

A Persistent Dementia-like Condition Following Treatment of Hepatitis C With Pegylated Interferon and Ribavirin

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Hepatitis C virus (HCV) is a viral illness that affects 1.8% of the US population. HCV becomes a chronic illness in the majority of exposures (55–85%).¹ Currently, approximately 3 million Americans are chronically infected, and there are 30,000 new cases each year.^{2,3} HCV is a slowly progressing disease that proceeds to cirrhosis in 20–30% of older patients after 20 years or more.⁴ We present a case of a dementia-like condition resulting from hepatitis C antiviral therapy, an outcome that has not been previously documented.

Case Report

A 54-year-old woman presented to our hepatitis C clinic in May of 2002, with a history of hepatitis C, which had been diagnosed in 2001. Her past history of possible exposure to hepatitis C included intravenous drug use from the late 1970s to the early 1980s and a tattoo (from a high-risk, nonparlor setting) in 1978. The patient also had a history of alcohol abuse but had been sober for 20 years. She was married and employed full-time as a care provider. Her symptoms included fatigue, nausea, abdominal pain, and joint pains. The patient had no additional medical problems other than a history of depression (which had resolved without medication) during a period of marital discord 4 years prior to her presentation to the clinic.

Her laboratory examinations revealed an alkaline phosphatase level of 62 U/L, aspartate transaminase of 58 U/L, alanine transaminase of 58 U/L, bilirubin of

0.3 mg/dL, prothrombin time of 10.7 sec, international normalized ratio of 1.0, alpha-fetoprotein of 3.0 ng/mL, thyroid-stimulating hormone of 2.1 mIU/mL, iron of 124/36% saturation, ferritin of 80 ng/mL, a platelet count of 177,000 K/uL, a white blood cell count of 3.9 K/uL, hemoglobin (hgb) of 12.3 g/dL, sodium of 143 mEq/L, potassium of 3.8 mEq/L, creatinine of 0.7 mg/dL, chloride of 104 mEq/L, and blood urea nitrogen of 14 mg/dL. Her genotype was 2A, and her viral load was 48,076 IU/mL. The patient was hepatitis B surface antibody–positive, hepatitis A immunoglobulin G (IgG)–negative, and cryoglobulin–negative.

In September of 2002, the patient underwent liver biopsy, which revealed grades 3–4 and stages 2–3 fibrosis. She decided to pursue antiviral therapy because of her genotype, low viral load, low body weight (155 pounds), and relatively high fibrosis for her age.

Treatment with pegylated interferon (IFN) and ribavirin was initiated in December of 2002. Within the first 4 weeks, the patient felt weak, tired, “mentally slower,” and was unable to work. She was started on a selective serotonin reuptake inhibitor for depression but stopped using it after 2 days because of headaches.

After 8 weeks of treatment, the patient developed lightheadedness and dizziness. At that time, her depression seemed manageable without antidepressants. Her hgb, however, was noted to be 10.1 g/dL. Her dose of ribavirin was decreased, and the patient was started on erythropoietin for symptomatic anemia. After starting erythropoietin, she developed lower back pain that was so severe that it necessitated an emergency room visit. The erythropoietin was, accordingly, discontinued.

Following 9 weeks of treatment, the patient’s anemia worsened, as her hgb measured 9.7 g/dL. Consequently, her pegylated IFN dose was decreased by 50%, which

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maintained her hgb above 10 g/dL. Because of her severe anemia, neither IFN nor ribavirin could be successfully increased during her treatment period.

After 23 weeks of treatment, the patient complained of worsening depression with suicidal thoughts. She had been followed by a psychiatrist during this period, and a trial of two different antidepressants had failed. The patient stopped further treatment for depression at this time.

Her antiviral therapy was ultimately completed at 23 weeks, with reduced doses of both pegylated IFN and ribavirin. By the end of treatment, she had negative viral loads, as determined by polymerase chain reaction assay. Her 12-week posttreatment viral load was 983 IU/mL. Three years after ending treatment, she has remained virus-free, according to transcription-mediated amplification testing.

