD-10 symptom checklist in the HCV group 4 weeks after starting HCV treatment.

Table 6 shows the correlation between the mean values of ribavirin and IFN doses and the ICD-10 symptom checklist in the HCV group 12 weeks after HCV treatment. It shows statistically insignificant correlation between the mean values of ribavirin and IFN doses and psychiatric complications according to the ICD-10 checklist in the HCV group 12 weeks after treatment.

Table 7 shows the correlation between the mean values of ribavirin and IFN doses and ICD-10 symptom checklist in the HCV group 24 weeks after treatment. It shows a highly statistically significant correlation between the mean values of ribavirin doses and severe depression without psychotic symptoms (mean 1200.0000) 24 weeks after starting HCV treatment.

Discussion

HCV infection is one of the major causes of liver disease in Egypt. There is a high prevalence of liver disease in the Egyptian population, mostly due to chronic infection with HCV. The overall prevalence of antibody to HCV in the general population is around 15–20% [10].

Demographic criteria

The study comprised 29 (32.2%) women and 61 (67.8%) men. Among the women, seven (23.3%) were HCV infected and received HCV treatment, 12 (40%) were HCV infected and excluded from treatment or underwent delayed treatment, and 10 (33.3%) were HBV infected and served as the control group. Among the men, 23 (76.7%) were HCV infected and received HCV treatment, 18 (60%) were HCV infected and excluded from treatment or underwent delayed treatment, and 20 (66.7%) were HBV infected and served as the control group.

The prevalence of HCV infection was significantly higher in the age group of 30–40 years, which is in agreement

Table 2 Effect of hepatitis C virus treatment on psychiatric disorders according to International Classification of Diseases-10 symptom checklist at 4 weeks after treatment

	ICD-10 before treatment [*N* (%)]				
ICD-10 at 4th week after treatment	No disorder	GAD	Mild depression	Mixed anxiety and depression	Total [*N* (%)]
No disorder	20 (80.0)	1 (33.3)	0 (0.0)	0 (0.0)	21 (70.0)
Mild depression	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)
Mixed anxiety and depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (3.3)
Other mixed anxiety and depression	1 (4.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (6.7)
Moderate depression	1 (4.0)	0 (0.0)	1 (100.0)	0 (0.0)	2 (6.7)
Panic disorder	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (3.3)
Total	25 (100.0)	3 (100.0)	1 (100.0)	1 (100.0)	30 (100.0)

$\chi^2=58.1$.
GAD, generalized anxiety disorder; ICD, International Classification of Diseases.
$^{**}P\leq 0.001$.

Table 3 Effect of hepatitis C virus treatment on psychiatric disorders according to International Classification of Diseases-10 symptom checklist at 12 weeks after starting hepatitis C virus treatment

	ICD-10 at 4th weeks after treatment [*n* (%)]						
ICD-10 at 12th weeks after treatment	No disorder	Mild depression	Mixed anxiety and depression	Other mixed anxiety and depression	Moderate depression	Panic disorder	Total [*n* (%)]
No disorder	11 (52.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (36.7)
Mild depression	2 (9.5)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)
Mixed anxiety and depression	4 (19.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (16.7)
Other mixed anxiety and depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (3.3)
Moderate depression	3 (14.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (13.3)
Severe depression without psychotic symptom	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (100.0)	1 (100.0)	4 (13.3)
Panic disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (3.3)
Bipolar affective	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Total	21 (100.0)	3 (100.0)	1 (100.0)	2 (100.0)	2 (100.0)	1 (100.0)	30 (100.0)

$\chi^2 = 63.7$.
ICD, International Classification of Diseases.
$^{**}P = 0.002$.

Table 4 Effect of hepatitis C virus treatment on psychiatric disorders according to International Classification of Diseases-10 symptom checklist at 24 weeks after starting hepatitis C virus treatment

	ICD-10 at 12th week after treatment [*n* (%)]								
ICD-10 at 24th week after treatment	No disorder	Mild depression	Mixed anxiety and depression	Other mixed anxiety and depression	Moderate depression	Severe depression without psychotic symptom	Panic disorder	Bipolar affective	Total
No disorder	10 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	12 (41.4)
Mild depression	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (17.2)
Mixed anxiety and depression	0 (0.0)	1 (33.3)	2 (40.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	5 (17.2)
Other mixed anxiety and depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Moderate depression	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	1 (100.0)	4 (13.8)
Severe depression without psychotic symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (3.4)
Panic disorder	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Total	10 (100.0)	3 (100.0)	5 (100.0)	1 (100.0)	4 (100.0)	4 (100.0)	1 (100.0)	1 (100.0)	29 (100.0)

$\chi^2 = 82$.
ICD, International Classification of Diseases
$^{**}P < 0.001$.

