# Cognitive Function in Hepatitis C Patients: Effect of Pegylated Interferon α and Ribavirin Therapy

**Marwa A Meguid and Mohamed Moussa**

Institute of Psychiatry, Internal Medicine and Hematology Department, Faculty of Medicine, Ain Shams University

## ABSTRACT

| | |
|---|---|
| **Introduction:** | Hepatitis C virus (HCV) represents the second most common blood-borne illness in the world, affecting up to 2% of the world's population. Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% with an average of 13.8%. Nowadays, combination therapy with Pegylated IFNα plus ribavirin (peg-IFNα/RBV) is the first-choice treatment for chronic hepatitis C (CHC). Cognitive impairment, or difficulty with thinking, has been well documented in persons with chronic liver disease. Clinical trials have identified several side effects of interferon-alpha (IFNα) therapy, including flu-like symptoms and depression. Some investigators have described cognitive symptoms such as impairments in memory and executive functions. |
| **Aim of the Study:** | Is to detect cognitive dysfunction in patients with HCV treated with peg-IFNα/RBV therapy. |
| **Subjects and Methods:** | Sixty Male and female patients from Ain Shams University Hospital with age ranging from 18-60 years old diagnosed as Hepatitis C by PCR with moderate viremia and having normal thyroid profile were recruited in this study after obtaining verbal consent following explanation of study protocol 40 patients were treated with peg-IFNα/RBV (Group A) nevertheless, 10 patients dropped out for different reasons, so group A actually included 30 patients. On the other hand, the remaining 20 patients were not receiving the same treatment due to lack of funding from their health Insurance System (Group B). On the 24th week of peg-IFNα/RBV therapy, all patients underwent laboratory investigations, abdominal ultrasonography, neuropsychological assessment including Wechsler Adult Intelligence scale, Wechsler Memory Scale–Revised (WMS-R) and Benton Visual retention Test. Patients were also interviewed using the Beck Depression Inventory (BDI), patients scoring more than 10 in BDI were excluded to eliminate the impact of depressive symptomatology on cognitive function. Hence the final sample was. |
| **Results:** | As adverse effect of administration of Peg Interferon, leucopenia, mild normocytic normochromic anemia and mild increase in the liver function were found in group A. Mean total IQ, Performance IQ and Verbal IQ scores were found to be less in patients group with a significant statistical difference between both groups (p=0.017) regarding total scores and performance scores had a high statistical significant difference (p=0.005) between groups. Highly statistical significant difference (p=0.000) was found between both groups regarding perception and long term memory as assessed by picture completion, and a high statistical significant difference (p=0.037) was found between both groups regarding Visuo-motor coordination as assessed by Block design. However sustained attention as measured by Digit symbol was not different statistically despite that patients on Interferon were scoring less in this test. On the other hand, abstract thinking as measured by similarities has been found to be affected having a significant statistical difference (p=0.013) between both groups as measured by Similarities testing. |
| **Conclusion:** | Cognitive Dysfunction is found to be a common problem in Hepatitis C patients and is found to be aggravated during treatment with Pegylated Interferon. These findings draw clinicians' attention to the importance of cognitive functions assessment in all hepatitis C patients at time of diagnosis and regular follow up is needed to detect mild cognitive impairment to allow early intervention to reduce the severity of cognitive dysfunction. |
| **key words:** | Cognitive dysfunction, hepatitis C infection, pegylated Interferon α, ribavirin. |

## INTRODUCTION

Hepatitis C virus (HCV) represents the second most common blood-borne illness in the world, affecting up to 2% of the world's population[1]. One hundred to 300 million people world-wide are estimated to be infected with HCV. Seventy-five percent will develop chronic infection and at least 15–20% of these individuals will eventually develop cirrhosis and are at risk of developing complications of end stage liver disease[2].

Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% with an average of 13.8%. In populations of blood transfusion recipients over the age of 30, HCV has been reported as high as 73% and in the general population aged 40–60 years it was estimated as high as 55%[3].

Interferon-α (IFNα) is a natural glycoprotein that exhibits antiviral, antiproliferative and immunomodulatory properties. The introduction of combination therapy, with IFNα injected subcutaneously three times a week and ribavirin given orally, was a major advancement in HCV therapy that allowed Sustained virologic response to be achieved in 40% of previously untreated patients[4].

