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%). Currently, approximately 3 million Americans are chronically infected, and there are 30,000 new cases each year. HCV is a slowly progressing disease that proceeds to cirrhosis in 20–30% of older patients after 20 years or more. 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...
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.\(^7\)\(^-\)\(^9\) Hepatitis C with cryoglobulinemia has been associated with vasculitic neuropsychopathy.\(^7\) Myelitis, encephalitis, and lymphoma have also been reported in the literature in accompaniment with hepatitis C.\(^9\)\(^,\)\(^10\)

IFN-alfa has been associated with a reversible slowing of psychomotor functions, loss of interest, frontal lobe dysfunction, Parkinsonism, and delirium.\(^11\) IFN-alfa 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-alfa–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

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. Successful antiviral therapy with sustained viral clearance is associated with improved quality of life and reduced risk of liver complications such as cirrhosis and hepatocellular carcinoma. Therefore, it is recommended that every individual with chronic HCV infection be considered for antiviral therapy. 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. 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. 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. Neuropsychiologic studies reveal metabolic abnormalities on proton magnetic resonance spectroscopy in the frontal white matter and basal ganglia, and abnormal electrophysiologic event–related potentials in untreated patients with chronic HCV infection. The abnormalities noted are suggestive of frontal-subcortical pathway involvement, similar to the involvement described in HIV infection.

The mechanism underlying these cognitive abnormalities is unclear. HCV may directly infect the central nervous system. HCV RNA has been detected in postmortem brain tissue and cerebral spinal fluid. 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, 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. 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. 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. 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 in 20–35% of patients treated with pegylated IFN and ribavirin, and higher rates have been noted with the utilization of standardized questionnaires. Clear differences have not been seen in the frequency of neuropsychiatric symptoms between pegylated IFN-alfa and ribavirin.