Table 5 Relation between the mean values of ribavirin and interferon doses and International Classification of Diseases-10 checklist in the hepatitis C virus group 4 weeks after treatment

	ICD-10 at 4 week after treatment	*N*	Mean	SD	*F*	*P*
Ribavirin	No disorder	21	1085.7143	101.41851	1.06	0.41
	Mild depression	3	1066.6667	115.47005		
	Mixed anxiety and depression	1	1200.0000			
	Other mixed anxiety and depression	2	900.0000	424.26407		
	Moderate depression	2	1100.0000	141.42136		
	Panic disorder	1	1200.0000			
Interferon	No disorder	21	138.0952	27.45342	0.96	0.46
	Mild depression	3	145.0000	31.22499		
	Mixed anxiety and depression	1	180.0000			
	Other mixed anxiety and depression	2	127.5000	10.60660		
	Moderate depression	2	150.0000	42.42641		
	Panic disorder	1	180.0000			

ICD, International Classification of Diseases.

with studies on the epidemiology of HCV infections. These studies found that the Nile delta region of Egypt had the highest prevalence rate of HCV in the world, with seroprevalence rates of 30–40% in villagers over the age of 30 years [11].

The Egyptian Demographic and Health Survey (EDHS) reported an increase in prevalence with age; prevalence was higher among 50–59-year-olds, and in rural areas compared with urban. The infection rate was modestly higher among men compared with women in areas along the Nile River.

Table 6 Correlation between the mean values of ribavirin and interferon doses and International Classification of Diseases-10 checklist in the hepatitis C virus group 12 weeks after hepatitis C virus treatment

	ICD-10 at 12 week after treatment	*N*	Mean	SD	*F*	*P*
Ribavirin	No disorder	11	1090.9091	186.83975	1.02	0.45
	Mild depression	3	866.6667	230.94011		
	Mixed anxiety and depression	5	1080.0000	109.54451		
	Other mixed anxiety and depression	1	1000.0000			
	Moderate depression	4	1050.0000	100.00000		
	Severe depression without psychotic symptom	4	1150.0000	100.00000		
	Panic disorder	1	1200.0000			
	Bipolar affective	1	1000.0000			
Interferon	No disorder	11	135.9091	32.31240	0.46	0.85
	Mild depression	3	145.0000	31.22499		
	Mixed anxiety and depression	5	138.0000	26.83282		
	Other mixed anxiety and depression	1	120.0000			
	Moderate depression	4	142.5000	28.72281		
	Severe depression without psychotic symptom	4	153.7500	30.92329		
	Panic disorder	1	135.0000			
	Bipolar affective	1	100.0000			

ICD, International Classification of Diseases.

Table 7 Correlation between the mean values of ribavirin and interferon doses and International Classification of Diseases-10 checklist in the hepatitis C virus group 24 weeks after treatment

	ICD-10 at 24 weeks after treatment	*N*	Mean	SD	*F*	*P*
Ribavirin	No disorder	12	1133.3333	98.47319	4.6	0.004**
	Mild depression	5	1000.0000	0.00000		
	Mixed anxiety and depression	5	1040.0000	167.33201		
	Other mixed anxiety and depression	1	600.0000			
	Moderate depression	4	1100.0000	115.47005		
	Severe depression without psychotic symptom	1	1200.0000			
	Panic disorder	1	1000.0000			
Interferon	No disorder	12	143.3333	29.56759	0.33	0.91
	Mild depression	5	150.0000	30.00000		
	Mixed anxiety and depression	5	138.0000	24.64752		
	Other mixed anxiety and depression	1	120.0000			
	Moderate depression	4	145.0000	41.23106		
	Severe depression without psychotic symptom	1	120.0000			
	Panic disorder	1	120.0000			

ICD, International Classification of Diseases.
**Very highly significant.

There is evidence showing that public shaving of beards is a route of acquiring HCV infection, and education programs may help reduce transmission in the future [12].

Several factors that correlate with a lower rate of chronicity have been identified, including younger age at infection and female sex [13].