Within 2 months of completing treatment, the patient attempted to return to work, where she noted significant difficulty "putting words and thoughts together." Feeling anxious and depressed, she cried at work and at home. She was unable to handle any stress or pressure and was re-evaluated by her psychiatrist, who prescribed another class of antidepressants. These medications were not tolerated because of their side effects.

The patient's emotional state and memory failed to improve over the next several months: she continued to complain of short-term memory loss, difficulty with motor skills, and attacks of rage. The patient was referred for neurologic consultation in December 2003.

The neurologic evaluation noted that the patient had normal cranial nerves, intact motor and sensory function, no evidence of ataxia or tremor, normal reflexes, and normal gait. Her speech was clear and appropriate, without aphasia or dysarthria, and her coordination was normal. The patient reported significant short-term memory loss such as losing objects at home, difficulty finding appropriate words, and an inability to describe how she could go from one familiar location to another. Her Mini-Mental State Examination (MMSE) score was 23, and her clock drawing was normal. She was appropriately concerned about her memory loss and her inability to carry out her usual daily activities. Further examination results, including electroencephalogram (EEG) and magnetic resonance imaging (MRI), were normal.

Two years after discontinuing her medications, the patient continued to have difficulty with her short-term memory. She was able to drive but was getting lost in familiar places, and she had difficulty with common household chores such as cooking because of slowness in planning and execution. She was able to manage household finances, though slowly, but she was unable to return to her prior employment.

Discussion

Hepatitis C and its treatment have been frequently associated with reversible neuropsychiatric disorders, including depression, anxiety, and fatigue.⁵⁻⁷ Hepatitis C with cryoglobulinemia has been associated with vasculitic neuropathy.⁸ Myelitis, encephalitis, and lymphoma have also been reported in the literature in accompaniment with hepatitis C.^{9,10}

IFN- α has been associated with a reversible slowing of psychomotor functions, loss of interest, frontal lobe dysfunction, Parkinsonism, and delirium.¹¹ IFN- α has been known to induce diffuse slowing in the EEG, with or without changes in the MMSE. These changes have been reversible and interpreted as mild IFN- α -induced encephalopathy.^{12,13} IFN, particularly pegylated IFN, has been associated with rare cases of progressive multifocal leukoencephalopathy, which is diagnosable by MRI.¹⁴

Neuropsychiatric complications from pegylated IFN and ribavirin are commonly transient and reversible upon discontinuation of the treatment. Our patient developed a dementia-like syndrome that persists more than 2 years after stopping treatment. She meets the criteria for dementia, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, (DSM-IV),¹⁵ with the development of multiple cognitive deficits, including aphasia, apraxia, impaired executive function, and the inability to learn new material. Our patient's dementia-like illness cannot be explained by persistence of the virus, structural abnormalities, seizure-like activity, metabolic abnormalities, or ongoing medication effect.

In spite of a multitude of neuropsychiatric complications associated with hepatitis C and its treatment,¹⁶ persistent dementia has not been reported previously. We present this case as an example of the potential development of long-term complications from a common, effective treatment for an increasingly common disease.

References

1. Wong W, Terrault N. Update on chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2005;3:507-520.
2. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med*. 1999;341:556-562.
3. Friedrich MJ. Third millennium challenge: hepatitis C. *JAMA*. 1999;282:221-222.
4. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology*. 2001;34(4 pt 1):809-816.
5. Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. *Gastroenterology*. 2003;124:1711-1719.
6. Hilsabeck RC, Hassanein TI, Ziegler EA, Carlson MD, Perry W. Effect of interferon-alpha on cognitive functioning in patients with chronic hepatitis C. *J Int Neuropsychol Soc*. 2005;11:16-22.
7. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology*. 2002;36(suppl 1): 237S-244S.