Pegylated interferons (peg-IFNs) are a conventional IFNs modified by conjunction with a 12-kDa (peg-IFNα 2b) or a 40-kDa (peg-IFNα 2a) polyethylene glycol molecule. The process of pegylation leads to increases in IFNs' molecular weight and plasma half-life and allows once-a-week dosing. Nowadays, combination therapy with Pegylated IFNα plus ribavirin (peg-IFNα/RBV) is the first-choice treatment for chronic hepatitis C (CHC)[4].

Cognitive impairment or difficulty with thinking has been well documented in persons with chronic liver disease. Early in the disease process, patients with HCV report symptoms that include fatigue, malaise, weakness, anorexia and occasionally, jaundice. Also prominent among patients with HCV are complaints of problems with thinking that have been described as "brain fog" or problems with attending to and recalling everyday information[5]. It has been proposed that cognitive dysfunction associated with HCV is due to the virus itself infecting the brain[6].

Clinical trials have identified several side effects of interferon-alpha (IFNα) therapy, including flu-like symptoms and depression. Some investigators have described cognitive symptoms such as impairments in memory and executive functions, while others have found no evidence of cognitive decline. Differences in assessment techniques, treatment variables and risk factors associated with different patient populations may have contributed to these discrepant findings[7].

Several physiological mechanisms have been proposed for the neurotoxic effects of IFNα, including actions mediated through neuroendocrine, neurotransmitter and cytokine pathways. IFNα has structural and functional similarities to adrenocorticotropic hormone and alterations in endocrine function may contribute to the somatic and mood symptoms of IFNα toxicity. There is some evidence for its action on β-endorphin and dopamine as well and the cognitive and behavioral symptoms of chronic IFNα administration have been compared to Parkinson's disease[7].

Diffuse slowing on quantitative EEG and reduced performances was reported on a cognitive screening measure after 2 and 4 weeks of IFN-a therapy which reversed after the end of treatment[8].

## SUBJECTS AND METHODS

The studied sample was collected from outpatient clinic of Hepatology Department, Ain Shams University Hospitals. 60 adult patients diagnosed as Hepatitis C by PCR with a result of moderate viremia were recruited. 40 patients were prescribed Peg-IFNα/RBV, however the remaining 20 patients were not receiving the same treatment due to lack of funding from their health Insurance System.

All subjects were interviewed at the 24th week of Peg-IFNα/RBV therapy (at the 24Th week of therapy complete medical work up was performed as well PCR was redone to ensure responsiveness to Pegylated Interferon–α therapy). After receiving an oral informed consent, all patients were interviewed using the Beck Depression Inventory (BDI). Patients scoring more than 10 in BDI were excluded to eliminate the impact of depressive symptomatology on cognitive function.

**Patients were then divided in two groups:**

Group A: Includes 40 patients who received Peg-IFNα/RBV therapy. They were interviewed at the 24th week of therapy using the BDI; 7 patients among them were scoring more than 10 and were excluded from the study and 3 patients refused to undergo assessment. So, group A finally included 30 patients.

Group B: This group included 20 patients with positive PCR results for HCV "moderate viremia" but not receiving Peg-IFNα/RBV therapy. Also those patients were interviewed using the BDI and scored less than 10.

The patients were selected according to the following inclusion criteria: Adult male and female patients were included, with age ranging from 18-60 years old, which is the recommended age range for Interferon therapy. Also patients should have normal thyroid profile.

On the other hand patients below 18 or above 60 years of age were excluded as well illiterate subjects. Patients with medical or psychiatric comorbidities, or history of substance abuse and head trauma were excluded in order to exclude

effect of comorbid conditions on cognitive function.

Group A patients were assessed at the 24th week of treatment with Peg-IFNα/RBV. At the same time Group B patients were also assessed using the following:

1. Laboratory investigations: Complete blood picture, Liver function tests, Kidney function test and Thyroid profile.

2. Abdominal ultrasonography.

3. Neuropsychological assessment:

- Wechsler Adult Intelligence Scale (WAIS) is the most commonly administered general intelligence test for adults and is also viewed as a broad assessment of cognitive functions. It is an individually administered measure of intelligence, intended for adults aged 16–89. It is the best standard and most widely used intelligence test in clinical practice today and is intended to measure human intelligence reflected in both verbal and performance abilities[9]. The Arabic Version by Louis Kamel Melika (1996) was used in this study[10]. It is formed of 11 subscales: Six verbal subscales and 5 performance subscales.