Prevalence was higher among married people (83.3%), and 65.6% of them were from rural areas. Supporting this result was a study that estimated the incidence of HCV in rural women at 0.5% per year [1]. Rural areas tend to have higher rates than cities and rates in the Nile Delta (lower Egypt) are higher than that in the Nile valley (middle and upper Egypt) [14–16].

Hepatitis was insignificantly prevalent among individuals with secondary educational (40%), followed by illiterate and highly educated (equal distribution of 24.4%). The highest prevalence of hepatitis was seen among laborers and housewives (62.2%), as they have less knowledge about hygiene and how to avoid infection and were at high risk for Schistosoma. Prevalence was equal among governmental and nongovernmental employees.

Seroprevalence of anti-HCV was reported to be 12.1% among rural primary schoolchildren, 18.1% among residents of rural villages, and 22% among army recruits [17].

An overall 61.1% of patients had an unknown source of infection, perhaps from living in a house with an infected family member. This result came in accordance with another study that showed that ~70% of acquired infections are due to unidentified risk factors [18].

Other risk factors included history of frequent visits to dentists (12.2%), blood transfusion (10%), history of an operation (8.9%) which reflect the need for hygiene during invasive medical, dental or paramedics procedures which documented nosocomical transmission such as during surgery [19]. A high prevalence of antibodies to HCV (anti-HCV) has been found among Egyptian blood donors (10–28%) [16].

Data suggest that certain sexual behaviors and HIV coinfection are factors that increase the transmission of HCV by sexual contact [20]. In our study we found that 7.8% of partners had the same illness.

The most common risk factors for transmission are drug use and sexual behaviors related to drug use. The factors most strongly associated with infection are injection-drug use and receipt of a blood transfusion before 1990, but in some cases no risk factors could be identified [21].

Poverty, high-risk sexual behavior, having less than 12 years of education, and having been divorced or separated

are linked to an increased risk for infection, but the reasons for some of these associations remain unclear [22].

Egypt has one of the highest HCV prevalence rates in the world (nearly 15% of the population). Continued prevalence in Egypt has been associated with transfusion of unscreened blood, invasive medical procedures including surgical operations, hemodialysis, and injections by unprofessional healthcare providers [23].

Results show that 32.2% of the studied patients had Bilharziasis. The risk factor for HCV transmission that specifically sets Egypt apart from other countries is a personal history of parenteral antischistosomal therapy (PAT). Eighty percent of those contaminated by HCV continue to have the virus chronically, although they remain asymptomatic for many years [10]. A history of PAT, discontinued only in the 1980s, has been previously implicated as a risk factor for HCV and HBV antibody positivity. Egypt's mass campaigns for PAT may represent the world's largest iatrogenic transmission of blood-borne pathogens [10,24].

The very high prevalence of HCV infection has been traced back to the mass campaigns to treat schistosomiasis before 1980 with repeated intravenous injections of tartar emetic (potassium antimony tartrate) without following rigorous hygiene standards [23].

With respect to past history of psychiatric disorders we found that 56.7% of infected patients did not have pre-existing psychiatric disturbances and 94.4% did not have a family history of psychiatric disorder, which was statistically insignificant.

Patients with pre-existing psychiatric disturbances do not appear to have a greater risk for development of depression or for suicidal attempts [25–27].

Other studies found that previous history of depressive disorder did not predict the development of depression symptoms [28,29]; other retrospective studies found that a history of psychiatric illness was associated with psychiatric disorder during treatment [30].

Nonetheless, some studies confirm that up to 30% of patients with pre-existing psychiatric illness can complete their IFN treatment course without any significant worsening of their psychiatric symptoms [31,32].

International Classification of Diseases-10 checklist

In this study, we highlighted the effects of HCV treatment on patients. Thirty HCV patients were enrolled to receive HCV treatment in the form of combined peg-IFN-α2b (100 g once weekly) with ribavirin (800–1000 mg/day) based on body weight (<70 or >70 kg).

It was found that the most common pre-existing psychiatric disorder was generalized anxiety disorder, affecting 10% of patients upon diagnosis or before starting any therapy (Table 1). This finding may be related to the patient awareness of the diagnosis and prognosis, to side effects induced by IFN-α treatment, fear and anxiety of the illness, anxiety about transmitting infection to others, and the possibility of future complications and death. Psychiatric complications increased highly significantly after treatment by 4 weeks as 10% of patients developed mild depression and 6.7% developed other mixed anxiety and depression and moderate depression, followed by mixed anxiety and depression and panic disorder (3.3%) (Table 2). This coincided with the results of two prospective studies, which reported an increase in anxiety symptoms over time during IFN treatment [33,34]; however, another reported a reduction in the number of patients with anxiety [35].