8. McKee DH, Young AC, Alonso-Dominguez A. Neurologic complications associated with hepatitis C virus infection. *Neurology*. 2000;55:459.
9. Khella SL, Souayah N. Hepatitis C: a review of its neurologic complications. *Neurologist*. 2002;8:101-106.
10. Tembl JJ, Ferrer JM, Sevilla MT, Lago A, Mayordomo F, Vilchez JJ. Neurologic complications associated with hepatitis C virus infection. *Neurology*. 1999;53:861-864.
11. Malaguarnera M, Laurino A, Di Fazio I, Pistone G, Castorina M, et al. Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res*. 2001;21:273-278.
12. Kamei S, Sakai T, Matsuura M, Tanaka N, Kojima T, et al. Alterations of quantitative EEG and mini-mental state examination in interferon-alpha-treated hepatitis C. *Eur Neurol*. 2002;48:102-107.
13. Kamei S, Tanaka N, Matsuura M, Arakawa Y, Kojima T, et al. Blinded, prospective, and serial evaluation by quantitative-EEG in interferon-alpha-treated hepatitis-C. *Acta Neurol Scand*. 1999;100:25-33.
14. Lima MA, Auriel E, Wuthrich C, Borenstein NM, Koralknik JJ. Progressive multifocal leukoencephalopathy as a complication of hepatitis C virus treatment in an HIV-negative patient. *Clin Infect Dis*. 2005;41:417-419.
15. American Psychiatric Association. Criteria for dementia. In: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000.
16. Telio D, Sockalingam S, Stergiopoulos V. Persistent psychosis after treatment with interferon alpha: a case report. *J Clin Psychopharmacol*. 2006;26:446-447.

Review

Cognitive Impairment in Hepatitis C Patients on Antiviral Therapy

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Chronic hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality.¹ Successful antiviral therapy with sustained viral clearance is associated with improved quality of life^{2,3} and reduced risk of liver complications such as cirrhosis and hepatocellular carcinoma.^{4,5} Therefore, it is recommended that every individual with chronic HCV infection be considered for antiviral therapy.⁶ However, there are relative and absolute contraindications to the use of pegylated interferon (IFN) and ribavirin, and treatment-related side effects are frequent and occasionally severe and irreversible. Consequently, the decision to

pursue treatment requires a careful weighing of risks and benefits for each HCV-infected individual.

Neuropsychiatric symptoms are prevalent in persons with chronic HCV.⁷⁻⁹ Cognitive dysfunction, characterized by forgetfulness, attention and concentration difficulties, poor word recall, and delayed reaction times, has been documented in 13–50% of individuals with chronic HCV infection using comprehensive neuropsychological test panels.^{9,10} Although cognitive abnormalities are more common in individuals with advanced fibrosis and medical comorbidities, they are present even in the absence of advanced fibrosis and significant psychiatric and medical comorbidities.^{8,10} Neurophysiologic studies reveal metabolic abnormalities on proton magnetic resonance spectroscopy in the frontal white matter and basal ganglia,¹⁰⁻¹² and abnormal electrophysiologic event-related potentials in untreated patients with chronic HCV infection.¹³ The abnormalities noted are suggestive of frontal-subcortical pathway involvement, similar to the involvement described in HIV infection.¹⁴

The mechanism underlying these cognitive abnormalities is unclear. HCV may directly infect the central nervous system. HCV RNA has been detected in post-mortem brain tissue and cerebral spinal fluid.^{15,16} The HCV identified in the central nervous system has been found to be more closely related to the virus present in the lymphoid system rather than in the circulation, suggesting a compartmentalization of infection. As HCV has the ability to replicate in extrahepatic sites, including peripheral blood mononuclear cells,^{17,18} it has been theorized that infected monocytes enter the central nervous system via the normal turnover cycle of resident microglia, which are replaced by circulating monocytes.^{16,19} Alternatively, the chronic inflammatory response induced by HCV may be responsible for the cognitive changes. Specific cytokines may affect cognition via alterations in neuroendocrine and neurochemical pathways.²⁰ Both the systemic cytokine response and the local cytokines produced by astrocytes and microglial cells could be involved. Indeed, the neuropsychiatric side effects of the cytokine, IFN, are supportive of the association between cytokines and cognitive abnormalities.²¹ As cognitive abnormalities are not seen in all HCV-infected patients, additional genetic, viral, or immunologic conditions predisposing to development of this “extrahepatic” complication must be present.