- Wechsler Memory Scale–Revised (WMS-R) to assess verbal and nonverbal memory abilities. It is an individually administered, clinical instrument for appraising major dimensions of memory function in adolescents and adults. The scale is intended as a diagnostic screening device for use as part of a general neuropsychological examination, or any other clinical examination requiring the assessment of memory functions. The functions assessed include memory for verbal and figural stimuli, meaningful and abstract material and delayed as well as immediate recall[11].

- Benton Visual retention Test is an individually administered test that measures visual perception and visual memory[12]. Benton Visual retention test had been translated to Arabic and validated previously[13].

**Statistical method:**

SPSS statistical package for social sciences (V.15) was used for data analysis. The methods used for statistical analysis were the following:

- Comparison between 2 independent mean groups for parametric data using Student t-test.
- Comparison between 2 related samples using Paired t-test.
- Comparison between more than 2 patient groups for parametric data using Analysis of variance (ANOVA).
- Correlation between 2 variable groups using Pearson correlation coefficient.

## RESULTS

The mean age of the studied group was 30.33±7.41 in group A and 28.80±4.25 in group B.

Table 1 shows the medical profile of the studied sample obtained from the laboratory investigations done at the 24th week of Peg-IFNα/RBV therapy for group A and done simultaneously for group B.

**Table 1:** Laboratory profile of the studied group.

| | Mean±SD | | t-test | p-value |
|---|---|---|---|---|
| | Group A | Group B | | |
| Hb | 12.32±1.38 | 13.11±0.58 | 4.268 | 0.000 VHS |
| TLC | 3.77±1.82 | 5.76±0.69 | 5.469 | 0.000 VHS |
| Platelet Count | 178.4±38.18 | 164.4±24 | 1.591 | 0.118 NS |
| TSH | 1.65±0.52 | 1.77±0.41 | -3.367 | 0.137 NS |
| Free T3 | 68±11.8 | 66.5±6.126 | 0.587 | 0.56 NS |
| Free T4 | 69.87±11.62 | 74.1±7.3 | -1.581 | 0.121 NS |
| ALT | 46.4±22.30 | 35.1±7.54 | 2.564 | 0.014 Sig. |
| AST | 41.67±17.07 | 30.9±7.9 | 2.632 | 0.011 Sig. |
| Creatinine | 0.81±0.1669 | 0.75±0.20 | 3.032 | 0.101 NS |

Leucopenia, mild normocytic normochromic anemia and mild increase in the liver function were found in patients group as effect of Peg Interferon use.

**Descriptive Analysis of Neurocognitive function:**

All patients (Group A and Group B) recruited in the study completed neuropsychological test including WAIS, WMS-R and Benton Visual retention test at the 24th week of Pegylated Interferon therapy. Mean total IQ, Performance IQ and Verbal IQ scores were found to be lower in group A with a significant statistical difference between both groups (p=0.017). Regarding total scores and performance scores high statistical significant difference (p=0.005) between groups has been found.

Assessment of recent and short term memory using the Associate learning subscale of the WMS-R revealed that group A patients were scored less than group B with a very high statistical significant difference (p=0.000) between both

groups indicating recent and short term memory impairment. Regarding long term memory, group A were scored less than group B with a statistical significant difference in information subscale of WMS-R (p=0.043) and a very high significant statistical difference (p=0.000) was found when assessed using the picture completion subscale of WAIS. However no significant statistical difference was found between both groups in immediate memory assessment by digit span subscale of WAIS.

On the other hand, the high statistical difference found between both groups regarding performance IQ (p=0.005) indicates impairment of perceptual organization which is assessed by various subscales of WAIS including picture

completion subscale measuring perception and long term memory (p=0.000), block design measuring visuomotor coordination (p=0.037) and processing function as measured by digit symbol for sustained attention assessment (p=0.058).

Assessment of concentration by the mental control subscale of WAIS revealed a high statistical significant difference (p=0.002) between both groups with lower scores in group A.