IFN is a potent inducer of proinflammatory cytokines. Cytokines cause a variety of changes in the brain and abnormalities in the hypothalamic–pituitary axis, neurotransmitter systems, or other mechanisms that lead to symptoms similar to major depression (anhedonia, reduced activity, restlessness, hyperalgesia, altered sleep, altered appetite, and poor memory) [36].

In the 12th week we reported a wide range of highly significant psychiatric consequences, including, in the order of frequency, mixed anxiety and depression (16.7%), moderate depression and severe depression without psychotic features (13.3%), and bipolar disorder (3.3%) (Table 3). These results matched with those of a recent prospective cohort study that found that, although only 11% of patients treated with peg-IFN/ribavirin met the criteria for major depression, more than one-third developed symptoms of moderate to severe depression during treatment [37].

Anxiety occurs in 30–45% especially during the first 2 months of treatment. Mild depression with symptoms like reduced self-esteem, anhedonia, loss of interest, rumination, a diminished libido, and spontaneous crying can be observed in 30–60% of patients, with 20–30% of treated patients developing moderate to severe depressive episodes [37–41].

In another study a structured interview was also used, and very high rates of IFN-major depressive disorder (62.9%) were found [42].

Case reports document that mania and psychosis occur in small numbers of IFN-treated patients, but no prospective studies have assessed their incidence in individuals with psychiatric disorders [33,43].

We also found highly significant psychiatric disorders after HCV treatment by 24 weeks. An increase in mild depression was seen in 17.2% of patients and decrease in severe depression without psychotic features was seen in 3.4% (Table 4). This may be due to a change in the dose of ribavirin at this time, as we identified a dose-related association between peg-IFN/ribavirin treatment and psychiatric disorders and a highly significant correlation between ribavirin dose with severe depression without psychotic symptoms at 24 weeks after treatment (Table 7).

Theoretically, ribavirin may have contributed to psychiatric side effects; however, another study observed no additional effect of comedication with ribavirin on psychiatric symptoms in patients treated for hepatitis C [44].

Higher doses and longer length of IFN treatment lead to worse mood problems [45]. However, we found good tolerability to IFN treatment in 70% of patients in the 4th week (Table 2), in 36.7% in the 12th week (Table 3) and in 11.4% of patients in the 24th week (Table 4). We found low rates of treatment discontinuation in psychiatric patients as only one case dropped out due to PCR positivity after 24 weeks.

The causal relationship between IFN-α administration and occurrence of mood disorders has been tackled by various research works focusing on the importance of the immune system in the pathophysiology of depression [5].

The action of IFN-α on the neuroendocrine system and on neuromodulating functions is based on the following hypotheses: the monoaminergic hypothesis – cytokines could have an influence on the mood through their modulating role on the serotoninergic system. IFN-α treatment is reported to produce (i) a decrease in tryptophan availability for serotonin synthesis, (ii) a decrease in the 5-hydroxy indole acetic acid level in the Locus control region and (iii) a modification of the central serotoninergic receptors. Moreover, selective inhibitors of serotonin transporters are effective in the treatment or prevention of depression caused by IFN-α [5].

As regards the serotonin -transporter hypothesis : in vivo, both INF- alpha and interleukin -4 increase the expression of serotonin transporter gene and INF-alpha increases the production of interleukin -4 by mononuclear cells which are not found in vivo. The serotoninergic system can also be altered by a peripheral action of IFN-α on tryptophan catabolism by activating a concurrent pathway (known as 'kynurenine pathway') to serotonin synthesis. Finally, serotonin-mediated vulnerability to the psychobehavioral effects of IFN-α could be due to a polymorphism of the serotonin transporter gene [46].

Concerning the other monoaminergic systems, IFN-α seems to have an amphetamine-like effect at its first administration, followed by a decrease in dopaminergic tone with chronic administration. Dopaminergic depletion, subsequent to psychostimulant abuse for instance, results in severe depressive syndromes. Interactions between IFN-α and the noradrenergic system have also been reported [5].

The neuroendocrinal hypothesis – when administered in a central or peripheral manner, IFN-α simulates/inhibits the corticotropin axis and alters the endorphin system as shown by the induction of analgesia, catatonia, and behavioral slowdown, which can be suppressed by opioid antagonists. IFN-α neurotoxin effects are successfully treated by naltrexone [47].