IFN-related neuropsychiatric side effects have been well recognized in the literature. Depressive symptoms have been reported by 20–35% of patients treated with pegylated IFN and ribavirin,^{22,23} and higher rates have been noted with the utilization of standardized questionnaires.²⁴ Clear differences have not been seen in the frequency of neuropsychiatric symptoms between pegylated IFN-alfa

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and standard IFN- α ,^{25,26} but IFN in combination with ribavirin has appeared to increase the rate of depression.²⁷ Resolution of neuropsychiatric side effects has been seen within 6 months of treatment discontinuation in the majority of patients,^{9,25} though anecdotal reports of symptoms lasting up to 24 months have been reported in the literature.^{27,28} The mechanism of IFN therapy causing cognitive side effects is unknown. Reductions of regional cerebral blood flow to specific areas of the brain associated with memory and language function have been described.²⁹ Inhibitions of neurotransmitter synthesis, uptake and release,³⁰ and reduced central dopamine activity³¹ have also been noted.

In general, the cognitive complications of pegylated IFN and ribavirin have not been studied as systematically as the psychiatric side effects. Confusion, delirium, inattention, short-term memory loss, deficits in executive functions, as well as extrapyramidal effects, have been reported, primarily in the non-HCV literature. In two studies of patients with various malignancies receiving IFN- α , neuropsychologic testing identified fronto-subcortical deficits.^{27,32} Reversible electroencephalogram abnormalities have also been identified.³³⁻³⁶

Among HCV-infected patients, IFN-based therapy has been associated with cognitive changes in some but not all studies. In the largest study to date, Fontana and colleagues used a battery of 10 neuropsychologic tests to evaluate cognitive function in 177 patients with chronic HCV undergoing re-treatment with pegylated IFN and ribavirin for 24 weeks and 57 patients treated for 48 weeks.⁹ A global deficit score was calculated at baseline, at Weeks 24 and 48 of treatment, and at 24 weeks posttreatment. Prior to treatment, 32% of patients had evidence of cognitive impairment. Patients reported increases in difficulty concentrating, emotional distress, and symptoms of depression during treatment, but there was no significant change in cognitive function overall during therapy. In contrast, Lieb and colleagues studied 38 patients with chronic HCV and hepatitis B virus and found a significant decrease of immediate recall in the Auditory-Verbal Learning Test and a significant reduction of words recited in the Controlled Oral Word Association Test after 12 weeks of low-dose IFN therapy.²⁹ These apparently conflicting results may reflect differences in the populations studied (and their propensity to develop cognitive dysfunction), frequency of retesting, and specific measures of cognition utilized. The cognitive changes did not significantly correlate with depressive symptoms or anxiety.^{9,27,37}

The case reported by Ruffner-Statzer and Bernstein describes a patient experiencing a decline in cognitive function during HCV treatment without recovery post-treatment.³⁸ The absence of baseline neuropsychiatric testing and a concurrent diagnosis of depression compli-

cate interpretation of the post-treatment outcome. Prior reports of irreversible cognitive impairment in association with IFN therapy have been infrequent,^{28,37} suggesting that it is a rare event. Nonetheless, irreversible cognitive impairment is a devastating outcome for any patient, and this report highlights the relative paucity of data on the possible long-term cognitive effects of IFN therapy in patients with chronic HCV infection. As cognitive impairment is frequent in patients with chronic HCV (~30%), there may be a subgroup of patients at risk for the worsening of cognition-related side effects with treatment. Pretreatment comorbidities and age may be important cofactors.