On the other hand, abstract thinking as measured by similarities in WAIS has been found to be impaired with a significant statistical difference (p=0.013) between both groups.

**Table 2:** Statistical Analysis of WAIS-R.

| WAIS-R | Domain of assessment | Mean±SD | | t-test | p-value |
| | | Group A | Group B | | |
|---|---|---|---|---|---|
| **TIQ** | | 99.4±8.43 | 104±4.58 | -2.486 | 0.017 Sig |
| **PIQ** | Perceptual organization and Processing | 100.2±9.43 | 106.1±4.55 | -2.949 | 0.005 H.S |
| **Picture Completion** | Perception and Long term memory | 8.33±1.64 | 11.6±1.84 | -6.545 | 0.000 VHS |
| **Block Design** | Visuo-motor Coordination | 8.47±1.52 | 9.6±2.21 | -2.149 | 0.037 Sig. |
| **Digit Symbol** | Sustained Attention | 10.73±2.5 | 11.1±1.97 | -0.550 | 0.585 NS |
| **VIQ** | Verbal Comprehension and Working Memory | 99.93±10,7 | 101.9±6.16 | -0.742 | 0.462 NS |
| **Comprehension** | Judgment and social Common Sense | 12.07±1.79 | 11.9±2.91 | 0.250 | 0.804 NS |
| **Similarities** | Abstract Thinking | 9.13±1.47 | 10.6±2.16 | -2.649 | 0.013 Sig. |
| **Digit Span** | Immediate Memory | 7.8±2.44 | 8.9±2.02 | -1.668 | 0.102 NS |
| **Arithmetic** | Concentration and Arithmetic Abilities | 8.8±2.63 | 8.4±2.3 | 0.553 | 0.583 NS |

**Table 3:** Statistical Analysis of WMS-R.

| WMS | Domain of assessment | Group A | Group B | t-test | p-value |
|---|---|---|---|---|---|
| **Ass. Learning** | Recent memory and Short term memory | 8.6±1.88 | 11.4±2.16 | -4.850 | 0.000 VHS |
| **Information** | Long term memory | 5.73±0.69 | 6±0 | -2.112 | 0.043 Sig. |
| **Mental Control** | Concentration | 5.07±1.59 | 6.2±0.76 | -3.351 | 0.002 HS |
| **Orientation** | Orientation | 5.87±0.5 | 6±0 | -1.439 | 0.161 NS |

**Regarding Benton Visual Retention test (BVRT):** Assessment of recruited patients for visual memory using the BVRT revealed that 64% of group A and 60% of group B had a difference scores >4 between the obtained error

and expected error with no significant statistical difference between both groups, however results suggested that there is visual memory impairment in both patients receiving and not receiving Peg-IFNα/RBV.

**Table 4:** Correlation of Benton Visual retention Test results to both groups.

|  | Group A | | Group B | |
|---|---|---|---|---|
|  | N | % | N | % |
| **Obtained Error Scores / Expected error scores <4** | 22 | 64% | 12 | 60% |
| **Obtained Correct Scores / Obtained correct scores <4** | 14 | 46.6% | 16 | 53.33% |

Test used: Chi square
P>0.05 Non significant

## DISCUSSION

The aim of this study was to compare cognitive dysfunction in HCV patients receiving Peg-IFNα/RBV versus patients who did not receive it. Several studies on CHC patients proved the occurrence of cognitive dysfunction in non cirrhotic patients, also studies on patients receiving Interferon for various medical conditions were found to have cognitive dysfunction.

In this study, cognitive function had been assessed in HCV patients who are receiving Peg-IFNα/RBV and those who are not receiving to compare the effect of treatment and its impact on cognitive function.

Our finding of leucopenia and normocytic anemia in group A patient as direct effect of Peg-IFNα/RBV treatment was previously reported[14].

Also we found significant increase in ALT and AST in group A. The same results were reached in previous study on an Egyptian sample[15].