Finally, IFN-α is known to cause disorders in thyroid function that are likely to contribute to the production or aggravation of mood disorders [5].

From the second group in our study – namely, patients with delayed therapy or excluded from HCV therapy – four patients were excluded because of addiction, because patients with intravenous drug histories seem more likely to discontinue treatment in the first 3 months compared with controls [26,48].

Two patients were excluded because of depression or suicide attempts because a history of major depression or suicide attempts is considered a contraindication for IFN-based therapy. However, treatment of patients with pre-existing psychiatric disorders can be initiated in close collaboration with an experienced psychiatrist in a well-controlled setting [49].

In six patients delayed therapy was due to increase in body weight to more than 100 kg, in six patients because of high degree of fibrosis (F4), and in six patients because of PCR positivity (four of them had improper lab results and two were pregnant).

Psychiatric disorders were common in patients suffering from hepatitis C whom were excluded from interferon therapy, 20% of those patients snowed mild depression and another 20% showed mixed anxiety and depression. Moderate depression and somatoform disorders were presented by 13.3% for each group (Table 1) independent of treatment with IFN-α and is not influenced by substance or alcohol abuse but may be related to the patient awareness of the diagnosis and prognosis [50,51], and exclusion of patient from therapy or delayed starting treatment may also be contributing factors.

Depression was one of the most common diagnoses in our HCV patients, as seen in other studies [52,53].

A high prevalence of depressive and anxiety symptoms has been reported by several studies, which found that the prevalence of depressed mood or depression scores were not different between treated and untreated patients [33,53].

The presence of antinuclear antibodies was associated with a more severe degree of depression. These results support the hypothesis that an HCV-driven cellular immune response, rather than HCV itself, plays an important role in the pathogenesis of depression [54].

On comparing patients with mild chronic hepatitis C with patients suffering from chronic hepatitis B has lead to the hypothesis of a direct effect of HCV on brain functions [55,56].

Panic disorder was reported in patients with HCV who received treatment (Tables 2–4). It was also reported in patients with HBV (6.7%) (Table 1). This finding suggests that anxiety disorders are not a specific consequence of HCV, but rather reflect the stress associated with awareness of the chronic progressive nature of these diseases and the nature of interventions needed for their treatment.

Also mild depression and mixed anxiety and depression affected 13.3% of patients each, followed by other mixed anxiety and depression, moderate depression, schizotypal disorder, dysthymia, and severe depression without psychotic symptoms, each affecting 6.7% of patients in the HBV group (Table 1).

Depression is considered the most common psychiatric side effect of IFN therapy and has been reported in patients with HBV, HCV, and malignant melanoma who

were treated with IFN. Serious disturbances have led to suicidal behavior or death in some cases [57].

With respect to the relation between liver function test and ICD-10 symptom checklist among HBV patients, a highly statistically significant relation was found between the mean values of AST enzymes and severe depression without psychotic symptoms. There is also a highly statistically significant relation between the mean values of AST enzymes and other mixed anxiety and depression. Results also show that there is a highly statistically significant relation between the mean values of ALT enzymes and dysthymia. There is also a highly statistically significant relation between the mean values of AST enzymes and other mixed anxiety and depression.

With respect to the relation between the abdominal ultrasound of the liver and spleen and ICD-10 symptom checklist in the HBV group, a highly statistically significant relation was found between the abdominal ultrasound of the liver and spleen and psychiatric disorders according to the ICD-10 symptom checklist among HBV patients, as 100% of patients with mild depression had a normal liver and spleen, 50% of patients with mixed anxiety and depression had an enlarged liver and spleen, and 100% of patients with severe depression without psychotic symptoms had portal tract thickening and enlarged spleen.

These findings come close to the findings of HCV and they show the importance of HBV as a research topic in future studies.

Conclusion and recommendations

We described a wide range of psychiatric disorders linked to HCV infection before starting treatment which included generalized anxiety disorder. Psychiatric disorders increased after receiving treatment and this group included mixed anxiety and depression and moderate depression. HCV infected patients regardless of IFN therapy and HBV infected patients also showed mild depression and mixed anxiety and depression.

As the HCV epidemic in Egypt is unique and well documented in the international medical scientific literature, HCV-related psychiatric consequences and HCV therapy-related psychiatric complications should be included in the differential diagnosis of patients, and patients should be assessed through consultation liaison psychiatry.

Conflicts of interest

There are no conflicts of interest.

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