For the clinician caring for patients with chronic HCV infection, attention to the presence of cognitive difficulties is important, and the growing literature regarding these complications suggests that increased use of neuropsychiatric testing may be warranted. In terms of treatment-related cognitive changes, larger-scale studies are needed to determine the consequences of cognitive dysfunction on quality of life and adherence to therapy, and to confirm or refute the role of IFN exposure in irreversible cognitive changes.

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References

1. Armstrong G, Alter M, McQuillan G, Margolis H. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology*. 2000;31:777-782.
2. Bonkovsky H, Snow K, Malet P, Back-Madruga C, Fontana R, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *J Hepatol*. 2007;46:420-431.
3. Ware J, Bayliss M, Mannocchia M, Davis G. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. *Hepatology*. 1999;30:550-555.
4. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvenuto L, et al. Sustained virological response to IFN- α is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology*. 2007;45:579-587.
5. Coverdale S, Khan M, Byth K, Lin R, Weltman M, et al. Effects of IFN treatment response on liver complications of chronic hepatitis C: 9-yr follow-up study. *Am J Gastroenterol*. 2004;99:636-644.
6. NIH Consensus Statement on Management of Hepatitis C: 2002. *NIH Consensus and State of the Science Statements*. 2002;19:1-46.
7. Hilsabeck R, Hassanein T, Carlson M, Ziegler E, Perry W. Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. *J Int Neuropsychol Soc*. 2003;9:847-854.
8. Forton D, Thomas H, Murphy C, Allsop J, Foster F, Main J. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology*. 2002;35:433-439.
9. Fontana R, Bieliauskas L, Lindsay K, Back-Madruga C, Wright EC, et al; HALT-C Trial Group. Cognitive function does not worsen during pegylated IFN and ribavirin re-treatment of chronic hepatitis C. *Hepatology*. 2007;45:1154-1163.
10. McAndrews M, Farcnik K, Carlen P, Damyanovich A, Mrkonjic M, et al. Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors. *Hepatology*. 2005;41:801-808.
11. Forton D, Allsop J, Main J, Foster G, Thomas H, Taylor-Robinson S. Evidence for a cerebral effect of hepatitis C virus. *Lancet*. 2001;358:38-39.