As the study aimed to assess cognitive function, eliminating effect of depression which occurs with Interferon therapy was essential. At time of assessment, after 24 weeks of starting Interferon therapy, 7 patients (17.5%) out of 40 receiving interferon scored >10 on BDI indicating the presence of depressive symptomatology and were excluded from the study. Several studies were done to detect depression in patients receiving Interferon The effect of IFN-α treatment was studied on the development of depression in patients with chronic hepatitis concluding that depressive symptoms increased during IFN-α treatment compared to baseline conditions without interferon[16]. Another study observed a rise in depressive symptoms during IFN-α treatment compared with matched controls[17]. It was also reported in 20% of patients included in similar study[18]. In another study depression appeared even more frequently: fourty three % of the patients developed depression during the treatment between week 7 and 20 and 3% developed suicidal thoughts[19].

Patients receiving Peg-IFNα/RBV scored less in all aspects of neurocognitive function studied. We observed a reduction in verbal scores and performance scores as well. These findings were going in accordance with previous study which found reduction in verbal and performance WAIS scores in HCV patients compared to healthy volunteers[20].

Various studies were performed to assess the degree of memory impairment in patients with CHC and those treated with Pegylated Interferon. Despite methodological differences and the use of different cognitive batteries for assessment, similar domains of cognitive function were assessed. In our study memory function namely short, recent and long term memory were affected more in patients receiving Peg-IFNα/RBV. Short term memory impairment was found in patients with CHC in an Egyptian sample[21]. Memory function were assessed using auditory verbal learning test and controlled oral word association test revealing worsening of immediate recall and word fluency[18]. Also cognitive performance was assessed using interviews on problems with memory, attention and concentration and revealed that 30% of patients complained of cognitive disturbances[22]. Immediate recall, short term memory and working memory were affected in most patients with chronic hepatitis after 3 months of low-dose treatment with IFN. Moreover, prolonged cognitive disturbances and difficulties in memory can be observed during 12 weeks after discontinuation of treatment in patients treated with Pegylated interferons[18]. In addition alteration in verbal recall and working memory was reported[23].

Significant impairment of concentration in this group of patients who received INF has been found. Findings reported in other studies showed that attention and concentration were the earliest affected tasks in the course of chronic liver disease in non cirrhotic patients[24]. Also impaired concentration, decreased alertness and worsening of verbal memory were previously reported[25]. Reduced alertness and psychomotor slowness have been reported after only a single dose of IFN in healthy volunteers[22].

These findings were going in accordance with previous studies examining cognitive function in CHC patients receiving Pegylated Interferon and patients receiving INF therapy for other medical conditions like cancer patients. Another study performed on patients receiving Pegylated Interferon revealed that psychomotor speed, visual search and sequencing, shifting, selective attention were affected[25].

In this study, it was observed that visuomotor coordination was impaired as assessed by block design subscales of WAIS. Our results regarding the visuoconstructive abilities measured by Benton visual retention test was going in accordance with previous study which found that visuoconstructive abilities are unaffected[25], same results had been previously reported[21,24].

## CONCLUSION

Cognitive Dysfunction is found to be a common problem in HCV patients and is found to be aggravated during treatment with Pegylated Interferon. These findings draw clinicians' attention to the importance of cognitive functions assessment in all HCV patients at time of diagnosis and regular follow up is needed to detect mild cognitive impairment to allow early intervention to reduce the severity of cognitive dysfunction. On the other hand, assessment of cognitive function is mandatory in those receiving Interferon therapy before starting treatment and follow up during the course of therapy is needed. Further studies are needed to get sufficient knowledge about cognitive function after the end of Interferon therapy.

## REFERENCES

1. Shepard CW, Finelli L and Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect.Dis. 2005 Sep;5(9):558-67.

2. Alter MJ. Epidemiology of hepatitis C. Hepatology 1997 Sep;26(3 Suppl 1):62S-5S.

3. El Sharkawi FZ, Chudy M, Hanschmann K-M, Kress J and Nübling CM. Consistency of quantitation of HCV genotype 4 from Egypt across three HCV-RNA amplification assays. Journal of Medical Virology 2008;80(12):2086-91.

4. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 2001 Sep 22;358(9286):958-65.

5. Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology 2002 Feb;35(2):433-9.

6. Forton DM, Allsop JM, Cox IJ, Hamilton G, Wesnes K, Thomas HC, et al. A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection. AIDS 2005 Oct;19 Suppl 3:S53-63.