12. Weissenborn K, Krause J, Bokemeyer M, Hecker H, Schuler A, et al. Hepatitis C virus infection affects the brain—evidence from psychometric studies and magnetic resonance spectroscopy. *J Hepatol.* 2004;41:845-851.
13. Kramer L, Bauer E, Funk G, Hofer H, Wolfgang J, et al. Subclinical impairment of brain function in chronic hepatitis C infection. *J Hepatol.* 2002;37:349-354.
14. Navia B, Rostasy K. The AIDS dementia complex: clinical and basic neuroscience with implications for novel molecular therapies. *Neurotox Res.* 2005;8:3-24.
15. Radkowski M, Wilkinson J, Nowicki M, Adair D, Vargas H, et al. Search for hepatitis C virus negative-strand RNA sequences and analysis of viral sequence in the central nervous system: evidence of replication. *J Virol.* 2002;76:600-608.
16. Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M. Detection and analysis of hepatitis C virus sequences in the cerebrospinal fluid. *J Virol.* 2002;76:10064-10068.
17. Ducoulombier D, Roque-Afonso AM, Di Liberto G, Penin F, Kara F, et al. Frequent compartmentalization of hepatitis C virus variants in circulating B cells and monocytes. *Hepatology.* 2004;39:817-825.
18. Radkowski M, Bednarska A, Horban A, Stanczak J, Wilkinson J, et al. Infection of primary human macrophages with hepatitis C virus in vitro: induction of tumor necrosis factor-alpha and interleukin 8. *J Gen Virol.* 2004;85:47-59.
19. Forton D, Taylor-Robinson S, Thomas H. Central nervous system changes in hepatitis C virus infection. *Eur J Gastroenterol Hepatol.* 2006;18:333-338.
20. Kronfol Z, Emick D. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry.* 2000;157:683-694.
21. Tilg H. New insights into the mechanism of IFN alfa: an immunoregulatory and anti-inflammatory cytokine. *Gastroenterology.* 1997;112:1017-1021.
22. Manns M, McHutchison J, Gordon S, Rustgi V, Shiffman M, et al. Pegylated IFN alfa-2b plus ribavirin compared with IFN alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet.* 2001;358:958-965.
23. Fried M. Side effects of therapy of hepatitis C and their management. *Hepatology.* 2002;36:S237-S244.
24. Asnis G, De La Garza R. IFN-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology and treatment approaches. *J Clin Gastroenterol.* 2006;40:322-335.
25. Kraus MR, Schafer A, Wikmann S, Reimer P, Scheurlen M. Neurocognitive changes in patients with hepatitis C receiving IFN alfa-2b and ribavirin. *Clin Pharmacol Ther.* 2005;77:90-100.
26. Mangia A, Ricci G, Persico M, Minerva N, Carretta V, et al. A randomized controlled trial of pegylated IFN alpha-2a or IFN alpha-2a plus ribavirin and amantadine vs IFN alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. *J Viral Hepat.* 2005;12:292-299.
27. Raison C, Borisov A, Broadwell S, Capuron L, Woolwine B, et al. Depression during pegylated IFN-alpha plus ribavirin therapy: prevalence and prediction. *J Clin Psychiatry.* 2005;66:41-48.
28. Myers C, Scheibel R, Forman A. Persistent neurotoxicity of systemically administered IFN-alpha. *Neurology.* 1991;41:672-676.
29. Lieb K, Engelbrecht M, Gut O, Fiebich B, Bauer J, et al. Cognitive impairment in patients with chronic hepatitis treated with IFN alpha: results from prospective study. *Eur Psychiatry.* 2006;21:204-210.
30. Tanaka H, Maeshima S, Shigekawa Y, Ueda H, Hamagami H, et al. Neuropsychological impairment and decreased regional cerebral blood flow by IFN treatment in patients with chronic hepatitis: a preliminary study. *Clin Exp Med.* 2006;6:124-128.
31. Turner E, Blackwell A. 5-Hydroxytryptophan plus SSRIs for IFN-induced depression: synergistic mechanisms for normalizing synaptic serotonin. *Med Hypotheses.* 2005;65:138-144.
32. Shuto H, Kataoka Y, Horikawa T, Fujihara N, Oishi R. Repeated IFN-alpha administration inhibits dopaminergic neural activity in the mouse brain. *Brain Res.* 1997;747:348-351.
33. Pavol M, Meyers CA, Rexer J, Valentine A, Mattis P, Talpaz M. Pattern of neurobehavioral deficits associated with IFN alfa therapy for leukemia. *Neurology.* 1995;45:947-950.
34. Rohatiner A, Prior P, Burton A, Smith A, Balkwill F, Lister T. Central nervous system toxicity of IFN. *Br J Cancer.* 1983;47:419-422.
35. Suter C, Westmoreland B, Sharbrough F, Hermann R. Electroencephalographic abnormalities in IFN encephalopathy: a preliminary report. *Mayo Clin Proc.* 1984;59:847-850.
36. Kamei S, Sakai T, Matsuura M, Tanaka N, Kojima T, et al. Alterations of quantitative EEG and mini-mental state examination in IFN-alpha-treated hepatitis C. *Euro Neurol.* 2002;48:102-107.
37. Moulignier A, Allo S, Zitroun R, Gout O. Recombinant IFN-alpha-induced chorea and frontal subcortical dementia. *Neurology.* 2002;58:328-330.
38. Ruffner-Statzer S, Bernstein AL. A persistent dementia-like condition following treatment of hepatitis C with pegylated IFN and ribavirin. *Gastroenterol Hepatol.* 2008;4:63-65.