7. Scheibel RS, Valentine AD, O'Brien S and Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. Journal of Neuropsychiatry and Clinical Neurosciences 2004;16(2):185-91.

8. Kamei S, Sakai T, Matsuura M, Tanaka N, Kojima T, Arakawa Y, et al. Alterations of quantitative EEG and Mini-Mental State Examination in interferon-α-treated hepatitis C. European Neurology 2002;48(2):102-7.

9. Wechsler D. WAIS-R: Manual : Wechsler Adult Intelligence Scale--Revised. Harcourt Brace Jovanovich [for] Psychological Corporation; 1981.

10. Melika LK. The Wechsler Adult Intelligence Scale. Dar EL Nahda El Arabia; 1996.

11. Wechsler D. WMS-R: Wechsler Memory Scale--Revised manual. Psychological Corp. Harcourt Brace Jovanovich; 1996.

12. Benton A. Benton revised visual retention test. Psychological Corporation; 1974.

13. Amir T. Benton visual retention test: Arabic translation. Kuwait: Dar Al-Kalm; 1989.

14. Gheorghe L, Grigorescu M, Iacob S, Damian D, Gheorghe C, Iacob R, et al. Effectiveness and tolerability of pegylated interferon alpha-2a and ribavirin combination therapy in Romanian patients with chronic hepatitis C: From clinical trials to clinical practice. Romanian Journal Gastroenterology 2005;14(2):109-15.

15. Sharaf Eldin N, Ismail S, Mansour H, Rekacewicz C, El-Houssinie M, El-Kafrawy S, et al. Symptomatic acute hepatitis C in Egypt: Diagnosis, spontaneous viral clearance and delayed treatment with 12 weeks of pegylated interferon alfa-2a. PLoS ONE 2008;3(12):e4085.

16. Weissenborn K, Krause J, Bokemeyer M, Hecker H, Schüler A, Ennen JC, et al. Hepatitis C virus infection affects the brain - evidence from psychometric studies and magnetic resonance spectroscopy. Journal of Hepatology 2004;41(5):845-51.

17. Malaguarnera M, Di Fazio I, Restuccia S, Pistone G, Ferlito L and Rampello L. Interferon alpha-induced depression in chronic hepatitis C patients: Comparison between different types of interferon alpha. Neuropsychobiology 1998;37(2):93-7.

18. Lieb K, Engelbrecht MA, Gut O, Fiebich BL, Bauer J, Janssen G, et al. Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): Results from a prospective study. Eur.Psychiatry 2006 Apr; 21(3):204-10.

19. McDonald EM, Mann AH and Thomas HC. Interferons as mediators of psychiatric morbidity. An investigation in a trial of recombinant alpha-interferon in hepatitis-B carriers. Lancet 1987 Nov 21;2(8569):1175-8.

20. Miyaoka H, Otsubo T, Kamijima K, Ishii M, Onuki M and Mitamura K. Depression from interferon therapy in patients with hepatitis C. Am.J.Psychiatry 1999 Jul;156(7):1120.

21. Nassef AM, Zaki-El-Din H, Abdel-Sameia AM, Barakat EM, Genidi E, Hamdi K, et al. Cognitive dysfunction in patients with chronic hepatitis C. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery 2008;45(1):251-67.

22. Reichenberg A, Gorman JM and Dieterich DT. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: A 72 week prospective study. AIDS 2005 Oct;19 Suppl 3:S174-8.

23. Fontana RJ, Bieliauskas LA, Back Madruga C, Lindsay KL, Kronfol Z, Lok AS, et al. Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. J.Hepatol. 2005 Oct;43(4):614-22.

24. Hilsabeck RC, Perry W and Hassanein TI. Neuropsychological impairment in patients with chronic hepatitis C. Hepatology 2002 Feb;35(2):440-6.

25. Pawelczyk T, Pawelczyk A, Strzelecki D and Rabe-Jablonska J. Pegylated interferon α and ribavirin therapy may induce working memory disturbances in chronic hepatitis C patients. General Hospital Psychiatry 2008;30(6):501-8.

### Corresponding Author:

Marwa Meguid
Address: Institute of Psychiatry, Ain Shams University Cairo, Egypt.
**E-mail:** marwameguid@hotmail.com
**Mob:** 002 0105752536